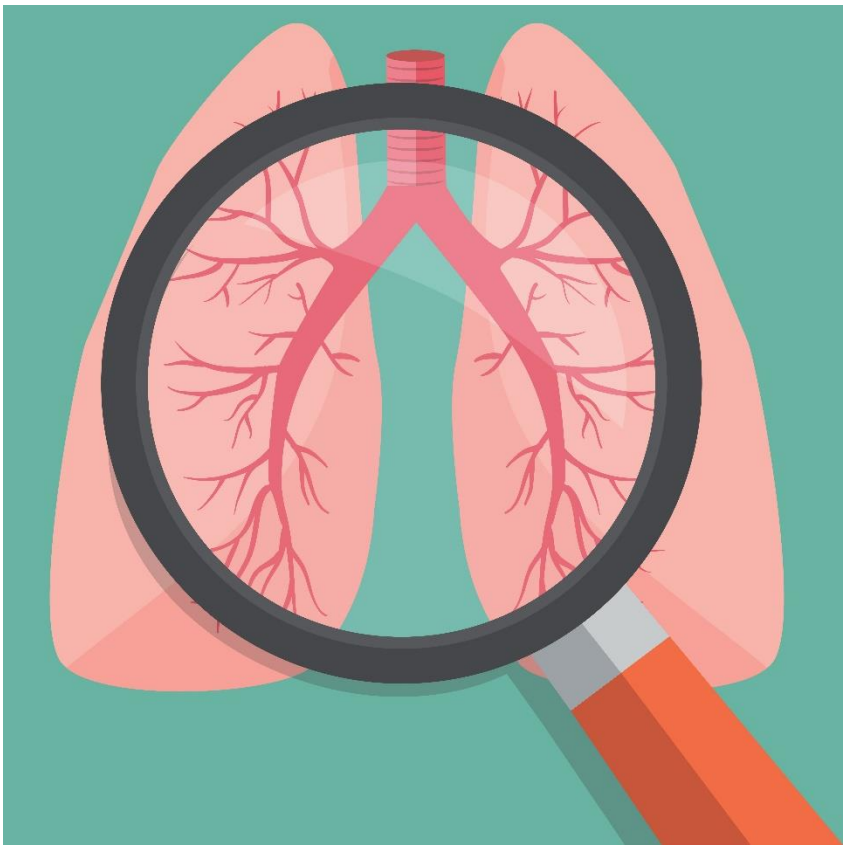
HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Lungenkarzinomscreening in Risikogruppen

Systematischer Review zum Nutzen/Schaden und zu Informationsstrategien (Teil 1)



eunethta

Endbericht

AIHTA Projektbericht Nr.: 132a | ISSN: 1993-0488 | ISSN-online: 1993-0496

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Lungenkarzinomscreening in Risikogruppen

Systematischer Review zum Nutzen/Schaden und zu Informationsstrategien (Teil 1)

Wien, Dezember 2020

Projektteam

Projektleitung & -management (**AIHTA**):

Priv. Doz. Dr. phil. Claudia Wild; Mag. rer.nat. Sabine Ettinger, MSc

Projektbearbeitung (**IAVEM**):

Univ.-Ass. Mag. Thomas Semlitsch; Dr. med. univ. Klaus Jeitler; Carolin Zipp, MA; Cornelia Krenn, MSc; Priv.-Doz. Dr. med. univ. Karl Horvath, alle IAVEM, Medizinische Universität Graz

Ko-Autor*innen (**IQWiG**):

Dipl.-Oecotrophologin Yvonne Zens MPH; Elke Hausner, MSc; Prof. Dr. med. Stefan Sauerland; Mareike Störchel; , Dr. Dipl.-Stat. Sibylle Sturtz, alle IQWiG, Köln

Ko-Autor*innen (**Avalia-t; ACIS**):

Leonor Varela Lema; Lucinda Paz Valiñas; Janet Puñal Riobóo; Paula Cantero Muñoz; María José Faraldo Vallés, alle Scientific-Technical Advice Unit (avalia-t) in Galician Knowledge Assessment Agency (ACIS)

Korrespondenz: claudia.wild@aihta.at

Studie wurde unterstützt durch EUnetHTA

Dieser Bericht soll folgendermaßen zitiert werden/This report should be referenced as follows:

EUnetHTA OTCA28, Semlitsch T et al. Lung cancer screening in risk groups. Collaborative assessment. Diemen (The Netherlands): EUnetHTA; 2020. 295 pages. Report No. OTCA28. Available from: https://www.eunethta.eu

Semlitsch T et al. Lungenkarzinomscreening in Risikogruppen , Systematische Review(s) zu Wirksamkeit und Nutzen, Informationsstrategien, Teil 1, AIHTA Projektbericht Nr.: 132a; Jahr. Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Interessenskonflikt

Alle beteiligten AutorInnen erklären, dass keine Interessenskonflikte im Sinne der Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org) bestehen.

IMPRESSUM

Medieninhaber und Herausgeber:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Wien – Österreich
https://www.aihta.at/

Für den Inhalt verantwortlich:
Priv.-Doz. Dr. phil. Claudia Wild, Geschäftsführung

Die **AIHTA Projektberichte** erscheinen unregelmäßig und dienen der Veröffentlichung der Forschungsergebnisse des Austrian Institute for Health Technology Assessment.

Die **AIHTA Projektberichte** erscheinen in geringer Auflage im Druck und werden über den Dokumentenserver „http://eprints.aihta.at/view/types/hta_report.html" der Öffentlichkeit zur Verfügung gestellt.

AIHTA Projektbericht Nr.: 132a

ISSN 1993-0488

ISSN online 1993-0496

Inhalt

Tabellenverzeichnis

Abkürzungsverzeichnis

COPD	Chronisch obstruktive Lungenerkrankung
CT	Computertomographie
DANTE	Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays
DLCST	Danish Lung Cancer Screening Trial
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IDR	Inzidenzdichtequotient
ITALUNG	Italian Lung Cancer Screening
ITT	Intention to treat
KI	Konfidenzinterval
LDCT	Niedrigdosis (Low-dose) Computertomographie
LSS	Lung Screening Study
LUSI	Lung Tumor Screening and Intervention Trial
MILD	Multicentric Italian Lung Detection
NELSON	NEderlands Leuvens Longkanker Screenings ONderzoek
NLST	National Lung Screening Trial
n.r.	Nicht berichtet
n.s.	Nicht signifikant
OR	Odds ratio
PICO	Population, Intervention, Kontrolle (Control), Endpunkt (Outcome)
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPI	Vorher-Nacher Studie (Pre–post-intervention)
RCT	Randomisierte kontrollierte Studie
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
SDM	Shared decision-making
SR	Systematischer Review
UKLS	UK Lung Cancer Screening Trial
WHO	World Health Organization

1 Hintergrund

Lungenkrebs bezeichnet ein bösartiges Zellenwachstum in der Lunge oder im Bronchialsystem [1]. Etwa 95% der bösartigen Veränderungen der Lunge können dem nicht-kleinzelligen Karzinom (79%) oder dem kleinzelligen Karzinom (16%) zugerechnet werden. Selten auftretende Tumore wie Karzinoidtumore machen die restlichen 5% der primären Lungentumore aus [2]. Lungenkrebs ist die vierthäufigste Krebserkrankung in der EU, an der jährlich mehr als 312.000 Menschen erkranken [3]. Die bei weitem die häufigste Ursache für Lungenkrebs ist das Rauchen. Etwa 90% der Lungenkrebsfälle bei Männern und etwa 80% bei Frauen sind darauf zurückzuführen [4, 5]. Weitere Risikofaktoren, die das Lungenkrebsrisiko erhöhen, sind eine familiäre Vorgeschichte von Lungenkrebs, die idiopathische Lungenfibrose, die chronisch obstruktive Lungenerkrankung (COPD) und eine Exposition gegenüber Schadstoffen wie Asbest, Chrom, Arsen, Radongas, Kohlenteer oder Luftschadstoffen [6-9].

Lungenkrebs: nicht-kleinzelliges (79%) oder kleinzelliges Karzinom (16%)

4. häufigste Krebserkrankung in EU

häufigste Ursache: Rauchen auch andere Risiken

Die Zielpopulation des vorliegenden EUnetHTA Assessment Reports zu Lungenkarzinom-Screening umfasst daher erwachsene Personen mit einem erhöhten Risiko für Lungenkrebs ohne (bestätigtes oder vermutetes) Lungenkarzinom, d.h. Raucher*innen oder ehemalige Raucher*innen sowie Personen mit anderen potenziellen Risikofaktoren für Lungenkrebs: Exposition gegenüber Arbeits- oder Umweltgifte (z.B. Radon, Asbest oder Feinstaub), Personen mit COPD, idiopathischer Lungenfibrose oder eine familiäre Vorgeschichte von Lungenkrebs.

Zielpopulation: Personen mit erhöhtem Risiko auf LungenCa

Für ein Screening auf Lungenkrebs können verschiedene bildgebende Verfahren eingesetzt werden, darunter das Thorax-Röntgen sowie die Niedrigdosis-Computertomographie (Low-Dose-CT [LDCT]). Auch Biomarker in der Atemluft oder im Blut können zum Screening auf Lungenkrebs eingesetzt werden, diese befinden sich derzeit aber noch in einem frühen Forschungsstadium. Ein Screening mittels LDCT wird zunehmend in der klinischen Routinepraxis angeboten, eine einheitliche Strategie für die Durchführung eines systematischen Screenings auf Lungenkrebs gibt es derzeit in Europa nicht. Screening-Programme zur Erkennung und Behandlung von Lungenkrebs in einem frühen Stadium könnten grundsätzlich einen großen Einfluss auf die hohe Mortalitätsrate dieser Krankheit haben. Ein bekanntes Problem des Lungenkrebsscreenings mittels LDCT ist auf der anderen Seite die hohe Rate falsch-positiver Befunde und eine mögliche Überdiagnose. Da in den letzten Jahren mehrere große randomisierte kontrollierte Studien (RCTs) zum Screening mittels LDCT abgeschlossen wurden, erscheint eine systematische Beurteilung der verschiedenen Optionen und organisatorischen Varianten eines Lungenkrebsscreening sinnvoll.

Screening-Verfahren: Thorax-Röntgen Niedrigdosis-Computertomographie (LDCT) Biomarker

derzeit kein systematisches Screening in Europa

große RCTs abgeschlossen: infolge Bewertung von LungenCa Screening

2 Zielsetzung, Fragestellung

Das Ziel des EUnetHTA Assessment Reports zu Lungenkarzinom-Screening ist die Zusammenfassung und Analyse der verfügbaren Evidenz zum Lungenkrebsscreening bei Personen mit erhöhtem Lungenkrebsrisiko (Personen mit aktuellem oder ehemaligem starken Tabakkonsum, Personen mit beruflicher oder umweltbedingter Radon-, Asbest- oder Feinstaubbelastung, Patient*innen mit COPD oder idiopathischer Lungenfibrose sowie Personen mit einer familiären Vorgeschichte von Lungenkrebs) durchzuführen. Zu diesem Zweck wurden vier Forschungsfragen definiert:

Ziel: Zusammenfassung und Analyse der verfügbaren Evidenz

- Forschungsfrage 1: Welchen Nutzen/Schaden hat ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem (bzw. keinem systematischen) Screening bei Personen mit erhöhtem Lungenkrebsrisiko? Da angenommen werden kann, dass kein Screening und Screening mittels Thorax-Röntgen vergleichbar sind, wird das Lungenkrebsscreening mittels Thorax-Röntgen, soweit sinnvoll und möglich, auch als Vergleichsintervention herangezogen.
- Forschungsfrage 2: Welchen Nutzen/Schaden hat die Screening auf Lungenkrebs mittels Biomarkern zusätzlich zur LDCT im Vergleich zum Screening mittels LDCT allein bei Personen mit erhöhtem Lungenkrebsrisiko?
- Forschungsfrage 3: Welchen Nutzen/Schaden haben organisatorische Varianten eines Screenings auf Lungenkrebs mittels LDCT (z.B. unterschiedliche Screening-Intervalle, Screening mit oder ohne Einladung) bei Personen mit erhöhtem Lungenkrebsrisiko?
- Forschungsfrage 4: Was ist die beste Strategie, um Personen der Zielgruppe über ein Lungenkrebsscreening-Programm zu informieren sowie um eine informierte Entscheidung hinsichtlich der Teilnahme am Screening zu optimieren?

4 Forschungsfragen:

FF1: Nutzen/ Schaden von Screening mit LDCT (oder Thorax Röntgen)?

FF2: Rolle von Biomarkern ?

FF3: Evidenz zu organisatorischen Varianten (Intervalle,..)?

FF4: beste Strategie für Information zu Screening?

Tabelle 2-1: PICO 1

Population	Erwachsene (Alter ≥18 Jahre) ohne (bestätigtes oder vermutetes) Lungenkarzinom (ICD-10 Code C34) mit erhöhtem Risiko für Lungenkrebs: ■ Population 1: aktive oder ehemalige Raucher*innen ■ Population 2: Personen mit weiteren potenziellen Risikofaktoren: berufliche oder umweltbedingte Radon-, Asbest- oder Feinstaubbelastung, COPD (ICD-10 Code J44), idiopathische Lungenfibrose (ICD-10 Code J84.1), familiäre Vorgeschichte von Lungenkrebs (ICD-10 Code C34)
Intervention	Systematisches Screening auf Lungenkrebs mittels LDCT
Vergleichs-intervention	Kein (bzw. kein systematisches) Screening (usual care) In einer Sensitivitätsanalyse wird auch ein Screening auf Lungenkrebs mittels Thorax-Röntgen als zusätzliche Vergleichsintervention für die Endpunkte Mortalität und Überdiagnosen berücksichtigt. Rationale: Ergebnisse der PLCO-Studie [10] lassen eine Vergleichbarkeit keines eines Screenings mittels Thorax-Röntgen und keines Screenings zumindest im Hinblick auf die Lungenkrebs-spezifische Mortalität.
Endpunkte	■ Mortalität (Gesamtmortalität, Lungenkrebs-spezifische Mortalität) ■ Morbidität ■ gesundheitsbezogene Lebensqualität ■ Schäden, die sich aus dem Screening selbst (z.B. Folgen der Strahlenbelastung) oder aus nachfolgenden diagnostischen Untersuchungen (zum Beispiel invasive Prozeduren wie Biopsien) ergeben, einschließlich Überdiagnosen[1], Konsequenzen aus falschen Screeningbefunden (falsch-positiv und falsch-negativ) ■ (Schwere) unerwünschte Ereignisse
Studiendesign	Randomisierte kontrollierte Studien (RCT)

Tabelle 2-2: PICO 2

Population	Siehe PICO 1
Intervention	Screening auf Lungenkrebs mittels Biomarker zusätzlich zur LDCT ■ Biomarker können als Test für die Auswahl von geeigneten Personen für ein Screening verwendet werden ■ Biomarker können als Test zur Charakterisierung unbestimmter Noduli verwendet werden, die beim CT-basierten Screening gefunden wurden
Vergleichs-intervention	Screening auf Lungenkrebs mittels LDCT alleine Rationale: alleiniges LDCT ist die empfohlene Screeningmaßnahme gemäß aktuellen Leitlinien
Endpunkte	Siehe PICO 1
Studiendesign	Siehe PICO 1

[1] Definiert als die Anzahl der Diagnosen (richtig positive Befunde), die zu Lebzeiten einer Person nicht klinisch auffällig geworden wären.

Tabelle 2-3: PICO 3

Population	Siehe PICO 1
Intervention	Jährliches systematisches Screening auf Lungenkrebs mittels LDCT wie in den Leitlinien empfohlen
Vergleichs-intervention	Systematisches Screening auf Lungenkrebs mittels LDCT mit anderen Screening-Intervallen (kürzer oder länger) bzw. Varianten eines systematischen Screenings (organisatorische Varianten, z.B. mit oder ohne Einladung)
Endpunkte	Siehe PICO 1
Studiendesign	Siehe PICO 1

Tabelle 2-4: PICO 4

Population	Siehe PICO 1
Intervention	Spezifische Informationsstrategie zum Lungenkrebsscreening (z.B. bestimmte Inhalte, bestimmte Verteilungsstrategien)
Vergleichs-intervention	Andere spezifische Informationsstrategie zum Lungenkrebsscreening als in der Interventionsgruppe (z.B. andere Inhalte, andere Verteilungsstrategien) bzw. keine spezifische Informationsstrategie zum Lungenkrebsscreening
Endpunkte	■ Teilnahmerate am Screening ■ Zufriedenheit der Teilnehmer*innen ■ Empowerment der Teilnehmer*innen ■ Verbessertes Wissen ■ Informierte Entscheidung
Studiendesign	RCTs; nicht-randomisierte kontrollierte Studien; prospektive Beobachtungsstudien; qualitative Studien

3 Methodik

Kooperation mit IQWiG

Für Forschungsfrage 1 wurden die Ergebnisse der Nutzenbewertung zum Lungenkrebsscreening mittels Niedrigdosis-Computertomografie bei Personen mit aktuellem oder ehemaligem Tabakkonsum Rauchern des Deutschen Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) (Berichtsnummer S19-02) [11] herangezogen.

Methode FF1:

systematische Literaturrecherche nach SR/ HTA und RCTs in mehreren Datenbanken Studienregister Referenzlisten

Für den IQWiG-Bericht wurde eine systematische Literaturrecherche nach relevanten qualitativ hochwertigen systematischen Übersichtsarbeiten (SRs) in den bibliografischen Datenbanken MEDLINE, Cochrane Database for Systematic Reviews und Health Technology Assessment Database durchgeführt. Die Suche wurde auf die letzten 6 Jahre vor 2019 beschränkt. Ziel war es, eine oder mehrere qualitativ hochwertige und aktuelle SRs zu auszuwählen, aus der oder denen Primärstudien identifiziert und anschließend bezüglich der spezifischen Einschlusskriterien des Berichtes selektiert wurden. Ergänzend wurde für den Zeitraum, der durch keinen aktuellen relevanten SR von hoher Qualität vorlag, eine systematische Literaturrecherche nach RCTs in den folgenden Datenbanken durchgeführt: MEDLINE, Embase und Cochrane Central Register of Controlled Trials. Darüber hinaus wurden folgende Informationsquellen und Suchtechniken berücksichtigt: Studienregister (ClinicalTrials.gov, WHO-ICTRP), Sichtung von Referenzlisten, Dokumente, die im Rahmen des IQWiG-Anhörungsverfahrens zur Verfügung gestellt wurden sowie Autorenanfragen.

EUnetHTA Bericht: Raucher*innen sowie weitere Risikogruppen

IQWiG: ursprünglich nur Raucher*innen

Für den EUnetHTA Assessment Report wurden die Einschlusskriterien zur Population für die Forschungsfrage 1 auf andere Risikofaktoren für Lungenkrebs erweitert (berufliche oder umweltbedingte Exposition gegenüber Schadstoffen, COPD, idiopathische Lungenfibrose und familiäre Vorgeschichte des Lungenkrebses). Deshalb wurde die Liste der ausgeschlossenen Studien im IQWiG-Bericht erneut gesichtet, um Studien zu Personen mit diesen Risikofaktoren zu identifizieren. Darüber hinaus wurden alle Studien, die bereits im IQWiG Bericht eingeschlossen waren, dahingehend gesichtet, ob Personen mit anderen Risikofaktoren für Lungenkrebs eingeschlossen waren. Ergebnisse zu diesen Subgruppen wurden, wenn möglich, extrahiert.

Methode FF2: systematische Literaturrecherche wie bei FF1

Für die Forschungsfrage 2 wurde eine systematische Literaturrecherche nach RCTs oder SRs in den folgenden Datenbanken durchgeführt: MEDLINE, Embase, Cochrane Central Register of Controlled Trials und Cochrane Database of Systematic Reviews. Darüber hinaus wurden die folgenden Informationsquellen und Suchtechniken berücksichtigt: Studienregister (ClinicalTrials.gov, WHO-ICTRP) und Sichtung von Referenzlisten.

Methode FF3: wie FF1 und FF2

Für die Forschungsfrage 3 wurden keine eigenen Literaturrecherchen durchgeführt. Es wurden jedoch alle Studien, die zu den Forschungsfragen 1 und 2 eingeschlossen waren, wenn möglich, zur Durchführung von Subgruppenanalysen für verschiedene Screening-Modalitäten herangezogen.

Methode FF4: zusätzliche systematische Literaturrecherche

Für die Forschungsfrage 4 wurde eine systematische Literaturrecherche in den bibliographischen Datenbanken MEDLINE, Embase und Cochrane Central Register of Controlled Trials und Cochrane Database for Systematic Reviews durchgeführt. Zusätzlich zur elektronischen Suche wurden die Referenzlisten der eingeschlossenen Studien und Übersichtsarbeiten gesichtet.

Die Sichtung der Literatur und Auswahl relevanter Primärstudien wurde von zwei Personen unabhängig voneinander durchgeführt. Diskrepanzen wurden durch Diskussionen zwischen den beiden Personen geklärt.

RoB-Beurteilung auf Studien und auf Endpunktebene

Eine Bewertung des Verzerrungspotenzials (Risk of Bias (RoB)) der eingeschlossenen RCTs erfolgte an Hand Cochrane RoB-Tools [12], zur Bewertung nicht-randomisierter Studien wurde das Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) Tool verwendet [13]. Das Verzerrungspotenzial wurde auf Studien- und Endpunktebene von zwei Personen unabhängig voneinander bewertet und eine Einstufung als niedrig oder hoch vorgenommen.

GRADE-Bewertung

alle Arbeitsschritte durch 2 Wissenschafter*innen

Zur Bewertung der Vertrauenswürdigkeit der verfügbaren Evidenz (certainty of evidence) wurde der Grading of Recommendations Assessment, Development and Evaluation (GRADE)-Ansatz angewandt [14]. Die Verlässlichkeit der Evidenz wurde auf der Endpunkt-Ebene bewertet (mögliche Stufen: hoch, mittel, niedrig oder sehr niedrig).

Datenextraktion

Die Datenextraktion zu Studiendesign, Charakteristika der Studien und der Population und die Ergebnisberichterstattung erfolgte in standardisierten Tabellen. Die Ergebnisse aus den einzelnen Studien wurden gemäß den vordefinierten Endpunkten beschrieben.

FF1-3: Meta- und Sensitivitätsanalysen Analyse von Effektmodifikatoren

Neben der Gegenüberstellung der Ergebnisse aus den einzelnen Studien wurden, sofern die methodischen Voraussetzungen erfüllt waren, für die Forschungsfragen 1 bis 3 Meta- und Sensitivitätsanalysen durchgeführt sowie Effektmodifikatoren untersucht. Für die Forschungsfrage 4 waren keine Meta-Analysen geplant bzw. wurden nicht durchgeführt.

4 Ergebnisse

4.1 Forschungsfrage 1: Nutzen/ Schaden von LungenCa Screening in Risikogruppen

4.1.1 Informationsbeschaffung

1 hochwertiger SR 9 RCTs identifiziert

Im Rahmen der Literaturrecherche nach SR konnte eine aktuelle und qualitativ hochwertige Übersichtarbeit (Snowsill 2018 [1]) eingeschlossen und als Basis für die Identifikation relevanter Primärstudien herangezogen werden. Es konnten insgesamt neun relevante RCTs (184 Dokumente) für die Forschungsfrage 1 identifiziert werden.

zumeist mit Raucher*innen nur 1 RCT auch mit anderen Risiken

Alle neun Studien untersuchten aktuelle oder ehemalige Raucher*innen, wobei eine Studie, die UK Lung Cancer Screening Trial (UKLS [15-24]), auch Personen mit anderen Risikofaktoren für Lungenkrebs einschloss.

Studienregister: 2 laufende + 1 geplante Studie

Bei der Sichtung der Studienregister wurden zwei laufende Studien und eine geplante Studie identifiziert. Darüber hinaus wurden eine abgeschlossene nicht-publizierte Studie sowie vier Studien mit unklarem Status gefunden. Das Datum der letzten Recherche war der 12. Juni 2020.

4.1.2 Studiencharakteristika

1 Studie ausgeschlossen

Bei einer Studie, der UKLS [3-12], handelt es sich um eine Machbarkeitsstudie, die grundsätzlich die Einschlusskriterien erfüllt, jedoch wurden keine Ergebnisse berichtet, die für die Analysen herangezogen werden kannten. Die UKLS wurde daher in weiterer Folge nicht berücksichtigt.

8 RCTs: 90.836 Teilnehmer*innen

Die übrigen acht Studien (Anzahl der randomisierten Studienteilnehmer*innen: 90.836) unterschieden sich hinsichtlich der verwendeten Screening-Strategien. In sechs Studien wurden die Teilnehmer*innen entweder einem Screening mit LDCT oder keinem Screening randomisiert zugeordnet. In den RCTs Danish Lung Cancer Screening Trial (DLCST) [25-40], Italian Lung Cancer Screening (ITALUNG) [29-39], Lung Tumor Screening and Intervention Trial (LUSI) [41-45], Multicentric Italian Lung Detection (MILD) [46-53] und NEderlands Leuvens Longkanker Screenings ONderzoek (NELSON) [54-93] wurden den Teilnehmer*innen der Kontrollgruppe weder zu Beginn noch während der Nachbeobachtung bildgebende Verfahren angeboten, außer es bestand Verdacht auf Lungenkrebs. In der DANTE-Studie (Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays) [93-97] wurde eine Erstuntersuchung mittels Thorax-Röntgen durchgeführt. Da diese Untersuchung sowohl in der Interventions- als auch in der Kontrollgruppe durchgeführt wurde und in der Kontrollgruppe im weiteren Verlauf der Studie kein Screening durchgeführt wurde, wurde die Studie auch als eine Studie angesehen, in der LDCT gegen kein Screening verglichen wurde. Im Gegensatz dazu wurden in den RCTs Lung Screening Study [LSS] [94-97] und National Lung Screening Trial (NLST) [98-172] ein Screening mittels LDCT mit einem Screening mittels Thorax-Röntgen verglichen. Beide Studien wurden in den USA durchgeführt.

6 RCTs zu LDCT vs. kein Screening

2 RCTs: auch Thorax Röntgen in KG und IG

LDCT vs. kein Screening: Europa

In allen RCTs, die ein Screening mittels LDCT versus kein Screening verglichen, wurden in den Studiengruppen ohne Screening alle endpunktspezifischen Daten über Register erhoben. Darüber hinaus wurden je nach Studie auch postalische oder telefonische Befragungen sowie Ergebnisse aus klinische Untersuchungen herangezogen. Alle RCTs wurden innerhalb Europas (Italien, Dänemark, Deutschland, Niederlande und Belgien) durchgeführt.

hohe Zahl an Teilnehmer*innen

Die Zahl der Teilnehmer*innen lag in sechs Studien bei 3.000 bis 4.000 Personen, während die NELSON- sowie NLST-Studien sogar 16.000 bzw. 53.500 Teilnehmer*innen hatten. Die Dauer der Screeningphase in den einzelnen RCTs betrug 1 bis 6 Jahre. Der geplante Follow-Up-Zeitraum 5 bis 10 Jahre (keine Informationen zur Dauer des Follow-Ups wurden in der LSS Studie berichtet). Mit Ausnahme der MILD- und NELSON-Studie betrug das Screeningintervall für alle Screening-Runden 1 Jahr. Die MILD-Studie war die einzige dreiarmige Studie, in der die Teilnehmer*innen der Interventionsgruppen entweder jährlich oder alle 2 Jahre gescreent wurden. Zu Beginn der Studie wurden die Teilnehmer*innen in Gruppen mit einem jährlichen oder zweijährlichen Screening randomisiert. Die Randomisierung in eine zusätzliche Kontrollgruppe ohne Screening begann erst später, was zu unterschiedlichen Gruppengrößen führte. In der NELSON-Studie wurde das Screeningintervall nach jeder Screeningrunde von 1 Jahr auf 2 Jahre und dann auf 2,5 Jahre verlängert.

Nachbeobachtung: 5-10 Jahre

Intervall: zumeist 1 Jahr, aber auch 2 Jahre, 2,5 Jahre

Studienpopulation: Raucher*innen – seit 20-30 Jahren oder frühere Raucher*innen

mehr Männer ≥ 49 Jahre bis 75 Jahre

Die Studien schlossen Männer und Frauen ein, die zu Studienbeginn rauchten (mindestens 20 oder 30 Packungsjahre) oder in den letzten 10 Jahren mit dem Rauchen aufgehört hatten (15 Jahre in der NLST). Ausnahmen sind die DANTE-Studie, in der nur Männer eingeschlossen wurden, sowie die NELSON-Studie, für die zunächst nur Männer rekrutiert wurden, während Frauen erst im weiteren Verlauf der Studie eingeschlossen wurden. Der Anteil an Frauen beträgt daher in der NELSON-Studie nur etwa 16%, während er in den anderen Studien bei mindestens 31% liegt. Das Alter der Teilnehmer*innen was in den Studien auf ≥ 49 Jahre bis 75 Jahre festgelegt, die MILD war die einzige Studie, die keine obere Altersgrenze festlegte. Die Teilnahmerate am Screening betrug in den jeweiligen Interventionsgruppen 81% bis 96%.

4.1.3 Berichtete Endpunkte

8 RCTs:
Mortalität:
Gesamtmortalität
Lungenkrebs-spezifische Mortalität
Überdiagnose

6 RCTs:
Lebensqualität
unerwünschte Ereignisse (UE)

Ergebnisse zu patientenrelevanten Endpunkten konnten aus allen acht Studien extrahiert werden. In allen RCTs wurden verwertbare Ergebnisse zu den Endpunkten Mortalität (Gesamtmortalität und Lungenkrebs-spezifische Mortalität) und Überdiagnose berichtet. Das Thorax-Röntgenscreening gilt nicht als geeigneter Komparator, um die Wirksamkeit des LDCT-Screenings im Hinblick auf die Konsequenzen aus falschen Screeningbefunden, gesundheitsbezogene Lebensqualität und unerwünschte Ereignisse im Vergleich zu keinem Screening zu beurteilen. Daher wurden für die Endpunkte nur jene sechs Studien berücksichtigt, die ein Screening mittels LDCT mit keinem Screening verglichen. In alle sechs Studien wurden verwertbare Ergebnisse zu den Folgen von falschen Screening-Ergebnissen berichtet. Für unerwünschte Ereignisse lagen verwertbare Angaben aus der DANTE-Studie vor. Für den Endpunkt gesundheitsbezogene Lebensqualität waren in den Studien entweder keine oder keine verwertbaren Daten verfügbar. Tabelle 4-1 gibt einen Überblick über die in den einzelnen Studien berichteten Endpunkte.

Tabelle 4-1: Forschungsfrage 1: Matrix der berichteten Endpunkte

RCT	Endpunkte				
	Mortalität	Morbidität			HRQoL
			Schaden durch Screening		
	Gesamtmortalität und Lungenkrebs-spezifische Mortalität	Unerwünschte Ereignisse	Konsequenzen aus falschen Screening-ergebnissen	Überdiagnosen	Gesundheitsbezogene Lebensqualität
LDCT Screening versus kein Screening					
DANTE	●	●	●	●	–
DLCST	●	–	●	●	–
ITALUNG	●	–	●	●	–
LUSI	●	–	●	●	–
MILD	●	–	●	●	–
NELSON	●	–	●	●	–
LDCT Screening versus Thorax-Röntgen-Sscreening					
LSS	●	x	x	●	x
NLST	●	x	x	●	x

Abkürzungen: LDCT=Niedrigdosis-Computertomographie; RCT=Randomisierte kontrollierte Studie

● *Ergebnisse berichtet und verwertbar.*

–: Keine Ergebnisse berichtet oder die Ergebnisse waren für die Nutzenbewertung nicht verwertbar.

x: Für diesen Endpunkt stellt das Thorax-Röntgen-Screening keine adäquate Vergleichsintervention dar, um den Effekt eines LDCT-Screenings versus keinem Screening zu untersuchen.

4.1.4 Studienqualität

Verzerrungspotenzial auf Studienebene:
4 RCTs: niedriger RoB
4 RCTs: hoher RoB

Gründe:
Gruppenzuteilung
Unterschiede bei Teilnehmer*innen etc.

Das Verzerrungspotenzial auf Studienebene wurde für vier RCTs (DLCST, ITALUNG, LUSI und NELSON) als niedrig und für die übrigen vier Studien als hoch eingestuft. Bei den Studien mit hohem Verzerrungspotenzial auf Studienebene war zumeist unklar, ob die die Verdeckung der Gruppenzuteilung adäquat erfolgte (DANTE, MILD und NLST). Bei den LSS Studie war unklar, ob die Berichterstattung ergebnisunabhängig erfolgte (z.B. fehlende Informationen zu den geplanten Endpunkten). In der MILD-Studie führten auch signifikante Unterschiede in den Charakteristika der Teilnehmer*innen zu Studienbeginn (Alter, Geschlecht, Raucherstatus und Packungsjahre) zwischen der Interventions- und der Kontrollgruppe zu einem hohen Verzerrungspotenzial.

Verzerrungspotenzial auf Endpunktebene:

einige niedrig, andere hoch

Das Verzerrungspotenzial auf Endpunktebene wurde für Gesamtmortalität, Lungenkrebs-spezifische Mortalität, Folgen falscher Screening-Ergebnisse und Überdiagnose in den Studien DLCST, ITALUNG und NELSON als niedrig eingestuft. Obwohl die LUSI-Studie ein niedriges Verzerrungspotenzial auf Studienebene zeigte, wurde aufgrund von Diskrepanzen zwischen den Publikationen im Hinblick auf die berichteten Ergebnisse, für alle Endpunkte das Verzerrungspotenzial auf Endpunktebene als hoch bewertet. Das Verzerrungspotenzial für den Endpunkt unerwünschte Ereignisse wurde für die Studie DANTE, die einzige Studie, die Ergebnisse zu diesem Endpunkt berichtete, als hoch eingestuft. Für alle Studien, für die das Verzerrungspotenzial bereits auf Studienebene als hoch bewertet wurde (DANTE, MILD, NLST und LSS), ergibt sich folglich auch ein hohes endpunktspezifisches Verzerrungspotenzial, so dass für diese Studien keine weitere endpunktspezifische Bewertung vorgenommen wurde.

Die Vertrauenswürdigkeit der Evidenz nach GRADE lag je nach Endpunkt bei niedrig bis hoch (siehe Tabelle A- 1).

4.1.5 Ergebnisse zu Wirksamkeit und Sicherheit

Mortalität

LDCT vs. kein Screening:
3 RCTs: niedriger RoB
3 RCTs: hoher RoB
Ergebnisse aus 8-11 J FU

Für den Vergleich Screening mittels LDCT versus kein Screening lagen für die Gesamtmortalität Ergebnisse aus drei Studien mit niedrigem (DLCST, ITALUNG und NELSON) und drei Studien mit hohem Verzerrungspotenzial (DANTE, MILD und LUSI) vor. Es wurden dabei die Ergebnisse für den jeweils längsten Beobachtungszeitraum, zwischen 8 und 11 Jahren, herangezogen.

Meta-Analyse von 3 RCTs, dann alle 6 RCTs:
beide:
kein Unterschied

Eine Meta-Analyse der drei Studien mit niedrigem Verzerrungspotenzial zeigte keinen statistisch signifikanten Unterschied zwischen den Gruppen (Inzidenzdichtequotient [IDR] 0,93 [95% Konfidenzintervall [KI] 0,69-1,26]; p = 0,434). Die gemeinsame Auswertung der RCTs mit niedrigem und hohem Verzerrungspotenzial (33.703 Personen) zeigte ebenfalls keinen statistisch signifikanten Effekt zugunsten des Screenings (IDR 0,95 [95% KI 0,88-1,03]; p = 0,164).

LDCT vs. Thorax Rx:
2 RCTs: hoher RoB
kein Unterschied

Für den Vergleich LDCT-Screening mit einem Thorax-Röntgenscreening lagen Ergebnisse zur Gesamtmortalität aus zwei Studien (LSS und NLST) mit hohem Verzerrungspotenzial vor. Die Sensitivitätsanalyse für diese beiden Studien (90.473 Personen) unter Verwendung der Daten für den jeweils längsten Beobachtungszeitraum widerspricht nicht den Ergebnissen für den Vergleich von LDCT-Screening versus kein Screening (IDR 0,97 [95% KI 0,92-1,02]; p = 0,168).

Subgruppen-Analysen zur Gesamtmortalität

keine Subgruppenanalysen für Tabakexposition und Sceeningstrategie

Für die Merkmale Ausmaß der Tabakexposition (z.B. Tabakkonsum, Raucherstatus) und Screeningstrategie (z.B. Anzahl der Screeningrunden) wurden keine Subgruppenanalysen durchgeführt, da die Studien nicht in geeigneten Subgruppen eingeteilt werden konnten oder es keine signifikanten Unterschiede zwischen den Studien bezüglich dieser Merkmale gab. Es konnten auch keine sinnvollen Subgruppenanalysen für einzelne Studienpopulationen durchgeführt werden.

Subgruppenanalysen zu potentiellen Effektmodifikatoren:

für Alter der Rx Geräte, CT-Zeilen, Größe des Screeningzentrums, Geschlecht der Teilnehmer*innen, Screeningintervall

Bei den sechs eingeschlossenen Studien von LDCT-Screening im Vergleich zu keinem Screening (DANTE, DLCST, ITALUNG, MILD, LUSI und NELSON) bzw. den beiden Studien zum Vergleich von LDCT-Screening und Thorax-Röntgenscreening (LSS und NLST) wurden jedoch das Alter der in den Studien verwendeten Geräte (einschließlich der Nutzung von LDCT-Geräten < 16 Zeilen versus ausschließliche Nutzung von LDCT-Geräten ≥ 16 Zeilen) sowie die Größe des Screeningzentrums (kleine versus große Zentren: < 3000 versus ≥ 3000 rekrutierte Studienteilnehmer*innen) als potenzielle Effektmodifikatoren untersucht. Darüber hinaus wurden verfügbare Daten aus vier Studien (DANTE, LUSI, NELSON und NLST) verwendet, um das Geschlecht der Teilnehmer*nnen als potentielle Effektmodifikatoren zu untersuchen. Auch wurde im Rahmen der dreiarmigen MILD-Studie die Länge des Screeningintervalls als Effektmodifikator untersucht, da das Screening in den beiden Interventionsgruppen entweder jährlich oder alle 2 Jahre durchgeführt wurde.

keine signifikanten Ergebnisse zu möglichen Effektmodifikatoren

Der Test auf Interaktion zeigte in keiner der Subgruppenanalysen für die Studien, in denen ein Screening mittels LDCT mit keinem Screening verglichen wurde, eine statistische Signifikanz. Auch die Berücksichtigung der Studien zum Vergleich gegen Thorax-Röntgen-Screening im Rahmen einer Sensitivitätsanalyse widerspricht diesen Ergebnissen nicht. Für die Gesamtmortalität zeigte sich daher keine Effektmodifikation aufgrund des Alters der CT-Geräte, der Größe des Zentrums, des Geschlechts der Teilnehmer*innen oder der Länge des Screeningintervalls.

LungenCa-spezifische Mortalität
LDCT vs. kein Screen:
3 RCTs: niedriger RoB
3 RCTs: hoher RoB

Für die Lungenkrebs-spezifische Mortalität lagen Ergebnisse aus drei Studien mit niedrigem (DLCST, ITALUNG und NELSON) und drei Studien mit hohem Verzerrungspotenzial RoB (DANTE, MILD und LUSI) zum Vergleich LDCT-Screening versus kein Screening vor. Aus alle Studien wurden die Ergebnisse für den jeweils längsten Beobachtungszeitraum verwendet, der zwischen 8 und 11 Jahren lag.

Meta-Analyse aus 3 RCTs: niedriger RoB kein Unterschied

Die Meta-Analyse der drei Studien mit niedrigem Verzerrungspotenzial zeigten keinen statistisch signifikanten Unterschied zwischen den Gruppen (IDR 0,80 [95% KI 0,60-1,06]; $p = 0,076$). Die gemeinsame Auswertung der Studien mit niedrigem und hohem Verzerrungspotenzial (33.703 Teilnehmer*innen) zeigte einen statistisch signifikanten Effekt zugunsten des LDCT-Screenings (IDR 0,81 [95% KI 0,72-0,91]; $p = 0,004$). Für den Vergleich LDCT-Screenings versus Thorax-Röntgen-Screening lagen Ergebnisse aus zwei Studien (LSS und NLST) mit hohem Verzerrungspotenzial vor (90.473 Teilnehmer*innen). Die Sensitivitätsanalyse widerspricht nicht den Ergebnissen des Vergleichs LDCT-Screenings mit keinem Screening (IRR 0,89 [95% KI 0,82-0,96]; $p = 0,010$).

Meta-Analyse aus 6 RCTs: Unterschied zugunsten von Screening

Subgruppen-Analysen für Lungenkrebs-spezifische Mortalität

keine Subgruppenanalysen für Tabakexposition und Sceeningstrategie

Für die Merkmale Ausmaß der Tabakexposition (z.B. Tabakkonsum, Raucherstatus) und Screeningstrategie (z.B. Anzahl der Screeningrunden) wurden keine Subgruppenanalysen durchgeführt, da die Studien nicht in geeigneten Subgruppen eingeteilt werden konnten oder es keine signifikanten Unterschiede zwischen den Studien bezüglich dieser Merkmale gab. Es konnten auch keine sinnvollen Subgruppenanalysen für einzelne Studienpopulationen durchgeführt werden.

Subgruppenanalysen zu potentiellen Effektmodifikatoren:

für Alter der Rx Geräte, CT-Zeilen, Größe des Screeningzentrums, Geschlecht und Alter der Teilnehmer*innen, COPD Screeningintervall

Bei den sechs eingeschlossenen Studien von LDCT-Screening im Vergleich zu keinem Screening (DANTE, DLCST, ITALUNG, MILD, LUSI und NELSON) bzw. den beiden Studien zum Vergleich von LDCT-Screening und Thorax-Röntgenscreening (LSS und NLST) wurden jedoch das Alter der in den Studien verwendeten Geräte (einschließlich der Nutzung von LDCT-Geräten < 16 Zeilen versus ausschließliche Nutzung von LDCT-Geräten ≥ 16 Zeilen) sowie die Größe des Screeningzentrums (kleine versus große Zentren: < 3000 versus ≥ 3000 rekrutierte Studienteilnehmer*innen) als potenzielle Effektmodifikatoren untersucht. Die Subgruppenanalyse für Studien zum LDCT-Screening im Vergleich zu keinem Screening, zeigte keine Effektmodifikation. Auch durch die Hinzunahme der Studien, die LDCT-Screening mit Thorax-Röntgen-Screening verglichen, konnte keine Veränderung des Effekts festgestellt werden. Darüber hinaus wurden verfügbare Daten aus vier Studien (DANTE, LUSI, NELSON und NLST) verwendet, um das Geschlecht und Alter der Teilnehmer*innen sowie das Vorliegen von COPD zu Studienbeginn (DLSCT) als potentielle Effektmodifikatoren zu untersuchen. Auch wurde im Rahmen der dreiarmigen MILD-Studie die Länge des Screeningintervalls als Effektmodifikator untersucht, da das Screening in den beiden Interventionsgruppen entweder jährlich oder alle 2 Jahre durchgeführt wurde.

keine signifikanten Ergebnisse zu möglichen Effektmodifikatoren

Der Test auf Interaktion zeigte für keine der Subgruppenanalysen eine statistische Signifikanz. Wo möglich, wurde auch eine Sensitivitätsanalyse unter Einschluss der Studien zum Vergleich LDCT-Screenings versus Thorax-Röntgen-Screening durchgeführt. Dies widersprach den Ergebnissen nicht. Für die Lungenkrebs-spezifische Mortalität ergab sich somit keine Effektmodifikation in Bezug auf Alter der CT-Geräte, die Größe des Studienzentrums, das Vorliegen von COPD bei Studienbeginn, Geschlecht und Alter der Teilnehmer*innen oder die Länge des Screeningintervalls.

Schlussfolgerung zum Nutzen bezüglich der Mortalität

Vertrauenswürdigkeit der Evidenz für Gesamtmortalität: hoch

Die Vertrauenswürdigkeit der Evidenz wurde für die beiden Endpunkte Gesamtmortalität bzw. Lungenkrebs-spezifische Mortalität als hoch bis moderat eingestuft. Für die Gesamtmortalität wurde die Vertrauenswürdigkeit der Evidenz als hoch eingestuft, da die Mehrzahl der Studien qualitativ hochwertige Evidenz lieferte. Insgesamt zeigte sich für ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem Screening ein geringer bis kein Unterschied in der Gesamtmortalität.

geringer (in Metaanalyse) bis kein Unterschied

Die Ergebnisse der Meta-Analysen weisen jedoch in Richtung einer Verringerung der Gesamtmortalität durch ein Screening mittels LDCT.

Für die Lungenkrebs-spezifische Mortalität wurde die Vertrauenswürdigkeit der Evidenz um eine Stufe auf moderat herabgestuft, weil die Auswertung der Studien mit niedrigem Verzerrungspotenzial allein keinen statistisch signifikanten Unterschied zwischen den Gruppen ergab. Somit kommt es durch ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem Screening wahrscheinlich zu einer Verringerung der Lungenkrebs-spezifischen Mortalität.

Vertrauenswürdigkeit der Evidenz für Lungenkrebs-spezifische Mortalität: moderat wahrscheinliche Verringerung der Mortalität

Der Schätzer für den absoluten Effekt zeigt für die Gesamtmortalität eine Reduktion um 5 Todesfälle pro 1000 Personen (95% KI -3 bis 12) sowie für die Lungenkrebs-spezifische Mortalität um 5 Todesfälle pro 1000 Personen (95% KI 3 bis 8) innerhalb von etwa 10 Jahren. Somit liegen die absoluten Effekte und die entsprechenden KIs für Gesamtmortalität und Lungenkrebs-spezifische Mortalität in einer ähnlichen Größenordnung. Zusammenfassend lässt sich sagen, dass ein Lungenkrebsscreening mittels LDCT die Mortalität im Vergleich zu keinem Screening reduzieren kann.

5 vermiedene Todesfälle pro 1.000 Personen innerhalb von 10 Jahren

Unerwünschte Ereignisse

Zum Endpunkt unerwünschte Ereignisse standen Daten aus nur einer Studie (DANTE; hohes Verzerrungspotenzial) zum Vergleich Screening mittels LDCT versus kein Screening zur Verfügung. In der Studie werden Ergebnisse zum Auftreten von unerwünschten Ereignissen nach einer Operation und zum Auftreten von unerwünschten Ereignissen mit einem Schweregrad ≥ 3 nach einer Operation im Beobachtungszeitraum von maximal 8 Jahre nach Randomisierung berichtet. Die Auswertung zeigte einen statistisch signifikanten Unterschied im Auftreten von unerwünschten Ereignisse nach einer Operation aufgrund eines verdächtigen Befundes zuungunsten des LDCT-Screenings (Odds Ratio [OR] 3,48, [95% KI 1,41-8,62]; p = 0,004). Die Einschränkung auf unerwünschte Ereignisse mit einem Schweregrad ≥ 3 zeigte ebenfalls einen statistisch signifikanten Unterschied zwischen den beiden Studiengruppen zuungunsten des LDCT-Screenings (OR 4,25 [95% KI 0,92-19,69]; p = 0,046).

nur 1 RCT unerwünschte Ereignisse (UE) nach Eingriffen Schweregrad ≥ 3

zu Ungunsten von LDCT

Schlussfolgerung zum Schaden bei unerwünschten Ereignissen

Die Vertrauenswürdigkeit der Evidenz für unerwünschte Ereignisse als wichtiger Endpunkt wurde als niedrig bewertet. Die Vertrauenswürdigkeit der Evidenz wurde wegen des hohen Verzerrungspotenzial der DANTE Studie sowie wegen schwerwiegender Limitationen in der Präzision um zwei Stufen herabgestuft, da die Ergebnisse auf einer relativ kleinen Studie beruhen, was zu einem großen Konfidenzintervall führt. Zusammenfassend lässt sich sagen, dass ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem Screening vermehrt zu unerwünschten Ereignisse führen kann.

hohes Verzerrungsrisiko

vermehrte UE

Konsequenzen von falsch-negativen Screening-Ergebnissen

Daten zu den Folgen falsch negativer Screening-Ergebnisse wurden in den Studien nicht berichtet.

keine Evidenz

Konsequenzen von falsch-positiven Screening-Ergebnissen

Zu den Folgen falsch-positiver Screening-Ergebnisse wurden sowohl Daten zu einer rein diagnostisch-interventionellen Abklärung als auch Daten zu chirurgisch-therapeutischen Eingriffen herangezogen, wenn Therapie und Diagnose von Lungengewebe unklarer Dignität nicht eindeutig voneinander zu trennen war. Komplikationen im Zusammenhang mit diesen Eingriffen bei Personen, bei denen in der Folge gutartige Befunde gefunden wurden, wurden auch für

falsch-positive Ergebnisse aus diagnostischer wie therapeutischer Abklärung

diesen Endpunkt berücksichtigt. Als Beobachtungszeitraum wurde der Zeitraum gewählt, in dem die Screeningphase in der jeweiligen Studie abgeschlossen war.

Evidenz aus 6 RCTs
3 RCTs: niedriger RoB
3 RCTs: hoher RoB

Für die Folgen falsch-positiver Screening-Ergebnisse lagen Ergebnisse aus drei Studien mit niedrigem (DLCST, ITALUNG und NELSON) und drei Studien mit hohem Verzerrungspotenzial (DANTE, MILD und LUSI) vor. Die Notwendigkeit einer invasiven diagnostischen Abklärung wurde in den Studien nur für die Interventionsgruppen erfasst. Die DANTE-Studie stellt eine Ausnahme dar. Obwohl in allen Studien das LDCT-Screening mit keinem Screening verglichen wurde, unterzogen sich in der DANTE-Studie alle Teilnehmer*innen zu Studienbeginn unabhängig von der Gruppenzuteilung einem Thorax-Röntgen-Screening und einer 3-tägigen Sputumzytologie. Es bleibt daher unklar, ob der Gruppenunterschied allein auf das LDCT-Screening zurückzuführen ist.

Problem: Ergebnisse aus Operationen und Biopsien mit unterschiedlichen Methoden erhoben

Die Darstellung der invasiven diagnostischen Verfahren war in den Studien unterschiedlich und beinhaltete in einigen Studien die gemeinsame Darstellung von Operationen und Biopsien, während in anderen Studien die Verfahren einzeln berichtet wurden. Für einige Studien liegen mehrere Operationalisierungen vor, die zeigen, dass dies einen starken Einfluss auf die Anzahl der Ereignisse hat. Daher wurde für diesen Endpunkt keine zusammenfassende Gesamtschätzung angegeben, sondern vielmehr eine Bandbreite (Minimum-Maximum) der Effektschätzer aus den einzelnen Studien dargestellt.

0,1% bis 1,5% der Teilnehmer*innen erhielten invasive diagnostische Abklärung

Zwischen 0,1% und 1,5% der zum Screening eingeladenen Studienteilnehmer*innen erhielten eine invasive diagnostische Abklärung, die nur durch ein falsch-positives Ergebnis des Screenings notwendig wurde. Operationen an Personen mit gutartigen Befunden wurden bei 0,1% bis 1,3% der zum Screening eingeladenen Studienteilnehmer*innen durchgeführt. Insgesamt ergab sich bei 0,1% bis 1,5% der Studienteilnehmer*innen eine Konsequenz in Folge falsch-positiver Befunde.

0,04 bis 0,3% der operierten hatte Komplikationen

In zwei Studien (DLCST und NELSON) wurde über Komplikationen bei operierten Personen mit letztlich gutartigem Befund berichtet. In der DLCST-Studie traten bei zwei von sieben operierten Patienten mit gutartigem Befund geringfügige Komplikationen auf, somit erlitten 0,1% aller zum Screening eingeladenen Studienteilnehmer*innen eine geringfügige Komplikation nach der Operation eines letztlich benignen Befundes. In der NELSON-Studie wurden Komplikationen nicht bei allen operierten Patient*innen mit gutartigem Befund berichtet, sondern nur bei jenen, die sich entweder einer Thorakotomie oder einer video-assistierten Thorakoskopie (VATS) unterziehen mussten. Insgesamt traten bei diesen Patient*innen mit gutartigem Befund drei schwere Komplikationen und 20 leichte Komplikationen auf. Somit lag die Rate von schwerwiegenden bzw. leichten Komplikationen bei 0,04% bzw. 0,3% aller zum Screening eingeladenen Teilnehmer*innen.

Schlussfolgerung zum Schaden hinsichtlich der Folgen falsch-positiver Screening-Ergebnisse

Schaden-Abschätzung aufgrund falsch-positiver Befunde basiert auf hochwertige Evidenz

Ein Screening auf Lungenkrebs mit LDCT führt zu Schäden aufgrund der Folgen falsch-positiver Screening-Ergebnisse im Vergleich zu keinem Screening. Die Schlussfolgerung stützt sich auf hochwertige Evidenz. Die Vertrauenswürdigkeit der Evidenz für diesen wichtigen Endpunkt wurde als hoch eingestuft, da die Mehrheit der RCTs qualitativ hochwertige Evidenz lieferte.

Überdiagnosen

3 RCTs: niedriger RoB
3 RCTs: hoher RoB

Zum Endpunkt Überdiagnosen lagen Daten aus drei Studien mit niedrigem (DLCST, ITALUNG und NELSON) und drei Studien mit hohem Verzerrungspotenzial (DANTE, LUSI, MILD) zum Vergleich LDCT-Screening versus kein Screening vor. Für den Vergleich LDCT-Screenings mit einem Thorax-Röntgen-Screening fanden sich Ergebnisse aus zwei Studien (LSS und NLST) mit hohem Verzerrungspotenzial.

keine Metaanalyse durchgeführt wegen hoher Heterogenität der Studien

Im vorliegenden Bericht wurde keine meta-analytische Zusammenfassung zu Überdiagnosen vorgenommen. Für die Überdiagnosen bezogen auf Personen, die während der Screening-Phase eine Lungenkrebsdiagnose erhielten, variierten die Anteile zwischen den Studien so stark, dass eine Gesamtschätzung nicht sinnvoll interpretiert werden konnte. Konkrete Gründe für die Heterogenität der Ergebnisse, wie z.B. einzelne Aspekte der Screening-Strategien oder Merkmale der Studienpopulation, konnten nicht identifiziert werden. Weniger ausgeprägt war die Heterogenität für den Anteil der Überdiagnosen im Verhältnis zu den zum Screening eingeladenen Teilnehmern*innen, somit war es grundsätzlich möglich, eine Gesamtschätzung für die Studien mit LDCT-Screening im Vergleich mit keinem Screening zu geben. Das Konfidenzintervall ist jedoch ähnlich breit wie die Spanne der einzelnen Punktschätzer in den Studien.

in 8 RCTs sehr unterschiedliche Werte berichtet

max 2,2%, min 0,1% aller zum Screening eingeladenen Teilnehmern*innen

Aus allen acht eingeschlossenen Studien konnte das Risiko einer Überdiagnose im Verhältnis zu allen zum Screening eingeladenen Teilnehmern*innen ermittelt werden. Unter den sechs Studien, in denen ein LDCT-Screening mit keinem Screening verglichen wurde, ist ITALUNG die einzige Studie, bei der über die gesamte Beobachtungsdauer in der Interventionsgruppe weniger Lungenkrebsfälle diagnostiziert wurden als in der Kontrollgruppe. Daher konnte in dieser Studie keine Überdiagnosen festgestellt werden. Auch beim Screening mit zweijährigem Intervall in der MILD-Studie wurden keine Überdiagnosen festgestellt. Das Risiko einer Überdiagnose war in den DANTE- und DLCST-Studien mit 2,2% bzw. 2,1% am höchsten. Für die RCTs LUSI und NELSON sowie das jährliche Screening in der MILD-Studie wurde das Risiko einer Überdiagnose für die Studienteilnehmer mit 0,9%, 0,6% bzw. 1,4% berechnet. In den beiden Studien, in denen ein LDCT-Screening mit einem Thorax-Röntgen-Screening verglichen wurde, wurde ein Überdiagnose-Risiko von 1,2% bzw. 0,1% errechnet.

Subgruppen-Analysen zu Überdiagnosen

Subgruppenanalysen zu geschlechts-spezifischer Effektmodifikation

Aus der DANTE- und NELSON-Studie lagen nur Daten für Männer vor. In der LUSI-Studie wurden Ergebnisse getrennt für Frauen und Männer berichtet, wobei es keinen Hinweis darauf gibt, dass es eine geschlechtsspezifische Effektmodifikation gibt. In der NLST-Studie, in der ein LDCT-Screening mit einem Thorax-Röntgen-Screening verglichen wurde, wurden ebenfalls nach Geschlecht getrennte Ergebnisse berichtet, die ebenfalls gegen eine solche Effektmodifikation sprechen.

keine Effektmodifikation durch Screening-intervalle

Für die MILD-Studie standen Daten für ein jährliches und zweijährliches Screeningintervall zur Verfügung. Die zahlenmäßigen Unterschiede in der Rate der Überdiagnosen zwischen den beiden Screening-Gruppen sind wahrscheinlich zufällig. Das Ergebnis deutet darauf hin, dass hinsichtlich des Risikos für Überdiagnosen keine Effektmodifikation durch ein unterschiedliches Screeningintervall vorliegt.

Schlussfolgerung zum Schaden von Überdiagnose

Die Diagnose von Lungenkrebs erfordert eine histologische oder zytologische Bestätigung. Es kann davon ausgegangen werden, dass fast alle Fälle mit der Diagnose Lungenkrebs auch behandelt wurden. Jedes diagnostische Verfahren und jede Behandlung/Therapie birgt das Risiko von Nebenwirkungen und Komplikationen.

Schaden wegen Überdiagnose und Folgeinterventionen (mit potentiellen Komplikationen)

Die Vertrauenswürdigkeit der Evidenz für eine Überdiagnose als wichtiger Endpunkt kann insgesamt als hoch eingeschätzt werden. Zusammenfassend lässt sich sagen, dass ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem Screening zu Überdiagnose führt und somit zu einem Schaden durch die daraus resultierenden invasiven Diagnoseverfahren und Behandlungen einschließlich der damit verbundenen Komplikationen und Nebenwirkungen.

Vertrauenswürdigkeit der Evidenz: hoch

Gesundheitsbezogene Lebensqualität

Daten zu gesundheitsbezogenen Lebensqualität wurden in den Studien nicht berichtet oder waren für die Bewertung nicht verwertbar.

keine Evidenz zu QoL

4.2 Forschungsfrage 2: Rolle von Biomarkern im LungenCa Screening

4.2.1 Informationsbeschaffung

Im Rahmen der Literaturrecherche konnten keine randomisierten kontrollierten Studien identifiziert werden, die für die Forschungsfrage 2 relevant wären.

kein RCT zur Fragestellung identifiziert

Darüber hinaus wurden bei der Sichtung der Studienregister keine laufenden RCTs sowie keine abgeschlossenen, nicht publizierten Studien identifiziert. Die letzte Recherche wurde am 7. Juli 2020 durchgeführt.

keine laufenden Studien

4.2.2 Ergebnisse zu Wirksamkeit und Sicherheit

Keine Ergebnisse verfügbar.

keine Ergebnisse

4.2.3 Schlussfolgerung

Da derzeit keine für die Beantwortung der Forschungsfrage relevanten RCTs vorliegen, kann keine Schlussfolgerung hinsichtlich des Nutzens oder Schadens der Verwendung von Biomarkern zusätzlich zu einer LDCT im Rahmen eines Screenings auf Lungenkrebs bei Personen mit erhöhten Lungenkrebsrisiko im Vergleich zu einem Lungenkrebsscreening mittels LDCT allein gezogen werden.

keine Schlussfolgerung zur Rolle von Biomarkern in Ermangelung von RCTs möglich

4.3 Forschungsfrage 3: Nutzen/ Schaden von organisatorischen Varianten (Intervalle,..)

4.3.1 Informationsbeschaffung

Die Ergebnisse aus jenen acht RCTs, die für die Forschungsfrage 1 vorlagen, wurden auch zur Beantwortung dieser Forschungsfrage herangezogen.

8 RCTs

4.3.2 Ergebnisse zu Wirksamkeit und Sicherheit

Im Rahmen der Forschungsfrage 1 wurden Subgruppenanalysen im Hinblick auf spezifische Charakteristika der Studienteilnehmer*innen sowie auf organisatorische Merkmale durchgeführt. Die Schlussfolgerungen aus diesen Analysen hinsichtlich klinischer Wirksamkeit und Sicherheit wurden bereits weiter oben dargestellt. Über diese Analysen hinaus konnten keine weiteren Subgruppenanalysen für verschiedene Screening-Strategien durchgeführt werden, da die Studien nicht in geeignete Subgruppen eingeordnet werden konnten oder es keine signifikanten Unterschiede zwischen den Studien hinsichtlich eines bestimmten Merkmals gab.

Ergebnisse aus Subgruppenanalysen zu organisatorischen Merkmalen

vgl. oben bei FF1

Bei einem der inkludierten RCTs (MILD) [46-53] handelte es sich jedoch um eine dreiarmige Studie, bei der die Teilnehmer*innen der Interventionsgruppen entweder jährlich oder alle 2 Jahre gescreent wurden. Gemäß einer 10-Jahres-Auswertung der MILD-Studie ergab sich für ein Screening alle 2 Jahre im Vergleich zum jährlichen Screening eine ähnliche Gesamtmortalität (Hazard Ratio [HR] 0,80 [95% KI 0,57-1,12]; p = 0,191) und eine ähnliche Lungenkrebs-spezifische Mortalität (HR 1,10 [95% KI 0,59-2,05]; p = 0,760).

nur 1 RCT zu unterschiedlichen Intervalle:

1- oder 2-jährig ähnliche Ergebnisse bei Gesamt- wie Lungenkrebs-spezifischer Mortalität

Die Vertrauenswürdigkeit der Evidenz zum Vergleich eines Lungenkrebsscreenings mittels LDCT alle 2 Jahre gegenüber einem jährlichen LDCT-Screening wurde als sehr gering eingestuft, da diese beiden Screeningintervalle bisher nur in einer einzigen Studie mit hohem Verzerrungspotenzial und schwerwiegenden Limitationen hinsichtlich der Präzision direkt miteinander verglichen wurden (siehe Tabelle 4-2).

hoher RoB

4.3.3 Schlussfolgerung

Die derzeit verfügbare Evidenz reicht nicht aus, um die Forschungsfrage zu beantworten, ob eine bestimmte Strategie hinsichtlich eines Lungenkrebsscreening im Vergleich zu anderen Screening-Strategien vorteilhaft ist.

nicht ausreichende Evidenz

4.4 Forschungsfrage 4: Beste Strategie für Information zu Screening

4.4.1 Informationsbeschaffung

Im Rahmen der Literaturrecherche konnten 15 relevante Studien identifizierten werden - fünf RCTs (10 Dokumente) [173-182], drei kontrollierte Beobachtungsstudien (3 Dokumente) [183-185] und sieben unkontrollierte Vorher-Nachher-Studien (pre-post-intervention; PPI) (10 Dokumente) [186-195]. Die letzte Recherche wurde am 24. Juli 2020 durchgeführt.

15 Studien identifiziert: 5 RCTs, 3 kontrollierte Beobachtungsstudien, 7 Vorher-Nachher Studien

4.4.2 Studiencharakteristika

Wirksamkeit verschiedene Informations- oder Einladungsmaterialien/ -strategien

Shared-Decision-Making-Strategien oder -instrumente

In zwei RCTs (2.012 bzw. 1.000 Personen) und einer nicht-randomisierten Vergleichsstudie (388 Personen) wurden verschiedene Informations- oder Einladungsmaterialien/-strategien (gezielte Einladung, telefonische Einladung bzw. Verteilung von Flugblättern versus Standardeinladungen bzw. keine Einladung) für die ein Lungenkrebsscreening verglichen, in den übrigen 12 Studienmit insgesamt 2.069 Teilnehmer*innen, darunter drei RCTs, wurde die Wirksamkeit verschiedener Shared-Decision-Making (SDM)-Strategien oder -instrumente bei Personen, die zu einem Lungenkrebsscreening eingeladen wurden, untersucht.

aktuelle oder ehemalige Raucher*innen,

potentielle Screening der Teilnehmer*innen

Die in den Studien bewerteten Interventionen waren sehr heterogen und umfassten den Versand von Informationsbroschüren zum Lungenkrebsscreening, Aufklärungsprogramme, die über Nutzen und Schaden des Lungenkrebsscreenings informieren, telefonische Beratung sowie die Verwendung verschiedener Arten von Entscheidungshilfen (Option Grids, web- oder videobasierte Entscheidungshilfen). Zwölf Studien wurden in den USA, zwei in Großbritannien und eine in Japan durchgeführt. Die Teilnehmer*innen der Studien waren Männer und Frauen, die für ein Lungenkrebsscreening in Frage kamen, d.h. aktuelle oder ehemalige Raucher*innen im Alter von 45 bis 55 Jahren und älter. Der Anteil der Frauen in den Studien lag bei 40% bis 65%. Das Durchschnittsalter der Studienteilnehmer*innen betrug 59-65 Jahre.

4.4.3 Berichtete Endpunkte

Ergebnisse zur Verbesserung des Wissensstandes bezgl. Nutzen/Schaden von LungenCa-Screening

Empowerment

Zufriedenheit mit Informationen

Teilnahmerate

Fragebögen

Mit Ausnahme von vier Studien lagen in alle Studien über Ergebnisse zur Verbesserung des Wissensstandes der Teilnehmer*innen im Hinblick auf Nutzen/Schaden eines Lungenkrebsscreenings vor. Das Empowerment der Teilnehmer*innen wurde in neun Studien evaluiert, wobei alle Studien auf die Lösung des Entscheidungskonflikts hinsichtlich einer Screeningteilnahme fokussierten. Die Befähigung einer informierten Entscheidung wurde in fünf Studien untersucht, die Zufriedenheit der Teilnehmer*innen mit den Informationen in drei Studien. In acht der Studien wurde auch die Teilnahmerate am Screening als ein Endpunkt definiert. Als Erhebungsinstrumente wurden mehrheitlich Fragebögen zum Wissen, dem Entscheidungskonflikt oder dem Bedauern der Entscheidung verwendet. Tabelle 4-2 gibt einen Überblick über die in den einzelnen Studien berichteten Endpunkte

Tabelle 4-2: Forschungsfrage 4: Matrix der berichteten Endpunkte

Studie (Design)	Outcomes				
	Wissensverbesserung	Informierte Entscheidung	Empowerment der Teilnehmer*innen	Zufriedenheit der Teilnehmer*innen	Teilnahmerate am Screening
Informationsstrategien für ein Lungenkrebsscreening					
Quaife 2020 (RCT)	●	-	●	●	●
Sharma 2018 (RCT)	-	-	-	-	●
Yoshida 2012 (non-RCT)	-	-	-	-	●
Strategien/Werkzeuge für eine informierten Entscheidung im Rahmen eines Lungenkrebsscreenings					
Hoffman 2018 (PPI)	●	●	●	-	●
Lau 2015 (PPI)	●	-	●	-	-
Lowenstein 2020 (non-RCT)	●	●	-	●	-
Mazzone 2017 (PPI)	●	-	-	-	-
Reuland 2018 (PPI)	●	-	-	-	●
Ruparel 2019 (RCT)	●	-	●	-	●
Sakoda 2019 (PPI)	●	●	-	-	-
Sferra 2020 (RCT)	●	●	●	-	-
Studts 2020 (PPI)	-	-	●	-	-
Tanner 2019 (non-RCT)	-	-	●	●	●
Volk 2014 (PPI)	●	-	●	-	-
Volk 2020 (RCT)	●	●	●	-	●

Abkürzungen: PPI=Pre-Post-Intervention (Vorher-Nachher-Studie); RCT=Randomisierte kontrollierte Studie; SDM=Shared-Decision-Making
●: Ergebnisse berichtet und verwertbar.
–: Keine Ergebnisse berichtet.

4.4.4 Studienqualität

2 RCTs: niedriger RoB
3 RCTs: hoher RoB

Das Verzerrungspotenzial auf Studienebene mittels Cochrane RoB Tool wurde für zwei RCTs als niedrig (Qualife 2020, Volk 2020) und für drei RCTs als hoch (Ruparel 2019, Sferra 2020, Sharma 2018) eingestuft. Die Hauptgründe für ein hohes Verzerrungspotenzial waren die unklare Generierung von Randomisierungssequenzen und fehlende Informationen über eine adäquate Verdeckung der Gruppenzuteilung. Das Verzerrungspotenzial auf Endpunktebene wurde für alle berichteten Endpunkte bei zwei RCTs als niedrig eingestuft. Für jene drei RCTs, bei denen das Verzerrungspotenzial bereits auf Studienebene als hoch eingestuft wurde, gab es folglich auch ein hohes Verzerrungspotenzial auf Endpunktebene.

Das Verzerrungspotenzial der übrigen Studien (kontrollierte Beobachtungsstudien und unkontrollierte Vorher-Nachher-Studien) anhand des ROBIS-I Tools wurde auf Endpunktebene für vier Studien als niedrig (Hoffman 2018, Lau 2015, Studts 2020, Volk 2014) und für 6 Studien als hoch (Lowenstein 2020, Mazzone 2017, Reuland 2018, Sakoda 2019, Tanner 2019, Yoshida 2012) eingestuft.

4 weitere Studien mit anderem Design: niedriger RoB
6: hoher RoB

Je nach bewertetem Endpunkt lag die Vertrauenswürdigkeit der Evidenz von GRADE bei sehr niedrig bis moderat (siehe Tabelle A- 1).

4.4.5 Ergebnisse zur Wirksamkeit und Sicherheit

Im vorliegenden Bericht wurde keine meta-analytische Zusammenfassung zu den Endpunkten in Forschungsfrage 4 vorgenommen, da sich die Studien sowohl hinsichtlich der Interventionen als auch hinsichtlich der Art der Endpunkterhebung sehr unterschiedlich waren.

keine Metaanalyse durchgeführt, da hohe Heterogenität

Verbessertes Wissen

Daten zur Veränderung des Wissensstandes hinsichtlich eines Lungenkrebsscreenings lagen aus zwei RCTs (Qualife 2020, Volk 2020) sowie mit vier weiteren Studien mit niedrigem Verzerrungspotenzial und zwei RCTs (Ruparel 2019, Sferra 2020) sowie vier weiteren Studien mit hohem Verzerrungspotenzial vor. Der Einsatz unterschiedlicher Einladungsstrategien für ein Lungenkrebsscreening (gezielte Einladung vs. Standard-Einladungsmaterial) hatte keinen Einfluss auf den Wissensstand der Studienteilnehmer*innen. Im Vergleich zu Standard-Informationsmaterialien zu Krebsscreenings wie sie aktuell in den USA oder Großbritannien verwendet werden, erhöhte die Verwendung von Entscheidungshilfen oder Informationsfilmen im gemeinsamen Entscheidungsprozess vor der Durchführung eines Lungenkrebsscreenings mittels LDCT das Wissen der Teilnehmer*innen über Nutzen und Risiken der Lungenkrebsvorsorge.

12 Studien zu verbessertem Wissen

Einsatz unterschiedlicher Einladungsstrategien: kein Einfluss auf Wissenstand

Entscheidungshilfen: Verbesserung

Informierte Entscheidung

Ergebnisse zum Endpunkt informierte Entscheidung lagen aus einem RCT (Volk 2020) und einer unkontrollierten Studie mit niedrigem Verzerrungspotenzial sowie einem RCT (Sferra 2020), einer nicht-randomisierten Vergleichsstudie und einer unkontrollierten Studie mit hohem Verzerrungspotenzial vor.

4 Studien zu informierter Entscheidung

Ein RCT (Volk 2020) und eine kontrollierte Beobachtungsstudie (Lowenstein 2020), die beide die Verwendung von Entscheidungshilfen im Informationsprozess im Rahmen eines Lungenkrebsscreenings im Vergleich zu Standardinformationsmaterialien für ein Krebs-Screening verglichen, berichteten über signifikant bessere Raten der SDM-Scores in den Studiengruppen die Entscheidungshilfen verwendeten. In einem weiteren RCT (Sferra 2020), in dem unterschiedliche Entscheidungshilfen miteinander verglichen wurden (Option Grids versus online Entscheidungshilfe), wurde kein Unterschied im Hinblick auf eine Informierte Endscheidung berichtet. Darüber hinaus wurde in zwei einarmigen Studien berichtet, dass sich die Mehrheit der Teilnehmer*innen nach erfolgter Intervention (Einsatz von Entscheidungshilfen, Schulungen) gut über das Lungenkrebsscreening informiert fühlte um eine Entscheidung hinsichtlich einer Screeningteilnahme zu treffen.

Entscheidungshilfen vs. Standardinformationen:

bessere Raten der SDM-Scores mit Entscheidungshilfen

Empowerment der Teilnehmer*innen

8 Studien zu Empowerment

Ergebnisse zum Empowerment der Teilnehmer*innen lagen aus zwei RCTs (Qualife 2020, Volk 2020) sowie drei unkontrollierten Studien mit niedrige Verzerrungspotenzial und zwei RCTs (Ruparel 2019, Sferra 2020), einer nicht-randomisierten Vergleichsstudie und einer unkontrollierten Studie mit hohem Verzerrungspotenzial vor.

Entscheidungshilfen vs. Standard-informationen:

niedriger Entscheidungskonflikt, weniger Bedauern

Beim Vergleich der Verwendung von Entscheidungshilfen oder Informationsfilmen mit schriftlichen Standardinformationsmaterialien im Rahmen Informationsprozess eines Lungenkrebsscreenings zeigte sich ein signifikant niedriger Entscheidungskonflikt bzw. weniger Bedauern über die Entscheidung in den Entscheidungshilfe-/Informationsfilmgruppen. Darüber hinaus berichteten alle unkontrollierten Studien, die den Einsatz von Entscheidungshilfen untersuchten, nach der Intervention über einen niedrigeren Entscheidungskonflikt der Studienteilnehmer*innen. Bei Vergleichen verschiedener Entscheidungshilfen zeigte sich in der Gruppe die Option Grids verwendete im Vergleich zur Verwendung von online Entscheidungshilfen signifikant bessere Werte in der Decisional Regret Scale.

unterschiedliche Einladungsstrategien: kein Unterschied beim Empowerment

Der Vergleich unterschiedlicher Einladungsstrategien für das Lungenkrebsscreening (gezieltes Einladung vs. Standardeinladungsmaterial) zeigte keinen Unterschied im Empowerment der Teilnehmer*innen.

Zufriedenheit der Teilnehmer*innen

3 Studien zu Zufriedenheit

Daten zur Teilnehmerzufriedenheit waren aus einem RCT (Qualife 2020) mit niedrigem Verzerrungspotenzial und zwei nicht-randomisierten Vergleichsstudien mit hohem Verzerrungspotenzial verfügbar.

unterschiedliche Einladungsstrategien, -materialien, Informationsmodi: kein Unterschied

Unterschiedliche Einladungsstrategien zum Screening (gezieltes Einladung vs. Standard-Einladungsmaterial), unterschiedliche Informationsmaterialen im Rahmen des Screenings (Entscheidungshilfe vs. Standard-Informationsmaterial) oder unterschiedliche Modi der Informationsvermittlung (persönliches Gespräch vs. telefonisch Beratung) führten zu keinem Unterschied in der Zufriedenheit der Teilnehmer*innen mit dem Informationsprozess oder der Zufriedenheit mit ihrer Entscheidung hinsichtlich einer Screeningteilnahme.

Teilnahmerate am Screening

7 Studien zur Teilnahmerate

Verwertbare Angaben zur Screening-Teilnahmerate lagen aus zwei RCTs (Qualife 2020, Volk 2020) und einer unkontrollierten Studie mit niedrigem Verzerrungspotenzial und zwei RCTs (Ruparel 2019, Sharma 2018) und zwei nicht-randomisierten Vergleichsstudien mit hohem Verzerrungspotenzial vor.

keine Unterschiede in Teilnahmerate am LungenCa Screening mit unterschiedlichen Einladungs- oder Informationsstrategien

In allen kontrollierten Studien (RCTs und Beobachtungsstudien) wurden keine Unterschiede in der Teilnahmerate am Lungenkrebsscreening zwischen den Studiengruppen mit unterschiedlichen Einladungs- oder Informationsstrategien berichtet. Darüber hinaus zeigte eine unkontrollierte Studie nach Durchsicht einer Entscheidungshilfe zum Lungenkrebsscreening im Vergleich zum Zeitpunkt vor der Intervention keine Veränderung im Anteil jener Personen die beabsichtigten am Lungenkrebsscreening teilzunehmen.

4.4.6 Schlussfolgerung

Evidenz unzureichend, um bestimmte Informationsstrategie zu favorisieren

Entscheidungshilfen haben wahrscheinlich positiven Effekt auf Entscheidungs-sicherheit

Insgesamt reicht die derzeitige Evidenz nicht aus, um die Wirksamkeit einer bestimmten Informationsstrategie für ein Lungenkrebsscreening verlässlich zu beurteilen. Die Verwendung von Entscheidungshilfen im Rahmen eines Lungenkrebsscreenings hat wahrscheinlich einen positiven Effekt auf das Wissen der Teilnehmer*innen über Nutzen und Schaden des Lungenkrebs-screenings und erhöht wahrscheinlich auch die Entscheidungssicherheit darüber, ob sie an einem Früherkennungsprogramm teilnehmen oder nicht.

Tabelle A- 1, Tabelle A- 2, Tabelle A- 3 geben einen Überblick über die wichtigsten Ergebnisse für alle Forschungsfragen.

5 Diskussion

Da jedes Screening Schaden durch falsche Screening-Ergebnisse und Überdiagnosen verursacht, ist die Durchführung eines Screenings nur dann gerechtfertigt, wenn der Schaden durch den Nutzen mehr als aufgewogen wird. Bei der Abwägung von Nutzen und Schaden muss auch berücksichtigt werden, dass die Ergebnisse für die verschiedenen Endpunkte unterschiedlich gewichtet werden.

jedes Screening hat auch Schaden, Nutzen muss daher überwiegen: Nutzen/ Schaden Abwägung

5.1 Nutzen

Die eingeschlossenen Studien haben gezeigt, dass das ein Lungenkrebsscreening mittels LDCT wahrscheinlich das Risiko an Lungenkrebs zu versterben bei (ehemaligen) starken Rauchern senkt. Ein Screening mittels LDCT verhindert, dass etwa 5 von 1.000 Personen (95% KI 3-8) innerhalb von etwa 10 Jahren an Lungenkrebs sterben. Auf der Grundlage der Studienergebnisse kann jedoch statistisch nicht nachgewiesen werden, dass auch die Gesamtmortalität durch das Screening verbessert wird. Es ist denkbar, dass aufgrund konkurrierender Todesursachen, insbesondere anderer tabakbedingter Krankheiten wie andere Krebsarten und Herz-Kreislauf-Erkrankungen, einige der vor dem Lungenkrebstod bewahrten Screening-Teilnehmer*innen zu einem vergleichbaren Zeitpunkt sterben und damit die Lebensspanne dieser Personen nicht wesentlich verlängert wird.

LungenCaScreening mit LDCT senkt wahrscheinlich LungenCa-spezifische Mortalität bei starken Raucher*innen

5 in 1.000 Personen innerhalb von 10 J Reduktion der Gesamtmortalität: kaum Unterschied

Die kürzlich veröffentlichte NELSON-Studie hat dieses Problem besonders hervorgehoben [55]. Trotz einer statistisch signifikanten Reduktion der Lungenkrebs-spezifischen Mortalität (IDR 0,76 [95% KI 0,61-0,94] wurde in der Hauptanalyse kein Effekt der Gesamtmortalität festgestellt (IDR 1,01 [95% KI 0,92-1,11]. Stattdessen ergab die Studie, dass andere Todesursachen tendenziell häufiger auftraten. Kritiker*innen haben daher argumentiert, dass das LDCT-Screening lediglich zu einem "Austausch der Mortalität durch Lungenkrebs gegen eine Mortalität anderer Ursache" [196] führen könnte, ohne einen Nutzen hinsichtlich der Gesamtmortalität zu haben [197]. Die von den Autor*innen der NELSON-Studie zitierten Zahlen beziehen sich jedoch nur auf Männer, während in der Meta-Analyse des EUnetHTA Assessment Reports eine zahlenmäßige Reduktion der Gesamtmortalität bei Frauen durchaus sichtbar war. Im EUnetHTA Assessment Report wurde aus der NELSON-Studie Daten sowohl für Männer als auch für Frauen (16% der Studienpopulation) herangezogen.

in NELSON-Studie besonders deutlich, dass andere Todesursachen häufiger auftraten: Männer

Metaanalyse in EUnetHTA-Bericht zeigt: Frauen (16% in NELSON) haben Reduktion auch der Gesamtmortalität

Insgesamt stehen die Ergebnisse für die Gesamtmortalität nicht im Widerspruch zu den Ergebnissen für die Lungenkrebs-spezifische Mortalität. Grundsätzlich weisen die beiden Schätzer der jeweiligen Meta-Analysen in die gleiche Richtung. Der absolute Effektschätzer und das entsprechende KI für die Gesamtmortalität sind zudem mit dem Effekt auf die die Lungenkrebs-spezifische Mortalität vergleichbar: Der Schätzer für den absoluten Effekt beträgt 5 pro 1.000 Personen (95% KI -3 bis 12) für die Gesamtmortalität und 5 pro 1.000 Personen (95% KI 3-8) für die Lungenkrebs-spezifische Mortalität innerhalb von etwa 10 Jahren. Es gilt daher als wahrscheinlich, dass sich der Effekt des LDCT-Screenings auf die Lungenkrebs-spezifische Mortalität auch im Gesamtüberleben widerspiegelt. Zusammenfassend lässt sich sagen, dass

Effektschätzer für Gesamt- und für Lungenkrebs-spezifische Mortalität weisen in gleiche Richtung

Verringerung der Mortalität

ein Lungenkrebsscreening mittels LDCT die Mortalität im Vergleich zu keinem Screening verringern kann.

5.2 Schaden

unerwünschte Ereignisse nach Eingriffen: nur wenige Daten verfügbar = UE bleibt unklar

Ergebnisse für unerwünschte Ereignisse nach einer Operation weisen grundsätzlich auf einen Schaden hin. Allerdings lagen nur sehr wenige Daten zu unerwünschten Ereignissen in den Interventions- und Vergleichsgruppen vor, so dass der tatsächliche Schaden auf der Grundlage dieser Daten unklar ist. Es kann jedoch davon ausgegangen werden, dass die Auswirkungen des Screenings auf die Rate der unerwünschten Ereignisse im Wesentlichen auf Überdiagnosen beruht.

Strahlenexposition als Risiko

Das Risiko für einen Schaden (Entwicklung anderer Krebsarten) durch eine Strahlenexposition beim Screening mittels LDCT ist zwar nicht vernachlässigbar, jedoch besteht allgemeiner Konsens darüber, dass dieses Risiko akzeptabel ist [198], da in einer Hochrisikopopulation mehr Krebstote vermieden werden als durch das CT-Screening verursacht werden.

keine Daten zu falsch-negativen Screening-Ergebnissen

Schaden durch Verzögerung der Behandlung

Zu den Folgen von falsch-negativen Screening-Ergebnissen lagen keine Daten vor. Im Fall von falsch-negativen Screening-Ergebnissen glauben Personen fälschlicherweise, dass sie keinen Lungenkrebs haben. Die bedeutendste Konsequenz wäre das Ignorieren von Symptomen, was die Diagnose und die nachfolgende Behandlung verzögern könnte. Sollte dies jedoch zu einem Anstieg der Mortalität führen, würde sich dies im Ergebnis der Lungenkrebs-spezifischen Mortalität widerspiegeln. Insgesamt wird aber der Einfluss des Fehlens von spezifischen Daten zu den Folgen falsch-negativer Screening-Ergebnisse auf die Nutzen-/Schadensabwägung als gering eingeschätzt.

falsch-positive Screening-Ergebnisse

Schaden durch Abklärungsdiagnostik und die damit verbundenen Komplikationen

1-15 von 1.000 Screening Teilnehmer*innen

auch Schaden durch Zufallsbefunde

Im Falle falsch-positiver Screening-Ergebnisse erleiden die Betroffenen Schaden durch den Erhalt eines besorgniserregenden Befundes, durch die anschließende Abklärungsdiagnostik und durch die damit verbundenen Komplikationen. Aus den Ergebnissen des EUnetHTA-Reports geht hervor, dass 1-15 von 1.000 zu einem Lungenkrebsscreening eingeladenen Personen eine invasive Abklärungsdiagnostik oder eine Lungenresektion bei anschließendem gutartigem Befund erhalten. Die häufigste Komplikation einer Lungenbiopsie ist ein Pneumothorax [199]. Das Risiko, einen Pneumothorax zu entwickeln, variiert in Abhängigkeit vom Biopsieverfahren und der Lage des Lungenknotens. Bei einigen dieser Personen wird eine Thoraxdrainage erforderlich sein. Es ist denkbar, dass die Entfernung eines benignen Lungenrundherdes auch Aufschluss über andere Diagnosen geben und zukünftige Komplikationen (z.B. Retentionspneumonie) verhindern könnte. Beispielsweise wurden in der NELSON-Studie Zufallsbefunde in der Screening-Gruppe dokumentiert [73]. Eine systematische Untersuchung von Zufallsbefunde beim LDCT-Screening wurde im EUnetHTA-Report nicht durchgeführt, da Angaben zu solchen Ereignissen und deren Folgen nur für die Screening-Gruppen vorlagen. Es bleibt daher unklar, ob diese Befunde Einzelpersonen nutzen oder schaden.

Überdiagnose: 0-22 von 1.000 Teilnehmer*innen positiver Befund (ohne Symptome)

Das Risiko einer Überdiagnose bezogen auf Personen mit einer Lungenkrebsdiagnose während der Screening-Phase variierte zwischen den Studien stark und lag bei 0% (keine Überdiagnosen in der ITALUNG-Studie) bis 63% (in der DLCST-Studie). Die Studien zeigten, dass bei etwa 0-22 von 1.000 Personen, die zum Lungenkrebsscreening eingeladen wurden, ein Lungenkrebs diagnostiziert wurde, der für den Rest ihres Lebens keine Symptome verursacht hätte.

Zur gesundheitsbezogenen Lebensqualität lagen keine verwertbaren Daten vor. Es kann davon ausgegangen werden, dass der Erhalt eines besorgniserregenden Befundes bei Screening-Teilnehmer*innen deren gesundheitsbezogene Lebensqualität beeinträchtigt. Da dieser Effekt bei falsch-positiven Befunden wahrscheinlich nur von kurzer Dauer sein dürfte, ist nur bei Screening-Teilnehmer*innen mit richtig-positivem Befunden mit einer relevanten Beeinträchtigung zu rechnen. Der Effekt des Screenings auf die gesundheitsbezogene Lebensqualität wird daher wahrscheinlich zumindest teilweise durch den Effekt auf das Ergebnis der Überdiagnose abgebildet.

Lebensqualität: keine Daten

Annahme, dass Befund bei richtig positiven LQ beeinträchtigt

5.3 Andere Risikogruppen

Neben dem Tabakrauchen, das als Hauptrisikofaktor für Lungenkrebs gilt, erhöhen auch mehrere andere Faktoren, wie Exposition mit Schadstoffen, Lungenkrankheiten oder eine familiäre Vorgeschichte von Lungenkrebs, das Risiko, an Lungenkrebs zu erkranken. Im Rahmen des EUnetHTA-Reports konnten nur RCTs identifiziert werden, die Ergebnisse zum Screening auf Lungenkrebs mittels LDCT bei aktuellen oder ehemaligen Raucher*innen berichteten. Derzeit gibt es daher keine direkte Evidenz aus RCTs zum Lungenkrebsscreening bei Personen mit anderen Risikofaktoren für Lungenkrebs als Tabakrauchen. Es ist auch nicht möglich, die vorliegenden Ergebnisse auf Personen mit anderen Risikofaktoren zu übertragen, da es (mögliche) Unterschiede zwischen den einzelnen Risikogruppen im Lungenkrebsrisiko per se, im Krankheitsverlauf, in der jeweiligen diagnostischen Genauigkeit des Screenings oder der diagnostischen Tests und in der Wirksamkeit der Behandlung gibt.

andere Faktoren als Rauchen als Risiko: Exposition mit Schadstoffen, Lungenkrankheiten, familiäre Vorgeschichte von LungenCa

keine Evidenz dazu Übertragbarkeit fraglich

5.4 Biomarker

Der Einsatz von Biomarkern könnte die Genauigkeit eines Screenings auf Lungenkrebs verbessern und falsch-positive Befunde und damit verbundene unnötige weitere diagnostische Abklärungen reduzieren. Studien in denen Daten aus den LDCT-Gruppen der RCTs zu Screening auf Lungenkrebs auswerteten, zeigten das Potenzial für eine höhere Spezifität und einen positiven prädiktiven Wert eines multimodalen Screenings mittels Biomarkern und LDCT im Vergleich zum Screening mittels LDCT allein. Dennoch liegen derzeit keine Vergleichsstudien vor, die eine solche multimodale Lungenkrebsscreening-Strategie mit LDCT und zusätzlichen Biomarkern im Vergleich zu einer Strategie mit LDCT allein untersuchen.

Biomarker zur Verbesserung der Genauigkeit des Screenings Verhinderung von invasiven Abklärungen

keine Vergleichsstudien: keine Evidenz

5.5 Screening-Strategien

Hinsichtlich organisatorischer Unterschiede im Screening (mit und ohne Einladung) konnten die Ansätze in den RCTs keiner Kategorie eindeutig zugeordnet werden. In einigen Studien (z.B. NELSON und LUSI) wurde eine Stichprobe aus Bevölkerungsregistern gezogen und Fragebögen zur Raucher-Anamnese verschickt. Die Rekrutierung in anderen Studien (z.B. MILD und DLCST) basierte auf öffentlichen Ankündigungen oder Kampagnen, um Teilnehmer*innen für das Screening zu gewinnen. Als dritte Option wurden potenziell in Frage kommende Personen von Allgemeinmediziner*innen identifiziert und eingeladen (z.B. ITALUNG). In einigen Studien wurden auch verschiedene Rekrutierungsstrategien kombiniert.

organisatorische Unterschiede in Rekrutierung: Evidenz ist keinen eindeutigen Kategorien (opportunistisch, organisiert) zuordenbar

Hinsichtlich der Screening-Intervalle waren die eingeschlossenen RCTs weitgehend vergleichbar und führten meist ein-jährliches Screening durch. Bei einem der RCTs (MILD) handelte es sich jedoch um eine dreiarmige Studie, bei der die Teilnehmer*innen der Interventionsgruppen entweder jährlich oder alle 2 Jahre zum Lungenkrebsscreening kamen. Den Ergebnissen dieses RCTs nach 10 Jahren Beobachtungsdauer zufolge zeigte sich beim Screening im Abstand von 2 Jahren im Vergleich zum jährlichen Screening ähnliche Raten in der Gesamtmortalität und der Lungenkrebs-spezifischen Mortalität. In Anbetracht der sehr geringen Qualität der verfügbaren Evidenz ist die Vertrauenswürdigkeit der Evidenz hinsichtlich eines Effekts auf die Mortalität durch ein Lungenkrebsscreening mittels LDCT alle 2 Jahre im Vergleich zum jährlichen Screening sehr unsicher. Fragen bezüglich der Durchführung eines Screenings auf Lungenkrebs werden jedoch in einer kürzlich gestarteten europäischen Studie (4-IN THE LUNG RUN) [200] untersucht.

Intervalle: Evidenz fast ausschließlich aus 1-jährigen Screeningrunden

1 RCT zu 2-jährigen Intervallen: ähnliche Ergebnisse bei Mortalität

EU-Studie (4-IN THE LUNG RUN) soll Fragen beantworten

5.6 Informationsstrategien

Ein Screening auf Lungenkrebs unterscheidet sich von anderen Krebsscreeningprogrammen dadurch, dass die Zielgruppe nicht eindeutig über Alter oder Geschlecht definiert werden kann, sondern Personen mit unterschiedlichen Risikofaktoren umfasst. Eine Herausforderung besteht daher darin, geeignete Personen für das Screening zu identifizieren und einzuladen. Ein weiterer wichtiger Punkt bei Screeningprogrammen ist es, potenzielle Teilnehmer*innen über den möglichen Nutzen und Schaden des diagnostischen Tests und den damit verbundenen Folgen zu informieren. Die derzeitige Evidenzlage zu generellen Informationsstrategien zum Screening auf Lungenkrebs ist jedoch unzureichend und erlaubt keine klare Aussage über eine geeignete Strategie. Im Rahmen eines Lungenkrebsscreenings könnte die Verwendung von Entscheidungshilfen für eine informierte Entscheidung und ein Shared-Decision-Making (SDM) von Vorteil sein, da dies das Wissen der Teilnehmer*innen über Nutzen und Schaden des Screenings erhöht und ihren Entscheidungskonflikt verringert. SDM erfordert jedoch eine angemessene Schulung der Ärzt*innen, die Bereitstellung geeigneter evidenzbasierter Werkzeuge wie Entscheidungshilfen sowie ausreichend zeitliche und personelle Ressourcen.

Zielgruppe basiert auf Risikofaktoren, nicht Alter/ Geschlecht

Informationsstrategie Teilnehmer*innen zu erreichen

keine klare Evidenz zu „best practice“

Entscheidungshilfen verbessern Wissen UND verringern Entscheidungskonflikt

für SDM Schulung & Werkzeuge erforderlich

6 Abschließende Schlussfolgerung

hochwertige Evidenz zu LungenCa Screening mit LDCT für Risikogruppen besagt,

dass wahrscheinlich von Vorteil

Aktuelle hochwertige Evidenz zeigt, dass ein Lungenkrebsscreening mittels LDCT im Vergleich zu keinem Screening bei (ehemaligen) starken Raucher*innen zu geringen oder keinen Unterschieden im Hinblick auf die Gesamtmortalität führt. Aktuelle Evidenz mit moderater Vertrauenswürdigkeit zeigt, dass das Lungenkrebsscreening mittels LDCT im Vergleich zu keinem Screening die Lungenkrebs-spezifische Mortalität wahrscheinlich reduziert. Da die absoluten Effekteschätzer und die entsprechenden Konfidenzintervalle für Gesamtmortalität und Lungenkrebs-spezifische Mortalität in einer ähnlichen Größenordnung liegen, erscheint es gerechtfertigt anzunehmen, dass das Screening auch einen positiven Effekt auf die Gesamtmortalität hat. Eine Zusammenfassung der beiden Teilergebnisse zur Mortalität zusammenfassen lässt daher insgesamt darauf schließen, dass ein Lungenkrebsscreening mittels LDCT einen Vorteil im Hinblick auf die Mortalität haben kann.

Nutzen steht Schaden durch falsch-positive Screening-Ergebnisse und Überdiagnosen gegenüber

Allerdings kann ein Screening auf Lungenkrebs mittels LDCT aufgrund der Folgen falsch-positiver Screening-Ergebnisse zu unerwünschten Ereignisse führen und somit Schaden verursachen. Darüber hinaus führt es zu Schaden auf Grund von Überdiagnosen. Über die Folgen falsch-negativer Screening-Ergebnisse wurde in den inkludierten Studien nicht berichtet. Ihr Einfluss auf die Abwägung von Nutzen und Schaden wird jedoch als gering eingeschätzt. Daten zu unerwünschten Ereignissen lagen nur aus einer Studie vor, für die gesundheitsbezogene Lebensqualität lagen keine verwertbaren Daten vor. Der Effekt des Screenings auf die Rate der unerwünschten Ereignisse und auf die gesundheitsbezogene Lebensqualität wird jedoch wahrscheinlich teilweise durch den Endpunkt Überdiagnosen erfasst.

Nutzen: Verringerung der Mortalität
5 von 1.000 Personen innerhalb von 10 Jahren

Schaden: 1-15 von 1.000 Personen erhalten invasive Eingriffe

Überdiagnosen: 0-22 von 1.000 Personen

Ein Screening auf Lungenkrebs mittels LDCT im Vergleich zu keinem Screening rettet wahrscheinlich etwa 5 von 1.000 Personen (95% KI 3-8) innerhalb von etwa 10 Jahren vor dem Tod an Lungenkrebs und kann möglicherweise die Lebenszeit einiger Screening-Teilnehmer*innen verlängern. Dem Nutzen in Bezug auf die Mortalität steht hauptsächlich der Schaden gegenüber, der sich aus falsch-positiven Screening-Ergebnissen und Überdiagnosen ergibt. Falsch-positive Screening-Ergebnisse führen mindestens bei 1 von 1.000 und maximal bei 15 von 1000 Personen zu invasiven Eingriffen, die ohne Screening nicht durchgeführt worden wären. Diese Eingriffe können Komplikationen wie das Auftreten eines Pneumothorax verursachen. Überdiagnosen werden wegen der unnötigen Folgediagnostik und Therapie einschließlich der daraus resultierenden Komplikationen als schädlich angesehen. Das Risiko für Überdiagnosen liegt in den einzelnen eingeschlossenen RCTs zwischen 0 und 22 pro 1.000 am Screening teilnehmenden Personen. Das Risiko für Überdiagnosen bei Vorliegen eines durch das Screening entdeckten Lungenkrebses liegt in den einzelnen Studien zwischen 0% und 63%. Dies unterstreicht, wie wichtig es für ein positives Nutzen-Schaden-Verhältnis ist, durch optimale Screening-Strategien das Risiko für Überdiagnosen gering zu halten.

Screeningstrategie muss Risiko für Überdiagnostik gering halten

Evidenz nur zu Raucher*innen, nicht zu anderen Risikopersonen

Für andere Personengruppen mit erhöhtem Risiko für Lungenkrebs als (ehemalige) starke Raucher*innen konnten keine Studien identifiziert werden, die ein Lungenkrebsscreening mittels LDCT im Vergleich zu keinem Screening untersuchten. Es ist auch nicht möglich, den potenziellen Nutzen des Lungenkrebsscreenings mittels LDCT bei (ehemaligen) starken Raucher*innen auf

Personen mit anderen Risikofaktoren für Lungenkrebs zu übertragen, da (mögliche) Unterschiede im Lungenkrebsrisiko, im Krankheitsverlauf, in der diagnostischen Genauigkeit des Screenings oder der diagnostischen Tests und in der Wirksamkeit der Behandlung bestehen.

keine Evidenz zu Biomarkern

Für die Verwendung von Biomarkern als Ergänzung zur LDCT im Rahmen eines Lungenkrebsscreenings liegen derzeit keine Erkenntnisse aus RCTs vor, daher ist keine Schlussfolgerung zu dieser Fragestellung möglich.

unzureichende Evidenz zu bester Rekrutierungsstrategie

Es kann auch keine Schlussfolgerung dahingehend gezogen werden, wie Personen, die für ein Lungenkrebsscreening in Frage kommen, am besten erreicht werden können, da in den derzeit verfügbaren Studien unterschiedliche Rekrutierungsstrategien verwendet wurden, ohne dass offensichtliche Unterschiede in der Wirksamkeit zwischen den Strategien bestehen. In Bezug auf das Screeningintervall ist die Gesamtevidenz unzureichend, um ein anderes Screeningintervall als 1 Jahr zu verwenden.

Intervall: 1- jährig

Entscheidungshilfen: Steigerung von Wissen, Reduktion von Entscheidungskonflikt

Aktuelle moderate Evidenz zeigt, dass die Verwendung von Entscheidungshilfen vor einem Screening mittels LDCT bei Personen, die für ein Lungenkrebsscreening in Frage kommen, wahrscheinlich das Wissen über Nutzen und Schaden des Lungenkrebsscreenings verbessert und wahrscheinlich ihren Entscheidungskonflikt für oder gegen die Teilnahme am Screening verringert.

7 Referenzen

[1] Snowsill T, Yang H, Griffin E, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess*. 2018; 22 (69): 1-276

[2] Humphrey L, Deffebach M, Pappas M, et al. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation Rockville (MD): Agency for Healthcare Research and Quality (US); 2013

[3] Lung Cancer Europe. *LuCE Report on lung cancer - Challenges in lung cancer in Europe*. 11.2016; Available from: https://www.lungcancereurope.eu/wp-content/uploads/2017/10/LuCE-Report-final.pdf [cited 08.06.2020].

[4] European Respiratory Society. *EUROPEAN LUNG white book; Chapter 9: Tobacco smoking*. Available from: https://www.erswhitebook.org/chapters/tobacco-smoking/ [cited 15.07.2020].

[5] European Respiratory Society. *EUROPEAN LUNG white book; Chapter 19: Lung cancer*. Available from: https://www.erswhitebook.org/chapters/lung-cancer/ [cited 15.07.2020].

[6] Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe. *S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms: Langversion 1.0; AWMF-Registernummer 020/007OL*. 02.2018; Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_l_S3_Lungenkarzinom_2018-03.pdf [cited 09.07.2019].

[7] Mazzone PJ, Silvestri GA, Patel S, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. *Chest*. 2018; 153 (4): 954-85

[8] Santaballa A, Pinto A, Balanya RP, et al. SEOM clinical guideline for secondary prevention (2019). *Clin Transl Oncol*. 2020; 22 (2): 187-92

[9] Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018; 16 (4): 412-41

[10] Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA*. 2011; 306 (17): 1865-73

[11] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Lungenkrebsscreening mittels Niedrigdosis-Computertomografie: Abschlussbericht; Auftrag S19-02*. 19.10.2020; Available from: https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentoese-verfahren/s-projekte/s19-02-lungenkrebsscreening-mittels-niedrigdosis-computertomografie.12379.html [cited 22.10.2020].

[12] Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Available from: www.training.cochrane.org/handbook [cited 08.06.2020].

[13] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016; 355: i4919

[14] Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011; 64 (4): 383-94

[15] Ali N, Lifford KJ, Carter B, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. *BMJ Open*. 2015; 5 (7): e008254

[16] Brain K, Carter B, Lifford KJ, et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. *Thorax*. 2017; 72 (10): 912-8

[17] Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax*. 2016; 71 (11): 996-1005

[18] Dunn CE, Edwards A, Carter B, et al. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. *Patient Education & Counseling*. 2017; 100 (8): 1572-9

[19] Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess*. 2016; 20 (40): 1-146

[20] Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax*. 2016; 71 (2): 161-70

[21] Marcus MW, Duffy SW, Devaraj A, et al. Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: the UKLS trial. *Thorax*. 2019; 74 (8): 761-7

[22] McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res (Phila)*. 2014; 7 (3): 362-71

[23] Nair A, Gartland N, Barton B, et al. Comparing the performance of trained radiographers against experienced radiologists in the UK Lung Cancer Screening (UKLS) trial. *Br J Radiol*. 2016; 89 (1066): 20160301

[24] Nair A, Screaton NJ, Holemans JA, et al. The impact of trained radiographers as concurrent readers on performance and reading time of experienced radiologists in the UK Lung Cancer Screening (UKLS) trial. *European Radiology*. 2018; 28 (1): 226-34

[25] Aggestrup LM, Hestbech MS, Siersma V, et al. Psychosocial consequences of allocation to lung cancer screening: a randomised controlled trial. *BMJ Open*. 2012; 2 (2): e000663

[26] Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. *Thorax*. 2014; 69 (6): 574-9

[27] Ashraf H, Tonnesen P, Holst Pedersen J, et al. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). *Thorax*. 2009; 64 (5): 388-92

[28] Bons LR, Sedghi Gamechi Z, Thijssen CGE, et al. Growth of the thoracic aorta in the smoking population: the Danish Lung Cancer Screening Trial. *International Journal of Cardiology*. 2020; 299: 276-81

[29] Heleno B, Siersma V, Brodersen J. Estimation of overdiagnosis of lung cancer in low-dose computed tomography screening: a secondary analysis of the Danish Lung Cancer Screening Trial. *JAMA Internal Medicine*. 2018; 178 (10): 1420-2

[30] Hoyer N, Wille MMW, Thomsen LH, et al. Interstitial lung abnormalities are associated with increased mortality in smokers. *Respiratory Medicine*. 2018; 136: 77-82

[31] Jensen MD, Siersma V, Rasmussen JF, et al. Direct and indirect healthcare costs of lung cancer CT screening in Denmark: a registry study. *BMJ Open*. 2020; 10 (1): e031768

[32] Malmqvist J, Siersma V, Thorsen H, et al. Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study. *BMJ Open*. 2020; 10 (2): e030871

[33] Pedersen JH, Ashraf H, Dirksen A, et al. The Danish Randomized Lung Cancer CT Screening Trial: overall design and results of the prevalence round. *J Thorac Oncol*. 2009; 4 (5): 608-14

[34] Petersen RH, Hansen HJ, Dirksen A, et al. Lung cancer screening and video-assisted thoracic surgery. *J Thorac Oncol*. 2012; 7 (6): 1026-31

[35] Rasmussen JF, Siersma V, Malmqvist J, et al. Psychosocial consequences of false positives in the Danish Lung Cancer CT Screening Trial: a nested matched cohort study. *BMJ Open*. 2020; 10 (6): e034682

[36] Rasmussen JF, Siersma V, Pedersen JH, et al. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). *Lung Cancer*. 2015; 87 (1): 65-72

[37] Roe OD, Markaki M, Tsamardinos I, et al. 'Reduced' HUNT model outperforms NLST and NELSON study criteria in predicting lung cancer in the Danish screening trial. *BMJ Open Respir Res*. 2019; 6 (1): e000512

[38] Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease: the randomised Danish Lung Cancer Screening Trial; status after five annual screening rounds with low-dose CT. *Thorax*. 2012; 67 (4): 296-301

[39] Sorensen L, Nielsen M, Petersen J, et al. Chronic obstructive pulmonary disease quantification using CT texture analysis and densitometry: results from the Danish Lung Cancer Screening Trial. *AJR: American Journal of Roentgenology*. 2020; 214 (6): 1269-79

[40] Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling. *Am J Respir Crit Care Med*. 2016; 193 (5): 542-51

[41] Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomization. *J Thorac Oncol*. 2015; 10 (6): 890-6

[42] Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *J Cancer Res Clin Oncol*. 2012; 138 (9): 1475-86

[43] Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening: results from the randomized German LUSI trial. *International Journal of Cancer*. 2020; 146 (6): 1503-13

[44] Gonzalez Maldonado S, Delorme S, Husing A, et al. Evaluation of prediction models for identifying malignancy in pulmonary nodules detected via low-dose computed tomography. *JAMA Netw Open*. 2020; 3 (2): e1921221

[45] Sommer G, Tremper J, Koenigkam-Santos M, et al. Lung nodule detection in a high-risk population: comparison of magnetic resonance imaging and low-dose computed tomography. *Eur J Radiol*. 2014; 83 (3): 600-5

[46] Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012; 21 (3): 308-15

[47] Pastorino U, Silva M, Sestini S, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial. *Annals of Oncology*. 2019; 30 (7): 1162-9

[48] Pastorino U, Sverzellati N, Sestini S, et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. *European Journal of Cancer*. 2019; 118: 142-8

[49] Pozzi P, Munarini E, Bravi F, et al. A combined smoking cessation intervention within a lung cancer screening trial: a pilot observational study. *Tumori*. 2015; 101 (3): 306-11

[50] Silva M, Prokop M, Jacobs C, et al. Long-term active surveillance of screening detected subsolid nodules is a safe strategy to reduce overtreatment. *Journal of Thoracic Oncology*. 2018; 13 (10): 1454-63

[51] Sverzellati N, Cademartiri F, Bravi F, et al. Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. *Radiology*. 2012; 262 (2): 460-7

[52] Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J*. 2011; 38 (2): 392-400

[53] Sverzellati N, Silva M, Calareso G, et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. *Eur Radiol*. 2016; 26 (11): 3821-9

[54] Bunge EM, Van den Bergh KAM, Essink-Bot ML, et al. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer*. 2008; 62 (3): 385-90

[55] De Koning HJ, Van der Aalst CM, De Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020; 382 (6): 503-13

[56] Gietema HA, Schilham AM, Van Ginneken B, et al. Monitoring of smoking-induced emphysema with CT in a lung cancer screening setting: detection of real increase in extent of emphysema. *Radiology*. 2007; 244 (3): 890-7

[57] Gietema HA, Zanen P, Schilham A, et al. Distribution of emphysema in heavy smokers: impact on pulmonary function. *Respir Med*. 2010; 104 (1): 76-82

[58] Han D, Heuvelmans MA, Van der Aalst CM, et al. New fissure-attached nodules in lung cancer screening: a brief report from the NELSON Study. *Journal of Thoracic Oncology*. 2020; 15 (1): 125-9

[59] Han D, Heuvelmans MA, Vliegenthart R, et al. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening. *British Journal of Radiology*. 2018; 91 (1090): 20170405

[60] Heuvelmans MA, Oudkerk M, De Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol*. 2013; 23 (7): 1836-45

[61] Heuvelmans MA, Vliegenthart R, De Koning HJ, et al. Quantification of growth patterns of screen-detected lung cancers: the NELSON study. *Lung Cancer*. 2017; 108: 48-54

[62] Heuvelmans MA, Walter JE, Peters RB, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the NELSON study. *Lung Cancer*. 2017; 113: 45-50

[63] Heuvelmans MA, Walter JE, Vliegenthart R, et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. *Thorax*. 2018; 73 (8): 779-81

[64] Horeweg N, Scholten ET, De Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol*. 2014; 15 (12): 1342-50

[65] Horeweg N, Van der Aalst CM, Thunnissen E, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. *Am J Respir Crit Care Med*. 2013; 187 (8): 848-54

[66] Horeweg N, Van der Aalst CM, Vliegenthart R, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. *Eur Respir J*. 2013; 42 (6): 1659-67

[67] Horeweg N, Van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol*. 2014; 15 (12): 1332-41

[68] Hubers AJ, Heideman DAM, Duin S, et al. DNA hypermethylation analysis in sputum of asymptomatic subjects at risk for lung cancer participating in the NELSON trial: argument for maximum screening interval of 2 years. *Journal of Clinical Pathology*. 2017; 70 (3): 250-4

[69] Oudkerk M, Heuvelmans MA. Screening for lung cancer by imaging: the Nelson study. *JBR-BTR*. 2013; 96 (3): 163-6

[70] Ru Zhao Y, Xie X, De Koning HJ, et al. NELSON lung cancer screening study. *Cancer Imaging*. 2011; 11 (Spec No A): S79-S84

[71] Takx RA, Vliegenthart R, Mohamed Hoesein FA, et al. Pulmonary function and CT biomarkers as risk factors for cardiovascular events in male lung cancer screening participants: the NELSON study. *Eur Radiol*. 2015; 25 (1): 65-71

[72] Takx RAP, Isgum I, Willemink MJ, et al. Quantification of coronary artery calcium in nongated CT to predict cardiovascular events in male lung cancer screening participants: results of the NELSON study. *J Cardiovasc Comput Tomogr*. 2015; 9 (1): 50-7

[73] Van de Wiel JCM, Wang Y, Xu DM, et al. Neglectable benefit of searching for incidental findings in the Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT. *Eur Radiol*. 2007; 17 (6): 1474-82

[74] Van den Bergh KAM, Essink-Bot ML, Borsboom GJ, et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. *Eur Respir J*. 2011; 38 (1): 154-61

[75] Van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer*. 2010; 102 (1): 27-34

[76] Van den Bergh KAM, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer*. 2008; 113 (2): 396-404

[77] Van den Bergh KAM, Essink-Bot ML, Van Klaveren RJ, et al. Informed participation in a randomised controlled trial of computed tomography screening for lung cancer. *Eur Respir J*. 2009; 34 (3): 711-20

[78] Van der Aalst CM, De Koning HJ, Van den Bergh KAM, et al. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. *Lung Cancer*. 2012; 76 (2): 204-10

[79] Van der Aalst CM, Van den Bergh KAM, Willemsen MC, et al. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. *Thorax*. 2010; 65 (7): 600-5

[80] Van der Aalst CM, Van Klaveren RJ, Van den Bergh KAM, et al. The impact of a lung cancer computed tomography screening result on smoking abstinence. *Eur Respir J*. 2011; 37 (6): 1466-73

[81] Van Iersel CA, De Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer*. 2007; 120 (4): 868-74

[82] Van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med*. 2009; 361 (23): 2221-9

[83] Van't Westeinde SC, Horeweg N, De Leyn P, et al. Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial. *Eur J Cardiothorac Surg*. 2012; 42 (3): 420-9

[84] Walter JE, Heuvelmans MA, De Bock GH, et al. Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: the NELSON study. *Thorax*. 2018; 73 (8): 741-7

[85] Walter JE, Heuvelmans MA, De Bock GH, et al. Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: the NELSON study. *Lung Cancer*. 2018; 125: 103-8

[86] Walter JE, Heuvelmans MA, De Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. *Lancet Oncol*. 2016; 17 (7): 907-16

[87] Walter JE, Heuvelmans MA, Ten Haaf K, et al. Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study. *Thorax*. 2019; 74 (3): 247-53

[88] Walter JE, Heuvelmans MA, Yousaf-Khan U, et al. New subsolid pulmonary nodules in lung cancer screening: the NELSON Trial. *Journal of Thoracic Oncology*. 2018; 13 (9): 1410-4

[89] Xu DM, Gietema H, De Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer*. 2006; 54 (2): 177-84

[90] Yousaf-Khan AU, Van der Aalst CM, Aerts JGJV, et al. Uniform and blinded cause of death verification of the NELSON lung cancer screening participants. *Lung Cancer*. 2017; 111: 131-4

[91] Yousaf-Khan U, Horeweg N, Van der Aalst C, et al. Baseline characteristics and mortality outcomes of control group participants and eligible non-responders in the NELSON lung cancer screening study. *J Thorac Oncol*. 2015; 10 (5): 747-53

[92] Yousaf-Khan U, Van der Aalst C, De Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax*. 2017; 72 (1): 48-56

[93] Yousaf-Khan U, Van der Aalst C, de Jong PA, et al. Risk stratification based on screening history: the NELSON lung cancer screening study. *Thorax*. 2017; 72 (9): 819-24

[94] Croswell JM, Baker SG, Marcus PM, et al. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. *Ann Intern Med*. 2010; 152 (8):

[95] Doroudi M, Pinsky PF, Marcus PM. Lung cancer mortality in the Lung Screening Study feasibility trial. *JNCI Cancer Spectrum*. 2018; 2 (3): pky042

[96] Gohagan J, Marcus P, Fagerstrom R, et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the lung screening study of the National Cancer Institute. *Chest*. 2004; 126 (1): 114-21

[97] Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*. 2005; 47 (1): 9-15

[98] Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized National Lung Screening Trial. *J Natl Cancer Inst*. 2010; 102 (23): 1771-9

[99] Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med*. 2013; 369 (10): 920-31

[100] Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. *Radiology*. 2015; 276 (1): 82-90

[101] Chudgar NP, Bucciarelli PR, Jeffries EM, et al. Results of the National Lung Cancer Screening Trial: where are we now? *Thorac Surg Clin*. 2015; 25 (2): 145-53

[102] Clark MA, Gorelick JJ, Sicks JD, et al. The relations between false positive and negative screens and smoking cessation and relapse in the National Lung Screening Trial: implications for public health. *Nicotine Tob Res*. 2016; 18 (1): 17-24

[103] Dillard TA, Patel RR, Schroeder C. Uneven distribution of cancer histology in the National Lung Screening Trial. *Am J Med Sci*. 2015; 350 (3): 219-21

[104] Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer*. 2014; 120 (21): 3401-9

[105] Gierada DS, Pinsky P, Nath H, et al. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. *J Natl Cancer Inst*. 2014; 106 (11): dju284

[106] Horeweg N, Nackaerts K, Oudkerk M, et al. Low-dose computed tomography screening for lung cancer: results of the first screening round. *J Comp Eff Res*. 2013; 2 (5): 433-6

[107] Jin GY, Lynch D, Chawla A, et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology*. 2013; 268 (2): 563-71

[108] Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013; 369 (3): 245-54

[109] Kruger R, Flynn MJ, Judy PF, et al. Effective dose assessment for participants in the National Lung Screening Trial undergoing posteroanterior chest radiographic examinations. *AJR Am J Roentgenol*. 2013; 201 (1): 142-6

[110] Larke FJ, Kruger RL, Cagnon CH, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. *AJR Am J Roentgenol*. 2011; 197 (5): 1165-9

[111] Marcus PM, Doria-Rose VP, Gareen IF, et al. Did death certificates and a death review process agree on lung cancer cause of death in the National Lung Screening Trial? *Clin Trials*. 2016; 13 (4): 434-8

[112] National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365 (5): 395-409

[113] National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013; 368 (21): 1980-91

[114] Park ER, Gareen IF, Jain A, et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. *Cancer*. 2013; 119 (7): 1306-13

[115] Patz EF Jr, Greco E, Gatsonis C, et al. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. *Lancet Oncol*. 2016; 17 (5): 590-9

[116] Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014; 174 (2): 269-74

[117] Pinsky PF, Church TR, Izmirlian G, et al. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer*. 2013; 119 (22): 3976-83

[118] Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med*. 2015; 162 (7): 485-91

[119] Pinsky PF, Gierada DS, Hocking W, et al. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. *Ann Intern Med*. 2014; 161 (9): 627-33

[120] Pinsky PF, Gierada DS, Nath H, et al. ROC curves for low-dose CT in the National Lung Screening Trial. *J Med Screen*. 2013; 20 (3): 165-8

[121] Pinsky PF, Gierada DS, Nath PH, et al. National Lung Screening Trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013; 268 (3): 865-73

[122] Pinsky PF, Nath PH, Gierada DS, et al. Short- and long-term lung cancer risk associated with noncalcified nodules observed on low-dose CT. *Cancer Prev Res (Phila)*. 2014; 7 (12): 1179-85

[123] Tammemägi MC, Berg CD, Riley TL, et al. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst*. 2014; 106 (6): dju084

[124] Tanner NT, Gebregziabher M, Hughes Halbert C, et al. Racial differences in outcomes within the National Lung Screening Trial: implications for widespread implementation. *Am J Respir Crit Care Med*. 2015; 192 (2): 200-8

[125] Tanner NT, Kanodra NM, Gebregziabher M, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *Am J Respir Crit Care Med*. 2016; 193 (5): 534-41

[126] Yip R, Henschke CI, Yankelevitz DF, et al. CT screening for lung cancer: alternative definitions of positive test result based on the National Lung Screening Trial and International Early Lung Cancer Action Program databases. *Radiology*. 2014; 273 (2): 591-6

[127] Yip R, Yankelevitz DF, Hu M, et al. Lung cancer deaths in the National Lung Screening Trial attributed to nonsolid nodules. *Radiology*. 2016; 281 (2): 589-96

[128] Young RP, Duan F, Chiles C, et al. Airflow limitation and histology shift in the National Lung Screening Trial: the NLST-ACRIN cohort substudy. *Am J Respir Crit Care Med*. 2015; 192 (9): 1060-7

[129] Abdel-Rahman O. Impact of current versus former smoking status on the outcomes of non-metastatic non-small cell lung cancer treated with upfront surgery: findings from the National Lung Screening Trial. *Expert Review of Respiratory Medicine*. 2019; 13 (6): 585-91

[130] Balekian AA, Wisnivesky JP, Gould MK. Surgical disparities among patients with stage I lung cancer in the National Lung Screening Trial. *Chest*. 2019; 155 (1): 44-52

[131] Brown D, Zingone A, Yu Y, et al. Relationship between circulating inflammation proteins and lung cancer diagnosis in the National Lung Screening Trial. *Cancer Epidemiology, Biomarkers and Prevention*. 2019; 28 (1): 110-8

[132] Cherezov D, Hawkins SH, Goldgof DB, et al. Delta radiomic features improve prediction for lung cancer incidence: a nested case-control analysis of the National Lung Screening Trial. *Cancer Med*. 2018; 7 (12): 6340-56

[133] De-Torres JP, Wisnivesky JP, Bastarrika G, et al. The prevalence of obstructive lung disease in a lung cancer screening cohort: analysis of the National Lung Screening Trial; American College of Radiology Image Network Cohort. *Ann Am Thorac Soc*. 2019; 16 (5): 641-4

[134] Gallardo-Estrella L, Pompe E, De Jong PA, et al. Normalized emphysema scores on low dose CT: validation as an imaging biomarker for mortality. *PLoS ONE*. 2017; 12 (12): e0188902

[135] Gierada DS, Pinsky PF, Duan F, et al. Interval lung cancer after a negative CT screening examination: CT findings and outcomes in National Lung Screening Trial participants. *European Radiology*. 2017; 27 (8): 3249-56

[136] Gu F, Cheung LC, Freedman ND, et al. Potential impact of including time to first cigarette in risk models for selecting ever-smokers for lung cancer screening. *Journal of Thoracic Oncology*. 2017; 12 (11): 1646-53

[137] Hopkins RJ, Duan F, Chiles C, et al. Reduced expiratory flow rate among heavy smokers increases lung cancer risk: results from the National Lung Screening Trial; American College of Radiology Imaging Network Cohort. *Ann Am Thorac Soc*. 2017; 14 (3): 392-402

[138] Iaccarino JM, Silvestri GA, Wiener RS. Patient-level trajectories and outcomes after low-dose CT screening in the National Lung Screening Trial. *Chest*. 2019; 156 (5): 965-71

[139] Kamel MK, Lee B, Harrison S, et al. Do the surgical results in the National Lung Screening Trial reflect modern thoracic surgical practice? *Journal of Thoracic and Cardiovascular Surgery*. 2019; 157 (5):

[140] Kumar V, Cohen JT, Van Klaveren D, et al. Risk-targeted lung cancer screening: a cost-effectiveness analysis. *Annals of Internal Medicine*. 2018; 168 (3): 161-9

[141] Lee C, Flynn MJ, Judy PF, et al. Body size-specific organ and effective doses of chest CT screening examinations of the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 208 (5): 1082-8

[142] Li Q, Balagurunathan Y, Liu Y, et al. Comparison between radiological semantic features and Lung-RADS in predicting malignancy of screen-detected lung nodules in the National Lung Screening Trial. *Clinical Lung Cancer*. 2018; 19 (2):

[143] Liu Y, Wang H, Li Q, et al. Radiologic features of small pulmonary nodules and lung cancer risk in the National Lung Screening Trial: a nested case-control study. *Radiology*. 2018; 286 (1): 298-306

[144] Lu H, Mu W, Balagurunathan Y, et al. Multi-window CT based Radiomic signatures in differentiating indolent versus aggressive lung cancers in the National Lung Screening Trial: a retrospective study. *Cancer Imaging*. 2019; 19 (1): 45

[145] National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019; 14 (10): 1732-42

[146] Nguyen XV, Davies L, Eastwood JD, et al. Extrapulmonary findings and malignancies in participants screened with chest CT in the National Lung Screening Trial. *Journal of the American College of Radiology*. 2017; 14 (3): 324-30

[147] Pinsky PF, Bellinger CR, Miller DP Jr. False-positive screens and lung cancer risk in the National Lung Screening Trial: implications for shared decision-making. *Journal of Medical Screening*. 2018; 25 (2): 110-2

[148] Pinsky PF, Gierada DS, Nath PH, et al. Lung cancer risk associated with new solid nodules in the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 209 (5): 1009-14

[149] Pompe E, De Jong PA, Lynch DA, et al. Computed tomographic findings in subjects who died from respiratory disease in the National Lung Screening Trial. *European Respiratory Journal*. 2017; 49: 1601814

[150] Robbins HA, Katki HA, Cheung LC, et al. Insights for management of ground-glass opacities from the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019; 14 (9): 1662-5

[151] Rojewski AM, Tanner NT, Dai L, et al. Tobacco dependence predicts higher lung cancer and mortality rates and lower rates of smoking cessation in the National Lung Screening Trial. *Chest*. 2018; 154 (1): 110-8

[152] Sonavane SK, Pinsky P, Watts J Jr, et al. The relationship of cancer characteristics and patient outcome with time to lung cancer diagnosis after an abnormal screening CT. *European Radiology*. 2017; 27 (12): 5113-8

[153] Thomas A, Pattanayak P, Szabo E, et al. Characteristics and outcomes of small cell lung cancer detected by CT screening. *Chest*. 2018; 154 (6): 1284-90

[154] Wong JYY, Bassig BA, Seow WJ, et al. Lung cancer risk in welders and foundry workers with a history of heavy smoking in the USA: the National Lung Screening Trial. *Occupational and Environmental Medicine*. 2017; 74 (6): 440-8

[155] Yip R, Henschke CI, Xu DM, et al. Lung cancers manifesting as part-solid nodules in the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 208 (5): 1011-21

[156] Zhu J, Nelson K, Toth J, et al. Nicotine dependence as an independent risk factor for atherosclerosis in the National Lung Screening Trial. *BMC Public Health*. 2019; 19 (1): 103

[157] National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology*. 2011; 258 (1): 243-53

[158] Bahl M. Incidental thyroid nodules in the National Lung Screening Trial: estimation of prevalence, malignancy rate, and strategy for workup. *Academic Radiology*. 2018; 25 (9): 1152-5

[159] De-Torres JP, Wisnivesky JP, Bastarrika G, et al. Exploring the impact of lung cancer screening on lung cancer mortality of smokers with obstructive lung disease: analysis of the NLST-ACRIN Cohort. *Archivos de Bronconeumologia*. 2020; In press: https://doi.org/10.1016/j.arbres.2020.03.023

[160] Gareen IF, Black WC, Tosteson TD, et al. Medical care costs were similar across the low-dose computed tomography and chest x-ray arms of the National Lung Screening Trial despite different rates of significant incidental findings. *Medical Care*. 2018; 56 (5): 403-9

[161] Hammer MM, Palazzo LL, Kong CY, et al. Cancer risk in subsolid nodules in the National Lung Screening Trial. *Radiology*. 2019; 293 (2): 441-8

[162] Kaminsky DA, Daphtary N, Estepar RSJ, et al. Ventilation heterogeneity and its association with nodule formation among participants in the National Lung Screening Trial: a preliminary investigation. *Academic Radiology*. 2020; 27 (5): 630-5

[163] Kaufman AR, Dwyer LA, Land SR, et al. Smoking-related health beliefs and smoking behavior in the National Lung Screening Trial. *Addictive Behaviors*. 2018; 84: 27-32

[164] Loomans-Kropp HA, Dunn BK, Kramer BS, et al. Thyroid incidentalomas in association with low-dose computed tomography in the National Lung Screening Trial. *American Journal of Epidemiology*. 2020; 189 (1): 27-33

[165] Munden RF, Chiles C, Boiselle PM, et al. Micronodules detected on computed tomography during the National Lung Screening Trial: prevalence and relation to positive studies and lung cancer. *Journal of Thoracic Oncology*. 2019; 14 (9): 1538-46

[166] Schreuder A, Jacobs C, Gallardo-Estrella L, et al. Predicting all-cause and lung cancer mortality using emphysema score progression rate between baseline and follow-up chest CT images: a comparison of risk model performances. *PLoS ONE*. 2019; 14 (2): e0212756

[167] Tanner NT, Thomas NA, Ward R, et al. Association of cigarette type with lung cancer incidence and mortality: secondary analysis of the National Lung Screening Trial. *JAMA Internal Medicine*. 21.10.2019 [Epub ahead of print]:

[168] Wang S, Chen A, Yang L, et al. Comprehensive analysis of lung cancer pathology images to discover tumor shape and boundary features that predict survival outcome. *Scientific Reports*. 2018; 8 (1): 10393

[169] Warkentin MT, Tammemagi MC, Freedman MT, et al. Factors associated with small aggressive non-small cell lung cancers in the National Lung Screening Trial: a validation study. *JNCI Cancer Spectrum*. 2018; 2 (1): pkx010

[170] White CS, Dharaiya E, Dalal S, et al. Vancouver Risk Calculator compared with ACR Lung-RADS in predicting malignancy: analysis of the National Lung Screening Trial. *Radiology*. 2019; 291 (1): 205-11

[171] Whittaker Brown SA, Padilla M, Mhango G, et al. Interstitial lung abnormalities and lung cancer risk in the National Lung Screening Trial. *Chest*. 2019; 156 (6): 1195-203

[172] Yong PC, Sigel K, De-Torres JP, et al. The effect of radiographic emphysema in assessing lung cancer risk. *Thorax*. 2019; 74 (9): 858-64

[173] Quaife SL, Ruparel M, Beeken RJ, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach'patients. *BMC Cancer*. 2016; 16: 281

[174] Quaife SL, Ruparel M, Dickson JL, et al. Lung Screen Uptake Trial (LSUT): Randomized Controlled Clinical Trial Testing Targeted Invitation Materials. *American Journal of Respiratory &Critical Care Medicine*. 2020; 201 (8): 965-75

[175] Ruparel M, Quaife SL, Ghimire B, et al. Impact of a Lung Cancer Screening Information Film on Informed Decision-making: A Randomized Trial. *Annals of the American Thoracic Society*. 2019; 16 (6): 744-51

[176] Sferra SR, Cheng JS, Boynton Z, et al. Aiding shared decision making in lung cancer screening: two decision tools. *Journal of Public Health*. 2020; In press: https://doi.org/10.1093/pubmed/fdaa063

[177] Sharma A, Bansal-Travers M, Celestino P, et al. Using a Smoking Cessation Quitline to Promote Lung Cancer Screening. *American Journal of Health Behavior*. 2018; 42 (6): 85-100

[178] Lowenstein LM, Escoto KH, Leal VB, et al. Randomized trial of a patient-centered decision aid for promoting informed decisions about lung cancer screening: Implementation of a PCORI study protocol and lessons learned. *Contemporary Clinical Trials*. 2018; 72: 26-34

[179] Volk RJ, Lowenstein LM, Leal VB, et al. Effect of a Patient Decision Aid on Lung Cancer Screening Decision-Making by Persons Who Smoke: A Randomized Clinical Trial. *JAMA Network Open*. 2020; 3 (1): e1920362

[180] M.D. Anderson Cancer Center. *PCORI-CER-1306-03385 Informed Decisions About Lung Cancer Screening*. 15.07.2019; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02286713 [cited 16.08.2020].

[181] University College London Hospitals. *Lung Screen Uptake Trial (Lung-SCREEN)*. 02.06.2020; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02558101 [cited 16.08.2020].

[182] University College London Hospitals. *Increasing uptake of lung cancer screening in individuals at high risk of lung cancer*. 27.05.2020; Available from: http://www.isrctn.com/ISRCTN21774741 [cited 16.08.2020].

[183] Lowenstein LM, Godoy MCB, Erasmus JJ, et al. Implementing Decision Coaching for Lung Cancer Screening in the Low-Dose Computed Tomography Setting. *JCO Oncol Pract*. 2020; 16 (8): e703-25

[184] Tanner NT, Banas E, Yeager D, et al. In-person and Telephonic Shared Decision-making Visits for People Considering Lung Cancer Screening: An Assessment of Decision Quality. *Chest*. 2019; 155 (1): 236-8

[185] Yoshida M, Kondo K, Nakanishi C, et al. Interventional study for improvement of lung cancer screening rate. *J Med Invest*. 2012; 59 (1-2): 127-35

[186] Hoffman AS, Hempstead AP, Housten AJ, et al. Using a Patient Decision Aid Video to Assess Current and Former Smokers'Values About the Harms and Benefits of Lung Cancer Screening With Low-Dose Computed Tomography. *MDM Policy & Practice*. 2018; 3 (1): 2381468318769886

[187] Housten AJ, Lowenstein LM, Leal VB, et al. Responsiveness of a Brief Measure of Lung Cancer Screening Knowledge. *J Cancer Educ*. 2018; 33 (4): 842-6

[188] Lau YK, Caverly TJ, Cao P, et al. Evaluation of a Personalized, Web-Based Decision Aid for Lung Cancer Screening. *American Journal of Preventive Medicine*. 2015; 49 (6): e125-9

[189] Mazzone PJ, Tenenbaum A, Seeley M, et al. Impact of a Lung Cancer Screening Counseling and Shared Decision-Making Visit. *Chest*. 2017; 151 (3): 572-8

[190] Reuland DS, Cubillos L, Brenner AT, et al. A pre-post study testing a lung cancer screening decision aid in primary care. *BMC Medical Informatics & Decision Making*. 2018; 18 (1): 5

[191] Sakoda LC, Meyer MA, Chawla N, et al. Effectiveness of a Patient Education Class to Enhance Knowledge about Lung Cancer Screening: a Quality Improvement Evaluation. *Journal of Cancer Education*. 2020; 35: 897-904

[192] Studts JL, Thurer RJ, Brinker K, et al. Brief Education and a Conjoint Valuation Survey May Reduce Decisional Conflict Regarding Lung Cancer Screening. *MDM Policy &Practice*. 2020; 5 (1): 2381468319891452

[193] Volk RJ, Linder SK, Leal VB, et al. Feasibility of a patient decision aid about lung cancer screening with low-dose computed tomography. *Preventive Medicine*. 2014; 62: 60-3

[194] M.D. Anderson Cancer Center. *PCORI-CER-1306-03385 Lung Cancer Screening Decision Aid Development and Testing*. 27.09.2019; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02282969 [cited 16.08.2020].

[195] UNC Lineberger Comprehensive Cancer Center. *Pre-Post Study for Supporting Appropriate Implementation of Lung Cancer Screening*. 20.09.2017; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03077230 [cited 16.08.2020].

[196] Autier P. Lung-Cancer screening and the NELSON trial. *N Engl J Med*. 2020; 382 (22): 2165

[197] Gigerenzer G. *Unstatistik des Monats: Lungenkrebs-Screening rettet Leben*. 28.02.2020; Available from: http://www.rwi-essen.de/unstatistik/100 [cited 05.03.2020].

[198] Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ*. 2017; 356: j347

[199] Manhire A, Charig M, Clelland C, et al. Guidelines for radiologically guided lung biopsy. *Thorax*. 2003; 58 (11): 920-36

[200] European Commission. *4-IN THE LUNG RUN: towards INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening*. 02.04.2020; Available from: https://cordis.europa.eu/project/id/848294/de [cited 07.10.2020].

8 Anhang

Forschungsfrage 1

Tabelle A- 1: Summary-of-findings Tabelle zu Lungenkrebsscreening mittels LDCT bei Personen ohne Verdacht auf Lungenkrebs mit aktuellem oder ehemaligem starken Tabakkonsum

Endpunkt	Erwartete absolute Effekte (95% KI) [a]		Relativer Effekt (95% KI)	Anzahl der Teilnehmer*innen (Studien)	Vertrauenswürdigkeit	Anmerkungen
	Risiko ohne Screening [b]	Risiko mit LDCT Screening [c]				
Mortalität						
Gesamtmortalität	8–11 Jahre nach Randomisierung: 5 (–3 to 12) weniger 101 pro 1000	96 pro 1000	IDR 0,95 (0,88–1,03); $p = 0,164$	IG: 17.234 KG: 16.469 (6 RCTs)	Hoch ++++	Ein Screening auf Lungenkrebs mittels LDCT führt im Vergleich zu keinem Screening zu einem geringen oder keinen Unterschied in der Gesamtmortalität.
Lungenkrebsspezifische Mortalität	8–11 Jahre nach Randomisierung: 5 (3–8) weniger 28 pro 1000	23 pro 1000	IDR 0,81 (0,72–0,91); $p = 0,004$	IG: 17.234 KG: 16.469 (6 RCTs)	Moderat [d] +++0	Ein Screening auf Lungenkrebs mittels LDCT verringert wahrscheinlich die Lungenkrebs-spezifische Mortalität im Vergleich zu keinem Screening. Ohne LDCT-Screening sterben wahrscheinlich 28 von 1000 Menschen an Lungenkrebs. Mit LDCT-Screening sterben wahrscheinlich 23 von 1000 Menschen an Lungenkrebs. Ein LDCT-Screening rettet wahrscheinlich etwa 5 von 1000 Menschen vor dem Tod durch Lungenkrebs innerhalb von etwa 10 Jahren. [e]
Morbidität						
Überdiagnosen	–	0 [f] (0–1,1) bis 22 (1–42) [g] pro 1000 [h]	Range (Minimum-Maximum) der Punktschätzungen für das Risiko von Überdiagnosen bezogen auf die zum Screening eingeladenen Personen in den einzelnen Studien: 0% bis 2,2%	IG: 15.917 KG: 15.189 (6 RCTs)	Hoch ++++	Ein Screening auf Lungenkrebs mittels LDCT kann wegen des höheren Risikos für Überdiagnosen, d.h. aus der daraus resultierenden invasiven Abklärungsdiagnostik und Behandlung einschließlich der damit verbundenen Komplikationen und Nebenwirkungen, im Vergleich zu keiner Früherkennung zu einem Schaden führen.

Endpunkt	Erwartete absolute Effekte (95% KI) [a]		Relativer Effekt (95% KI)	Anzahl der Teilnehmer*innen (Studien)	Vertrauenswürdigkeit	Anmerkungen
	Risiko ohne Screening [b]	Risiko mit LDCT Screening [c]				
						In den eingeschlossenen Studien wird durch das Screening bei 0 bis 22 von 1000 Screening-Teilnehmern ein Lungenkrebs entdeckt, der für den Rest des Lebens keine Symptome verursacht hätte. Das aus den einzelnen Studien errechnete Risiko für Überdiagnosen bezogen auf Personen, bei denen während der Screening-Phase Lungenkrebs diagnostiziert wurde, liegt zwischen 0% und 63%.
Konsequenzen aus falsch-negativen Screening Ergebnissen	–	–	–	–	–	Keine Ergebnisse berichet.
Konsequenzen aus falsch-positiven Screening Ergebnissen	1–15 pro 1000 –	 –	Siehe OTCA28 Report Tabelle 4.15	IG: 17.234 KG: – (6 RCTs)	Hoch ++++	Ein Screening auf Lungenkrebs mittels LDCT könnte aufgrund der Konsequenzen falsch-positiver Screening-Ergebnisse zu Schäden führen. In den eingeschlossenen Studien erhalten 1 bis 15 Personen pro 1000 einen invasiven diagnostischen Test oder eine Operation mit anschließendem gutartigen Befund. [i]
UEs nach Operation wegen auffälliger Befunde [j]	Maximal 8 Jahre: 12 (2–37) mehr 5 pro 1000	 17 pro 1000	OR 3,48 (1,41–8,62); $p = 0{,}004$	IG: 1.264 KG: 1.186 (1 RCT)	Niedrig [k] ++00	Ein Screening auf Lungenkrebs mittels LDCT kann die UEs im Vergleich zu keiner Früherkennung erhöhen. Ohne LDCT-Screening können 5 von 1000 Personen nach der Operation ein UE erleiden, 2 davon ein UE mit Schweregrad ≥ 3. Mit LDCT-Screening können 17 von 1000 Personen ein UE nach der Operation haben, 8 davon ein UE mit dem Schweregrad ≥ 3.
UEs mit Schweregrad ≥ 3 nach Operation [j]	Maximal 8 Jahre: 6 (0–36) mehr 2 pro 1000	 8 pro 1000	OR 4,25 (0,92–19,69); $p = 0{,}046$	IG: 1.264 KG: 1186 (1 RCT)	Niedrig ++00 [k]	Beim LDCT-Screening kann es bei 12 Personen zu einem zusätzlichen UE nach der Operation kommen, 6 davon ein UE mit Schweregrad ≥ 3.
Health-related quality of life						
Gesundheitsbezogene Lebensqualität	–	–	–	–	–	Keine Ergebnisse bzw. keine verwertbaren Ergebnisse berichtet.

Abkürzungen: IG=Interventionsgruppe; IDR= Inzidenzdichtequotient; KI=Konfidenzintervall; KG=Kontrollgruppe; LDCT=Low-Dose Computertomographie; OR=Odds Ratio; RCT=Randomisierte kontrollierte Studie; UE=Unerwünschte Ereignisse.

a Zur Berechnung der absoluten Effekte wurde der IDR aus der Meta-Analyse auf das mediane Risiko in der Kontrollgruppe (Basline-Risiko) angewandt.
b Medianes Risiko der Kontrollgruppe pro 1000 Personen.
*c Medianes Risiko der Interventionsgruppe pro 1000 zum Screening eingeladenen Teilnehmer*innen.*
d Heruntergestuft um 1 Stufe, weil die Auswertung der Studien mit einem geringen Verzerrungspotenzial allein keinen statistisch signifikanten Unterschied zwischen den Gruppen zeigte.
e Mittlere Beobachtungszeit seit der Randomisierung.
f Basierend auf den Ergebnissen der ITALUNG-Studie. In der Interventionsgruppe wurden weniger Lungenkrebsfälle diagnostiziert als in der Kontrollgruppe. Damit sind keine Überdiagnosen nachweisbar.
g Basierend auf den Ergebnissen der DANTE-Studie.
h Unter Verwendung der Gesamtzahl der Lungenkrebsdiagnosen in der Interventionsgruppe als Nenner.
*i Unter allen zum Screening eingeladenen Teilnehmer*innen erlitten 0,1 % bis 0,3 % (0,04 %) eine (schwerwiegende) Komplikation nach Operation eines benignen Befunds.*
j Ergebnisse der DANTE-Studie, die als einzige Studie verwertbare Daten zu diesem Endpunkt berichtete.
k Heruntergestuft um 2 Stufen wegen hohem Verzerrungspotenzial auf Studienebene und breiten KI.

Forschungsfrage 2

Keine relevanten Studien verfügbar.

Forschungsfrage 3

Tabelle A- 2: Summary-of-findings Tabelle zu Lungenkrebsscreening mittels LDCT alle 2 Jahre im Vergleich zu jährliches Screening bei Personen ohne Verdacht auf Lungenkrebs mit aktuellem oder ehemaligem starken Tabakkonsum

Endpunkt	Erwartete absolute Effekte (95% KI) [a]		Relativer Effekt (95% KI)	Anzahl der Teilnehmer*innen (Studien)	Vertrauens-würdigkeit	Anmerkungen
	Risiko bei Screening alle 2 Jahre	Risiko bei jährlichem Screening				
Mortality						
Gesamtmortalität	10 Jahr nach Randomisierung: 13 (–8 bis 28) weniger 51 pro 1000 64 pro 1000		HR 0,80 (0,57–1,12); $p = 0,191$	IG: 1.186 KG: 1.190 (1 RCT)	Sehr niedrig [b] +000	Die Evidenz ist sehr unsicher, was die Auswirkungen eines Screenings auf Lungenkrebs mittels LDCT im Vergleich zum jährlichen LDCT-Screening auf die Gesamtmortalität betrifft.
Lungenkrebs-spezifische Mortalität	10 Jahr nach Randomisierung: 2 (–7 bis 17) mehr 18 pro 1000 16 pro 1000		HR 1,10 (0,59–2,05); $p = 0,760$	IG: 1.186 KG: 1.190 (1 RCT)	Sehr niedrig [b] +000	Die Evidenz ist sehr unsicher, was die Auswirkungen eines Screenings auf Lungenkrebs mittels LDCT im Vergleich zum jährlichen LDCT-Screening auf die Lungenkrebs-spezifische Mortalität betrifft.
Alle weiteren Endpunkte	–		–	–	–	Für diese Intervention wurden die Ergebnisse zu anderen Endpunkten als irrelevant erachtet, da die Mortalitätsergebnisse von sehr geringer Vertrauenswürdigkeit waren. Darüber hinaus waren die Ergebnisse zu anderen Endpunkte sehr ungenau.

Abkürzungen: IG=Interventionsgruppe; HR=Hazard Ratio; KI=Konfidenzintervall; KG=Kontrollgruppe; LDCT=Low-Dose Computertomographie; RCT=Randomisierte kontrollierte Studie.

a Zur Berechnung der absoluten Effekte, wurde die HR auf das Risiko in der Kontrollgruppe mit jährlichem Screening angewandt.

b Heruntergestuft um 3 Stufen wegen (i) hohem Verzerrungspotenzial auf Studienebene, (ii) schwerwiegender Limitation hinsichtlich der Präzision, weil eine unabhängige Replizierung der Ergebnisse durch eine zweite Studie fehlt und (iii) schwerwiegender Limitation hinsichtlich der statistischen Präzision.

Forschungsfrage 4

Tabelle A- 3: Summary-of-findings Tabelle zu unterschiedlichen Informationsstrategien für ein Lungenkrebsscreening mittels LDCT bei Personen ohne Verdacht auf Lungenkrebs mit aktuellem oder ehemaligem starken Tabakkonsum

Endpunkt	Erwartete absolute Effekte (95% KI)	*N* (%) soweit nicht anders angegeben	Anzahl der Teilnehmer*innen (Studien)	Vertrauenwürdigkeit	Anmerkungen
Informationsflugblätter zur Steigerung der Awareness für ein Lungenkrebsscreening					
Wissensverbesserung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Informierte Entscheidung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Zufriedenheit der Teilnehmer*innen	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Teilnahmerate am Screening	–	93 (38,8) vs 92 (37,7), *p* = n.r.	IG: 240 KG: 244 (1 non-RCT)	Sehr niedrig [a] +000	Es ist unsicher, ob Informationsflugblätter die Teilnahmerate am Screening verbessern.
Gezielte Screening-Einladung					
Wissensverbesserung	–	5,7 (2,3) vs 5,5 (2,3) [b], *p* = ns	IG: 388 KG: 415 (1 RCT)	Niedrig [c] ++00	Gezielte Einladungen zum Screening resultieren im Vergleich zu Standard-Einladungsmaterialien vermutlich in keinem oder einem geringen Unterschied in der Wissensverbesserung der Teilnehmer*innen hinsichtlich eines Lungenkrebsscreenings.
Informierte Entscheidung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Empowerment der Teilnehmer*innen	–	≥ 83,2% vs ≥ 76,2% [d], *p* = ns	IG: 388 KG: 415 (1 RCT)	Niedrig [c] ++00	Gezielte Einladungen zum Screening resultieren im Vergleich zu Standard-Einladungsmaterialien vermutlich in keinem oder einem geringen Unterschied im Empowerment der Teilnehmer*innen.
Zufriedenheit der Teilnehmer*innen	–	≥ 98,7% vs ≥ 97,3% [e], *p* = n.r.	IG: 388 KG: 415 (1 RCT)	Niedrig [c] ++00	Gezielte Einladungen zum Screening resultieren im Vergleich zu Standard-Einladungsmaterialien vermutlich in keinem oder einem geringen Unterschied in der Zufriedenheit der Teilnehmer*innen.
Teilnahmerate am Screening	–	OR 1,47 (0,91–2,40), *p* = 0,177	IG: 416 KG: 429 (1 RCT)	Niedrig [c] ++00	Gezielte Einladungen zum Screening resultieren im Vergleich zu Standard-Einladungsmaterialien vermutlich in

Endpunkt	Erwartete absolute Effekte (95% KI)	*N* (%) soweit nicht anders angegeben	Anzahl der Teilnehmer*innen (Studien)	Vertrauenwürdigkeit	Anmerkungen
					keinem oder einem geringen Unterschied in der Teilnahmerate am Screening.
Telefonische Einladung zum Screening					
Wissensverbesserung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Informierte Entscheidung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Empowerment der Teilnehmer*innen	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Zufriedenheit der Teilnehmer*innen	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Teilnahmerate am Screening	–	OR 1,10 (0,70–1,72), $p = 0,98$	IG: 213 KG: 218 (1 non-RCT)	Sehr niedrig [f] +000	Es ist unsicher, ob eine telefonische Einladung zusätzlich zu einer Informationsbroschüre die Teilnahmerate am Screening im Vergleich zu einer Informationsbroschüre alleine verbessert.
Einsatz von Entscheidungshilfen zur Information über das Lungenkrebsscreening					
Wissensverbesserung	–	Signifikanter Unterschied zugunsten der Entscheidungshilfe (Siehe OTCA28 Report Tabelle 4.29)	IG: 265 KG: 284 (1 RCT, 1 non-RCT)	Moderat [g] +++0	Die Verwendung von Entscheidungshilfen erhöht im Vergleich zu Standardinformationsmaterial wahrscheinlich das Wissen über Lungenkrebsscreening.
Informierte Entscheidung	–	Signifikanter Unterschied zugunsten der Entscheidungshilfe (Siehe OTCA28 Report Tabelle 4.31)	IG: 257 KG: 275 (1 RCT, 1 non-RCT)	Moderat [g] +++0	Die Verwendung von Entscheidungshilfen verbessert im Vergleich zu Standardinformationsmaterial wahrscheinlich eine informierte Entscheidung im Hinblick auf ein Lungenkrebsscreening.
Empowerment der Teilnehmer*innen	–	−14,9 (−20,1 to −9,7) [h], $p < 0,001$	IG: 234 KG: 233 (1 RCT)	Moderat [g] +++0	Die Verwendung von Entscheidungshilfen verbessert im Vergleich zu Standardinformationsmaterialien wahrscheinlich das Empowerment der Teilnehmer*innen im Hinblick auf eine Entscheidung über die Teilnahme an einem Lungenkrebsscreening.
Zufriedenheit der Teilnehmer*innen	–	4,8 (0,8) vs 4,7 (0,6) [i], $p < 0,001$	IG: 30 KG: 51 (1 non-RCT)	Sehr niedrig [f] +000	Es ist unsicher, ob die Verwendung von Entscheidungshilfen die Zufriedenheit der Teilnehmer*innen im Vergleich zu Standardinformationsmaterialien verbessert.

Endpunkt	Erwartete absolute Effekte (95% KI)	*N* (%) soweit nicht anders angegeben	Anzahl der Teilnehmer*innen (Studien)	Vertrauenwürdigkeit	Anmerkungen
Teilnahmerate am Screening	–	OR 0,70 (0,47–1,03) [i], $p = 0,07$	IG: 237 KG: 238 (1 RCT)	Moderat [g] +++0	Die Verwendung von Entscheidungshilfen resultieren im Vergleich zu Standardinformationsmaterialien wahrscheinlich in keinem oder einem geringen Unterschied in der Teilnahmerate am Screening.
Option grids im Vergleich zu online Entscheidungshilfen					
Wissensverbesserung	–	64,7% vs 62,4% [k], $p = 0,43$	IG: 128 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung von Option Grids resultieren im Vergleich zur Verwendung von online Entscheidungshilfen vermutlich in keinem oder einem geringen Unterschied in der Wissensverbesserung der Teilnehmer*innen hinsichtlich eines Lungenkrebsscreenings.
Informierte Entscheidung	–	97,4 vs 98,6 [m], $p = 0,60$	IG: 128 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung von Option Grids resultieren im Vergleich zur Verwendung von online Entscheidungshilfen vermutlich in keinem oder einem geringen Unterschied hinsichtlich einer informierten Entscheidung der Teilnehmer*innen.
Empowerment der Teilnehmer*innen	–	6,0 vs 10,2 [h], $p = 0,0198$	IG: 128 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung von Option Grids kann im Vergleich zu einer Online-Entscheidungshilfe das Empowerment der Teilnehmer*innen im Hinblick auf eine Entscheidung über die Teilnahme an einem Lungenkrebsscreening verbessern.
Zufriedenheit der Teilnehmer*innen	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Teilnahmerate am screening	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Imformationsfilm zum Lungenkrebsscreening					
Wissensverbesserung	–	MD 0,62 (0,17–1,08) [n], $p = 0,007$	IG: 120 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung eines Informationsfilms zusätzlich zu einer Broschüre kann im Vergleich zur Informationsbroschüre alleine das Wissen der Teilnehmer*innen über das Lungenkrebsscreening verbessern.
Informierte Entscheidung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Empowerment der Teilnehmer*innen	–	8,5 (1,25) vs 8,24 (1,49) [o], $p = 0,007$ [p]	IG: 120 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung eines Informationsfilms zusätzlich zu einer Broschüre kann im Vergleich zur Informationsbroschüre alleine das Empowerment der Teilnehmer*innen

Endpunkt	Erwartete absolute Effekte (95% KI)	*N* (%) soweit nicht anders angegeben	Anzahl der Teilnehmer*innen (Studien)	Vertrauenwürdigkeit	Anmerkungen
					im Hinblick auf eine Entscheidung über die Teilnahme an einem Lungenkrebsscreening verbessern.
Zufriedenheit der Teilnehmer*innen	–	–	–	--	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Teilnahmerate am Screening	--	76,7% vs 78,9% [q], *p* = 0,66	IG: 120 KG: 109 (1 RCT)	Niedrig [l] ++00	Die Verwendung eines Informationsfilms zusätzlich zu einer Broschüre resultieren im Vergleich zur Informationsbroschüre alleine vermutlich in keinem oder einem geringen Unterschied in der Teilnahmerate am Screening.
Art der Vermittlung einer SDM Beratung (persönlich versus telefonisch)					
Wissensverbesserung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Informierte Entscheidung	–	–	–	–	Für diese Intervention wurden keine Studien gefunden, die diesen Endpunkt untersuchten.
Empowerment der Teilnehmer*innen	–	11,3 (3,4) vs 12,1 (3,4) [o], *p* = n.r.	I: 69 KG: 68 (1 non-RCT)	Sehr niedrig [f] +000	Es ist unsicher, ob eine persönliche SDM-Beratung das Empowerment der Teilnehmer*innen im Vergleich zur telefonischen Beratung verbessert.
Zufriedenheit der Teilnehmer*innen	–	26,7 (2,8) vs 24,6 (5,6) [r], *p* = n.r.	I: 69 KG: 68 (1 non-RCT)	Sehr niedrig [f] +000	Es ist unsicher, ob eine persönliche SDM-Beratung die Zufriedenheit der Teilnehmer*innen im Vergleich zur telefonischen Beratung verbessert.
Teilnahmerate am Screening	–	88,4% vs 88,2% [q], *p* = n.r.	I: 69 KG: 68 (1 non-RCT)	Sehr niedrig [f] +000	Es ist unsicher, ob eine persönliche SDM-Beratung die Teilnahmerate am Screening im Vergleich zur telefonischen Beratung verbessert.

Abkürzungen: IG=Interventionsgruppe; KG=Kontrollgruppe; KI=Konfidenzinterval; LDCT=Low-Dose Computertomographie; MD=Mittlerer Gruppenunterschied; n.r.=nicht berichtet; ns=nicht signifikant; OR=Odds Ratio; RCT=Randomisierte kontrollierte Studie; SD=Standardabweichung; SDM=Shared Decision-Making.

a Heruntergestuft um 3 Stufen wegen Indirektheit der Ergebnisse (Studie aus Japan), schwerwiegende Limitationen in der Präzision, da die Ergebnisse nur auf einer kleinen Beobachtungsstudie beruhen und hohem Verzerrungspotenzial auf Studienebene

b Wissensscore; Mittelwert (SD).

c Heruntergestuft um 2 Stufen wegen schwerwiegende Limitationen in der Präzision, da die Ergebnisse nur auf einem kleinen RCT beruhen.

d Anteil der Personen mit einem Entscheidungskonflikt.

*e Anteil der Teilnehmer*innen, die mit ihrer Entscheidung zufrieden waren.*

*f Heruntergestuft um 3 Stufen wegen schwerwiegende Limitationen in der Präzision, da die Ergebnisse nur auf einer Beobachtungsstudie mit geringer Anzahl an StudienTeilnehmer*innen beruhen und hohem Verzerrungspotenzial auf Studienebene.*

g Heruntergestuft um 1 Stufe wegen Limitationen in der Präzision
h Decisional Conflict Scale; Mittelwert (95% KI).
i Zufriedenheitssscore; Mittelwert (SD).
j Geplantes Screening innerhalb eines Jahres.
*k Anteil der Teilnehmer*innen mit richtigen Antworten.*
l Heruntergestuft um 2 Stufen wegen Limitationen in der Präzision, da die Ergebnisse nur einem kleinen RCT beruhen und hohem Verzerrungspotenzial auf Studienebene.
m Mittlerer CollaboRATE SDM Score.
n Objektiver Wissenssscore; Mittelwert 95% KI).
o Decisional Conflict Scale; Mittelwert (SD).
p Multivariable Analyse unter Verwendung einer multiplen linearen Regression (die davon ausgeht, dass die Restfaktoren und nicht die Rohwerte normal verteilt sind), angepasst an die Baseline-Werte, das Alter, das Bildungsniveau, die ethnische Zugehörigkeit, Index of Multiple Deprivation Score und die Dauer des Tabakkonsums.
*q Anteil der Teilnehmer*innen mit durchgeführtem LDCT-Screening.*
r Decisional satisfaction Score; Mittelwert (SD).

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

LUNG CANCER SCREENING IN RISK GROUPS

Project ID: OTCA28

Version 1.5, 25.11.2020

This report is part of the project/joint action '724130/EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014–2021)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	**19/08/2020**	First draft
V1.1	**09/09/2020**	First draft, completed version
V1.2	**07/10/2020**	Input from co-author has been processed
V1.3	**07/10/2020**	Input from dedicated reviewers has been processed
V1.4	**12/11/2020**	Input from external experts has been processed
V1.5	**25/11/2020**	Input from medical editor has been processed

Disclaimer

The content of this assessment represents a consolidated view based on the consensus within the authoring team, it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), the EUnetHTA participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

The HTA Core Model developed within EUnetHTA was used when producing the contents and structure of this assessment report. The assessment elements, specified in Core Model Version 3.0, are indicated in footnotes to the respective domains to provide further orienting support. HTA Core Model Version 3.0 is available at https://www.eunethta.eu/hta-core-model-3-0/.

Assessment Team

ASSESSMENT TEAM			
		Organisation listed	Individual names listed
Authoring team	Author(s)	Institute for General Practice and Evidence-based Health Services Research, Medical University of Graz (IAMEV), Austria Austrian Institute for Health Technology Assessment (AIHTA), Austria	Thomas Semlitsch Klaus Jeitler Carolin Zipp Cornelia Krenn Karl Horvath
	Co-Author(s)	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Germany	Yvonne Zens Elke Hausner Stefan Sauerland Mareike Störchel Sibylle Sturtz
		Galician Agency for Health Knowledge Management (Avalia-t; ACIS), Spain	Leonor Varela Lema Lucinda Paz Valiñas Janet Puñal Riobóo Paula Cantero Muñoz María José Faraldo Vallés
Dedicated Reviewer(s)		Regione Emilia-Romagna (RER), Italy	Paolo Giorgi Rossi
		University for Health Sciences, Medical Informatics and Technology (UMIT), Austria	Petra Schnell-Inderst Nikolai Mühlberger
Observer(s)		Institute of Family Medicine and Public Health, University of Tartu (UTA), Estonia	Raul Kiivet
Project Manager(s)		Austrian Institute for Health Technology Assessment (AIHTA), Austria	Sabine Ettinger

Acknowledgements

	Organisation listed	Description of tasks
External expert(s)	Giuseppe Gorini (specialist in epidemiology), Italy	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all project phases.
	Giulia Picozzi (specialist in radiology), Italy	
	Vicenta Labrador Cañadas (Spanish Ministry of Health; head of population screening programs unit), Spain	
	Pilar Garrido López (specialist in oncology), Spain	
Medical Editor(s)	Compuscript Ltd., Ireland	Medical editing

Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

How to cite this assessment

Please, cite this assessment as follows:

EUnetHTA OTCA28 Authoring Team. Lung cancer screening in risk groups. Collaborative assessment. Diemen (The Netherlands): EUnetHTA; 2020. 252 pages. Report No. OTCA28. Available from: https://www.eunethta.eu

Contact the EUnetHTA Secretariat at EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

LIST OF ABBREVIATIONS

ACRIN	American College of Radiology Imaging Network
ATS	American Thoracic Society
BOLD	Burden of Obstructive Lung Disease
CAD	Computer-aided detection
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed tomography
DANTE	Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays
DLCST	Danish Lung Cancer Screening Trial
DEE	Diesel engine exhaust
ERS	European Respiratory Society
ESR	European Society of Radiology
FBS	Fibrobronchoscopy
FDG	Fluorodeoxyglucose
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GBDS	Global Burden of Disease Study
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GROWCAT	Nodule category based on volume doubling time (growth)
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
IRR	Incidence rate ratio
ITALUNG	Italian Lung Cancer Screening
ITT	Intention to treat
LCS	Lung cancer screening
LDCT	Low-dose computed tomography
LSS	Lung Screening Study
LUSI	Lung Tumor Screening and Intervention Trial
MD	Mean difference

MeSH	Medical Subject Headings
MILD	Multicentric Italian Lung Detection
NCCN	National Comprehensive Cancer Network
NELSON	NEderlands Leuvens Longkanker Screenings ONderzoek
NHS	National Health Service
NLST	National Lung Screening Trial
NODCAT	Nodule category based on volume
n.r.	Not reported
n.s.	Not significant
NSCLC	Non–small-cell lung cancer
OR	Odds ratio
PET-CT	Positron emission tomography-computed tomography
PICO	Population, Intervention, Control, Outcome
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPI	Pre–post-intervention
PYs	Person-years
RCT	Randomised controlled trial
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
SABR	Stereotactic ablative radiotherapy
SCLC	Small-cell lung cancer
SDM	Shared decision-making
SHS	Second-hand smoke
SMD	Standardised mean difference
SR	Systematic review
TNM	Tumour node metastasis
UKLS	UK Lung Cancer Screening Trial
USPSTF	US Preventive Services Task Force
VATS	Video-assisted thoracoscopic surgery
VDT	Volume doubling time
WHO	World Health Organization

EXECUTIVE SUMMARY OF THE ASSESSMENT OF LUNG CANCER SCREENING FOR RISK GROUPS

Introduction

Lung cancer is a malignant growth of cells in the lung or bronchial system. Some 95% of lung malignancies can be classified as non–small-cell carcinoma (79%) or small-cell carcinoma (16%). Rarely occurring tumours such as carcinoid tumours account for the remaining 5% of primary lung cancers. Lung cancer is the fourth most frequently diagnosed cancer in the EU, affecting more than 312,000 people annually. Smoking is by far the most important cause of lung cancer, accounting for 90% of cases among men and 80% among women. Further risk factors that increase lung cancer risk are family history, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD) and exposure to agents such as asbestos, chromium, arsenic, radon gas, coal tar and air pollutants. Therefore, the target population in this assessment is adult individuals without lung cancer (confirmed or suspected) at elevated risk of lung cancer, that is, persons with a history of smoking or current smokers and individuals with other potential risk factors: occupational or environmental toxins (e.g., radon, asbestos or fine particles), COPD, idiopathic pulmonary fibrosis or a family history of lung cancer. Lung cancer screening programmes for the detection and treatment of lung cancer at an early stage may have a major impact on the high mortality rate of this disease. Different imaging technologies can be used for lung cancer screening, including chest X-ray and (low-dose) computed tomography (LDCT or CT). Breath and blood biomarkers can also be used to screen for lung cancer. While biomarkers are still at an early stage of development, screening with LDCT is increasingly offered in routine clinical practice. There is currently no agreed policy for lung cancer screening in Europe. Because several large randomised controlled trials (RCTs) on LDCT screening have been completed in recent years, a systematic assessment of the different options and organisational variants for lung cancer screening is timely.

Objectives and scope

The aim of this EUnetHTA assessment is to provide a reliable synthesis and analysis of the available evidence on lung cancer screening in risk groups (individuals with a history of smoking or current smokers, those with occupational or environmental exposure to radon, asbestos or fine particles, patients with COPD or idiopathic pulmonary fibrosis, and individuals with a family history of lung cancer). For this purpose four research questions were defined:

- **Research question 1:** What is the benefit/harm of screening for lung cancer using LDCT compared to no (or no systematic) screening in individuals at elevated risk of lung cancer? As there is reason to assume comparability of no screening and screening using chest X-ray, screening for lung cancer using chest X-ray will also be taken into account as a comparator, if reasonable.
- **Research question 2:** What is the benefit/harm of screening for lung cancer using biomarkers in addition to LDCT compared to screening using LDCT alone for individuals at elevated risk of lung cancer?
- **Research question 3:** What is the benefit/harm of organisational variants of systematic screening for lung cancer using LDCT (e.g., screening at different intervals, with/without invitation) for individuals at elevated risk of lung cancer?
- **Research question 4:** What is the best strategy to inform individuals in the target group about a lung cancer screening programme to optimise informed choices regarding participation?

Table 0.1: Scope of the assessment: PICO 1

Description	Project scope
Population	Adults (age ≥18 years) without lung cancer (confirmed or suspected) (ICD-10 code C34) at elevated risk of lung cancer: • Population 1: Persons with a history of smoking or current smokers • Population 2: Persons with other potential risk factors: occupational or environmental toxins (e.g., radon, asbestos or fine particle exposure), COPD (ICD-10 code J44), idiopathic pulmonary fibrosis (ICD-10 code J84.1) or a family history of lung cancer (ICD-10 code C34)
Intervention	Systematic screening for lung cancer using low-dose computed tomography
Comparison	No (systematic) screening (usual care) In a sensitivity analysis, screening for lung cancer using chest X-ray was also taken into account as an additional comparator for mortality and consequences resulting from overdiagnoses as outcomes. Rationale: Results from the PLCO study [1] give reason to assume comparability of no screening and screening using chest X-ray at least in terms of their effect on lung cancer specific mortality.
Outcomes	• Mortality (overall mortality, lung cancer mortality) • Morbidity • Health-related quality of life • Harms resulting from screening itself (e.g., consequences from radiation exposure) or from subsequent diagnostic interventions (e.g., invasive biopsy) including overdiagnoses,[1] and consequences resulting from false screening results (false positive and false negative) • (Serious) adverse events
Study design	Randomised controlled trials

Table 0.2: Scope of the assessment: PICO 2

Description	Project scope
Population	See PICO 1
Intervention	Screening for lung cancer using biomarkers in addition to low-dose computed tomography (LDCT): • Biomarkers can be used as a test for selection of individuals undergoing screening • Biomarkers can be used as a test for characterisation of undetermined nodules found during CT-based screening
Comparison	Screening for lung cancer using LDCT alone Rationale: LDCT alone is the recommended screening intervention according to current guidelines
Outcomes	See PICO 1
Study design	See PICO 1

[1] Defined as the number of diagnoses (true positive findings) that would not have become clinically relevant during a person's lifetime.

Table 0.3: Scope of the assessment: PICO 3

Description	Project scope
Population	See PICO 1
Intervention	Annual systematic screening for lung cancer using low-dose computed tomography (LDCT) as recommended in guidelines
Comparison	Systematic screening for lung cancer using LDCT with differences in the screening interval (shorter or longer) or type of systematic screening (organisational variants, e.g. with invitation)
Outcomes	See PICO 1
Study design	See PICO 1

Table 0.4: Scope of the assessment: PICO 4

Description	Project scope
Population	See PICO 1
Intervention	Specific information strategy for lung cancer screening (e.g., content, mode of distribution)
Comparison	A specific information strategy for lung cancer screening different from the one used in the intervention group (e.g., different content, different mode of distribution) No specific information strategy for lung cancer screening
Outcomes	• Screening participation rate • Participant satisfaction • Participant empowerment • Increased knowledge • Informed decision-making
Study design	Randomised controlled trials; nonrandomised controlled trials; prospective observational studies; qualitative studies

Methods

The target population for the rapid relative effectiveness assessment was composed of adults (age ≥ 18 years) at elevated risk of lung cancer but without lung cancer at the time of the screening (confirmed or suspected). Research question 1 investigated systematic screening for lung cancer using LDCT. No (or no systematic) screening was considered as the comparator. Within a sensitivity analysis, screening for lung cancer using chest X-ray was taken into account as an additional comparator for mortality and consequences resulting from overdiagnoses as outcomes. Research question 2 investigated screening for lung cancer using biomarkers in addition to LDCT compared to lung cancer screening using LDCT alone.

The following patient-relevant outcomes were considered for the assessment:

- Mortality (overall mortality, lung cancer mortality);
- Morbidity;
- Health-related quality of life (HRQoL);

- Harms resulting from screening itself (e.g., consequences from radiation exposure) or from subsequent diagnostic interventions (e.g., invasive biopsy), including overdiagnoses,[2] and consequences resulting from false screening results (false positive and false negative); and
- (Serious) adverse events.

Only randomised controlled trials (RCTs) were included in the benefit assessment. There was no restriction with regard to study duration.

For research question 1, the results of the German national benefit–harm assessment report on screening for lung cancer using LDCT in people with a history of smoking or current smokers conducted by one of the co-authors (IQWiG; report number S19-02) [1] were used. For the IQWiG report, a systematic literature search for relevant high-quality systematic reviews (SRs) was conducted using the bibliographic databases MEDLINE, Cochrane Database for Systematic Reviews and Health Technology Assessment Database. The search was restricted to the last 6 years before 2019. The aim was to select one or more high-quality and up-to-date SRs from which primary studies were identified and then selected according to the specific inclusion criteria of the report.

In addition, for the time period not covered by an up-to-date relevant SR of high quality [2], systematic literature searches for RCTs were conducted in the following databases: MEDLINE, Embase and Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were also considered: study registries, reference lists, documents made available from consultation procedures and author inquiries.

For the present EUnetHTA rapid relative effectiveness assessment, the inclusion criteria for research question 1 were extended to other risk factors for lung cancer (occupational or environmental exposure to harmful substances, COPD, idiopathic pulmonary fibrosis and family history of lung cancer). Therefore, the list of studies excluded from the IQWiG report was rescreened to identify studies on these risk factors. In addition, all studies already included for research question 1 were checked regarding the proportion of people reporting other exposures, and results for these subgroups were extracted, if possible.

For research question 2, systematic literature searches for RCTs or SRs were conducted in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

In addition, the following sources of information and search techniques were considered: study registries and reference lists.

For research question 3, no separate literature searches were performed, but all studies included for research questions 1 and 2 were used to perform subgroup analysis for different screening modalities, if possible.

For research question 4, systematic literature searches in the bibliographic databases MEDLINE, Embase and Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews were performed.

In addition to the electronic search, bibliographic references for the original articles and reviews included were checked.

[2] Defined as the number of diagnoses (true positive findings) that would not have become clinically relevant during a person's lifetime.

Selection of relevant primary studies was performed by two persons independently of each other. Discrepancies were resolved by discussion between the two. The data extraction was carried out in standardised tables. A risk of bias (RoB) assessment of the RCTs included was performed according to the Cochrane RoB tool, while the assessment for nonrandomised studies on interventions was carried out according to the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool. RoB was evaluated at the study and outcome levels and classified as low or high. To rate the quality of the overall evidence available for a given outcome, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied. The quality of evidence was evaluated at the outcome level (possible levels: high, moderate, low or very low). The results from the individual studies were described according to outcomes.

In addition to comparing the results from the individual studies, meta-analyses and sensitivity analyses were carried out and effect modifiers were examined, provided that the methodological requirements were met.

Finally, the benefits and harms of lung cancer screening using LDCT were assessed across outcomes, resulting in a summary statement.

Results

Research question 1

Information retrieval

Information retrieval identified nine randomised trials (184 documents) as relevant for the research question. All nine studies investigated current or former smokers, and one study, the UK Lung Cancer Screening Trial (UKLS) [3-12], also included individuals with other risk factors.

Two ongoing studies and one planned study were identified. In addition, one completed study without reported results was identified and four studies with unclear status. The last search was performed on 12th June 2020.

Characteristics of the studies included in the assessment

One study, the UKLS [3-12], is a feasibility study that basically fulfils the inclusion criteria of the report, but no results that could be used for the benefit assessment were reported. A more detailed presentation of the UKLS is therefore not given in what follows.

The remaining eight studies (number of randomised subjects: 90,836) differed with regard to the screening strategies applied. In six studies the subjects were assigned to either screening with LDCT or no screening. In the Danish Lung Cancer Screening Trial (DLCST) [13-28], Italian Lung Cancer Screening (ITALUNG) [29-39], Lung Tumor Screening and Intervention Trial (LUSI) [40-44], Multicentric Italian Lung Detection (MILD) [45-52] and NEderlands Leuvens Longkanker Screenings ONderzoek (NELSON) trial [53-92], participants in the control group were not offered any imaging procedures at baseline or during follow-up unless lung cancer was suspected. In the Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays (DANTE) study [93-97], a baseline examination using chest X-ray was performed. Since this examination was performed in both the intervention group and the control group and no further screening was performed in the control group during the course of the study, the study was also classified as a study comparing LDCT versus no screening. By contrast, the Lung Screening Study [LSS] [98-101] and

National Lung Screening Trial (NLST) [102-176] compared LDCT screening and screening using chest X-ray. Both studies are US-American RCTs.

In the study groups without screening, the endpoint-specific data were all collected via registers. In addition, depending on the study, postal or telephone inquiries and clinical examinations were also used. All studies were conducted within Europe (Italy, Denmark, Germany, Netherlands and Belgium).

The number of participants in six studies ranged from 3,000 to 4,000, while the NELSON and NLST studies had approximately 16,000 and 53,500 participants, respectively. The duration of the screening phase ranged from 1 to 6 years and the follow-up period planned ranged from 5 to 10 years (in LSS, no information was available on the follow-up duration). With the exception of the MILD and NELSON studies, the screening interval was 1 year throughout all screening rounds. The MILD study was the only three-arm study, in which participants in the intervention group were screened either annually or every 2 years (biennially). At the beginning of the study, participants were randomised to annual or biennial screening. Randomisation to an additional control group started later, resulting in different group sizes. In the NELSON study, the screening interval after each screening round was extended from 1 year to 2 years and then to 2.5 years.

The studies included men and women who smoked at baseline (at least 20 or 30 pack-years) or stopped smoking less than 10 years previously (15 years in NLST). Exceptions are the DANTE study, which only examined men, and the NELSON study. In the latter, only men were initially recruited, with women recruited only in the further course of the study. The authors justified this on the basis of the lower proportion of women with long-term exposure to cigarette consumption in the Dutch population and an associated increase in effort to recruit the desired number of cases. The percentage of women in the NELSON study is therefore only approximately 16%, while in the other studies it is at least 31%. The age set for participants in the studies ranged from ≥ 49 years to 75 years; MILD was the only study not to set an upper age limit.

The screening participation rate (adherence to screening) ranged from 81% to 96% among the intervention groups. Of the studies using no screening as the comparator, three reported contamination of between 1% and 7%, although it is unclear how valid this information is. A study with chest X-ray screening as the comparator reported contamination of 4%. For the other four studies, no information on contamination was available.

Overview of outcomes relevant for the assessment

Data on patient-relevant outcomes could be extracted from eight studies. All studies reported evaluable data for the mortality (overall mortality and lung cancer mortality) and overdiagnosis endpoints. Chest X-ray screening is not considered an adequate comparator for investigating the effect of LDCT screening with regard to the consequences of false screening results, HRQoL and adverse events compared to no screening. Therefore, for consequences of false screening results, HRQoL and adverse events as endpoints, only the six studies comparing LDCT screening to no screening were considered. All six studies reported evaluable data on the consequences of false screening results. For adverse events, evaluable data from the DANTE study were available. For the HRQoL endpoint, either no data or no evaluable data were available in the studies.

RoB assessment and quality of the evidence

The RoB was rated as low for four studies (DLCST, ITALUNG, LUSI and NELSON) at the study level and as high for the remaining four studies. For the studies with high RoB at the study level, it was unclear whether the allocation concealment was adequate (DANTE, MILD and NLST). For LSS it was unclear whether reporting was independent of the results (e.g., lack of information on the planned endpoints). In the MILD study, significant differences in baseline characteristics (age, sex, smoking status and pack-years) between the intervention and control groups also led to high RoB.

The RoB for the outcomes overall mortality and lung cancer mortality, consequences of false screening results and overdiagnosis was rated as low in the DLCST, ITALUNG and NELSON studies. Although the LUSI study showed low RoB at the study level, high RoB was found for all outcomes, partly because of discrepancies between publications regarding the results. The RoB for the outcome adverse events was rated as high for DANTE, which is the only study that reported results for adverse events.

For all the studies for which RoB at the study level was already classified as high (DANTE, MILD, NLST and LSS), there is therefore high RoB at the outcome level, so no further outcome-specific assessment was performed for these studies.

Depending on the outcome assessed, the quality of the evidence ranged from low to high.

Results on clinical effectiveness and safety

Mortality

For **overall mortality**, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, MILD and LUSI) were available for comparison against no screening. The data for the longest observation period, which ranged from 8 to 11 years since randomisation, were used for all studies.

Since the studies considered did not have sufficiently comparable study designs (e.g., with regard to screening intervals, selection criteria for study participants and evaluation of the findings) to allow a meta-analysis based on a fixed-effects model, meta-analyses with a random-effects model were used. The three studies with low RoB showed no statistically significant difference between the groups (incidence rate ratio [IRR] 0.93, 95% confidence interval [CI] 0.69–1.26; p = 0.434). The combined analysis of studies with low and high RoB (data for 33,703 individuals) also showed no statistically significant effect in favour of screening (IRR 0.95, 95% CI 0.88–1.03; p = 0.164).

For the comparison of LDCT screening versus chest X-ray screening, data on overall mortality were available from two studies (LSS and NLST) with high RoB. The sensitivity analysis for these two studies using the data for the longest observation period does not contradict the results for the comparison of LDCT screening versus no screening (IRR 0.97, 95% CI 0.92–1.02; p = 0.168; N = 90,473).

Subgroup analyses

No subgroup analyses were performed for the characteristics strength of exposure to tobacco (e.g., tobacco consumption, smoker status) and screening strategy (e.g., number of screening rounds) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristic. There were also no usable subgroup analyses conducted for individual study populations.

However, in the six studies included for comparison of LDCT screening to no screening (DANTE, DLCST, ITALUNG, MILD, LUSI and NELSON) and the two studies comparing LDCT screening to chest X-ray screening (LSS and NLST), the age of the devices used in the studies (including use of LDCT devices with < 16 slices vs exclusive use of LDCT devices with ≥ 16 slices) and the size of the screening centre (small vs large centres: < 3000 vs ≥ 3000 study participants recruited) as potential effect modifiers were investigated.

Furthermore, available data from four studies (DANTE, LUSI, NELSON and NLST) were used to investigate the sex of participants as a potential effect modifier.

In addition, within the three-arm MILD study, the length of the screening interval was investigated as an effect modifier, as screening was performed either annually or every 2 years (biennial) in the two intervention groups.

The test for interaction did not show statistical significance in any of the subgroup analyses for the studies comparing LDCT screening against no screening. In addition, a sensitivity analysis considering the studies comparing LDCT screening against chest X-ray screening did not contradict these results.

Therefore, there was no effect modification for overall mortality due to CT device age, centre size, the sex of the participants or screening interval length.

For **lung cancer mortality**, data were available from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, MILD and LUSI) for comparison to no screening. For all studies, the data for the longest observation period were used, which ranged from 8 to 11 years since randomisation.

The three studies with low RoB showed no statistically significant difference between the groups (IRR 0.80, 95% CI 0.60–1.06; $p = 0.076$). The combined analysis of studies with low and high RoB (data for 33,703 participants) showed a statistically significant effect in favour of LDCT screening (IRR 0.81, 95% CI 0.72–0.91; $p = 0.004$).For comparison of LDCT screening to chest X-ray screening, data from two studies (LSS and NLST) with high RoB were available for lung cancer mortality. The sensitivity analysis does not contradict the results for comparison of LDCT screening to no screening (IRR 0.89, 95% CI 0.82–0.96; $p = 0.010$; $N = 90,473$).

Subgroup analyses

No subgroup analyses were performed for the subgroup characteristics strength of exposure to tobacco (e.g., tobacco consumption, smoker status) and screening strategy (e.g. number of screening rounds) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristic. There were also no usable subgroup analyses conducted within individual study populations.

However, in the six studies comparing LDCT screening to no screening (DANTE, DLCST, ITALUNG, MILD, LUSI and NELSON) and the two studies comparing LDCT screening to chest X-ray screening, the age of the CT devices used in the studies (including use of LDCT devices with < 16 slices vs exclusive use of LDCT devices with ≥ 16 slices) and the size of the screening centre (small vs large centres: < 3000 vs ≥ 3000 study participants recruited) were investigated as potential effect modifiers for lung cancer mortality.

The subgroup analysis for studies comparing LDCT screening to no screening showed no effect modification. Even when the studies comparing LDCT screening to chest X-ray screening were added, no effect modification was found.

For lung cancer mortality it was also possible to investigate the following additional potential effect modifiers on the basis of available subgroup analyses or appropriately stratified evaluations of several studies: the presence of COPD at baseline (DLSCT), sex (DANTE, LUSI, NELSON and NLST), age of participants (NELSON) and screening interval length (MILD: annual or biennial screening).

The test for interaction did not show statistical significance in any of the subgroup analyses. When possible, a sensitivity analysis including studies comparing LDCT screening to chest X-ray screening was carried out. This did not contradict the results. There was no effect modification for lung cancer mortality with regard to CT device age, centre size, presence of COPD at study initiation, sex and age of the participants or screening interval length.

Conclusion on the benefit regarding mortality

The quality of the evidence ranked from high to moderate across the two suboutcomes. For overall mortality the quality of the evidence was rated as high, since the majority of the studies provided high-quality evidence. To that extent, screening for lung cancer with LDCT results in little or no difference in overall mortality when compared with no screening. The results of the meta-analyses, however, point in the direction of a reduction in overall mortality. For lung cancer mortality, the quality of the evidence was downgraded by one level to moderate because the evaluation of the studies with low RoB alone showed no statistically significant difference between the groups. Thus, screening for lung cancer with LDCT probably reduces lung cancer mortality when compared with no screening.

The estimate for the absolute effect is a reduction by 5 deaths per 1,000 persons (95% CI –3 to 12) for overall mortality and by 5 deaths per 1,000 persons (95% CI 3–8) for lung cancer mortality within approximately 10 years. Thus, the absolute effects and the corresponding CIs are of a similar order of magnitude for overall and lung cancer mortality.

Taking this further consideration into account, the quality of the evidence for mortality as a critical outcome can be assessed as low in summary. This rating of low comprises results showing a reduction in lung cancer mortality in contrast to nonsignificant results for overall mortality. In conclusion, screening for lung cancer with LDCT may reduce mortality when compared with no screening.

Adverse events

For adverse events, data were available from only one study (DANTE; high RoB) for comparison against no screening. DANTE reported data for the occurrence of adverse events after surgery and for the occurrence of adverse events of a severity level ≥ 3 after surgery. The results were presented for the longest observation period since randomisation (maximum 8 years). The evaluation showed a statistically significant difference in the incidence of adverse events after surgery for suspicious findings to the disadvantage of LDCT screening (odds ratio [OR] 3.48, 95% CI 1.41–8.62; $p = 0.004$). Further restriction to adverse events of severity ≥ 3 also showed a statistically significant difference between the two study groups to the disadvantage of LDCT screening (OR 4.25, 95% CI 0.92–19.69; $p = 0.046$).

Conclusion on harm regarding adverse events

The quality of the evidence for adverse events as an important outcome was rated as low. For DANTE, the quality of the evidence was downgraded by two levels because of the high RoB and serious imprecision, as the results are based on one relatively small study, leading to a large CI. In conclusion, screening for lung cancer with LDCT may increase adverse events when compared with no screening.

Consequences of false-negative screening results

Data on consequences of false negative screening results were not reported in the studies.

Consequences of false-positive screening results

For consequences of false-positive screening results, data for purely diagnostic interventional clarification were used as well as data on surgical therapeutic interventions if the treatment and diagnosis of lung tissue of unclear distinction could not be clearly separated. Complications associated with these procedures in persons for whom benign findings were subsequently found were also considered for this outcome. The observation period chosen was that at which the screening phase in the respective study was completed.

For consequences of false-positive screening results, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, MILD and LUSI) were available.

The need for invasive diagnostic workup was recorded in the studies only for the intervention groups. The DANTE study is an exception. Although all studies compared LDCT screening to no screening, in the DANTE study all participants underwent chest X-ray screening and 3-day sputum cytology at baseline regardless of group allocation. It therefore remains unclear whether the group difference is due solely to LDCT screening.

The presentation of invasive diagnostic procedures differed in the studies and in some studies included joint presentation of operations and biopsies, while in other studies the procedures were reported individually. For some studies, several operationalisations are available that show that this has a strong impact on the number of events. Therefore, no summary overall estimate was given for this endpoint, but rather a range (minimum–maximum) of effect estimates from the individual studies.

Between 0.1% and 1.5% of the study participants invited to screening received an invasive diagnostic workup that was only made necessary by a false-positive result from the screening. Surgery on individuals with benign findings was performed in 0.1%–1.3% of the participants invited for screening. Overall, between 0.1% and 1.5% of the study participants experienced a consequence of false-positive findings.

Complications in individuals with final benign findings who underwent surgery were reported for two studies (DLCST and NELSON). In the DLCST study, minor complications occurred in two out of seven patients with benign findings who underwent surgery, so 0.1% of all participants invited for screening suffered a minor complication after surgery for benign findings. In the NELSON study, complications were not reported for all patients with benign findings who underwent surgery, but only for those who underwent either thoracotomy or video-assisted thoracoscopic surgery (VATS). A total of three serious complications and 20 minor complications occurred in these patients with benign findings who underwent surgery. Thus, 0.04% and 0.3% of all participants invited to the screening experienced serious and minor complications, respectively.

Conclusion on harm regarding consequences of false-positive screening results

Screening for lung cancer with LDCT leads to harm due to consequences of false-positive screening results when compared with no screening. The conclusion is based on high-quality evidence. The quality of the evidence for this important outcome was rated as high because the majority of the studies provided high-quality evidence.

Overdiagnosis

For overdiagnosis, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, LUSI, MILD) were available for comparison against no screening. For comparison of LDCT screening to chest X-ray screening, data on overdiagnosis were available from two studies (LSS and NLST) with high RoB.

In this report, a summary overall estimate of overdiagnosis is not given. For overdiagnosis of individuals who received a lung cancer diagnosis during the screening phase, the proportions between the studies varied so much that an overall estimate could not be interpreted meaningfully. Concrete reasons for the heterogeneity of the results, such as individual aspects of the screening strategy and characteristics of the study population, could not be identified. The heterogeneity was less clear for the proportion of overdiagnoses in relation to participants invited to screening and it was generally possible to give an overall estimate for the studies for comparison against no screening. However, the associated CI is as wide as the range for individual point estimators in the studies. Thus, the pooled estimator with 95% CI has no additional information. In order to present the results transparently and uniformly, the proportion of overdiagnoses is given for both reference values as a range (minimum–maximum) of the point estimates of the individual studies.

From all eight studies included, the risk of overdiagnosis could be determined in relation to all participants invited to screening.

Among the six studies comparing LDCT screening to no screening, ITALUNG is the only study with fewer lung cancer cases diagnosed in the intervention group than in the control group in the overall follow-up. Thus, no overdiagnosis could be detected in this study. No overdiagnosis was found in the biennial screening of the MILD study either. The risk of overdiagnosis was highest in the DANTE and DLCST studies, at 2.2% and 2.1%, respectively. For LUSI, NELSON and the annual screening in the MILD study, the risk of overdiagnosis calculated for study participants is 0.9%, 0.6% and 1.4%, respectively. In the two studies comparing LDCT screening to chest X-ray screening, an overdiagnosis risk of 1.2% and 0.1% was calculated for LSS and NLST.

Data that could be used to calculate the risk of overdiagnosis in the presence of a lung cancer diagnosis were available from five studies, including four studies comparing LDCT screening to no screening (DLCST, ITALUNG, LUSI and NELSON). The result for the DLCST study was particularly striking, as an overdiagnosis risk of 63.2% was calculated (using the total number of lung cancer diagnoses in the intervention group as the denominator). For the LUSI and NELSON studies the overdiagnosis risk is 28.6% and 16.2%, respectively. In the ITALUNG study no overdiagnosis could be detected. An overdiagnosis risk of 2.8% was calculated for the NLST study in the comparison against chest X-ray screening.

Subgroup analyses

For the DANTE and NELSON studies, only data for men were available. For the LUSI study, data were available separately for women and men. These data do not suggest that there is an effect modification by sex. The NLST study comparing LDCT screening to chest X-ray screening also reported separate data by sex, which again indicate no effect modification.

For the MILD study, data were available for annual and biennial screening. Numerical differences in the rate of overdiagnosis between the two screening groups are probably random. This is suggested by the fact that the 95% CI for the two estimators overlap and contain the point estimates of the other group. Therefore, this result also suggests no effect modification by screening interval on overdiagnosis.

Conclusion on harm regarding overdiagnosis

Diagnosis of lung cancer requires histological or cytological confirmation. It can be assumed that almost all cases with a lung cancer diagnosis were also treated. Every diagnostic procedure and treatment/therapy carries the risk of side effects and complications.

The quality of the evidence for overdiagnosis as an important outcome can be assessed as high in summary. In conclusion, screening for lung cancer with LDCT leads to harm compared to no screening in terms of overdiagnosis, that is, from the resulting invasive diagnostic procedures and treatment including associated complications and side effects.

Health-related quality of life

Data on HRQoL were not reported in the studies or were not usable for the benefit assessment.

Research question 2

Information retrieval

Information retrieval identified no randomised trials that were relevant for research question 2.

In addition, no ongoing randomised trials and no completed studies without reported results were identified. The last search was performed on 7th July 2020.

Results on clinical effectiveness and safety

No results available.

Conclusion

In the absence of eligible RCTs, no conclusion can be drawn with regard to the benefit or harm of the use of biomarkers in addition to LDCT in screening for lung cancer in at-risk groups when compared to lung cancer screening using LDCT alone.

Research question 3

Information retrieval

Results from the eight RCTs used for research question 1 were also used to answer this research question.

Results on clinical effectiveness and safety

For research question 1, subgroup analyses were carried out with regard to participant and organisational characteristics. The conclusions from these analyses regarding clinical effectiveness and safety are presented above.

Beyond these analyses, no further subgroup analyses could be performed for different screening strategies because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to a particular characteristic.

However, one of the RCTs, MILD, was a three-arm study in which participants in the intervention groups were screened either annually or every 2 years (biennially). According to the 10-year data for the MILD study, biennial when compared to annual LDCT screening results in similar overall mortality (hazard ratio [HR] 0.80, 95% CI 0.57–1.12; p = 0.191) and similar lung cancer mortality (HR 1.10, 95% CI 0.59–2.05; p = 0.760).

The quality of the evidence on biennial versus annual LDCT screening was rated as very low because these two screening intervals have only been directly compared so far in a single study that has high RoB and lacks the necessary statistical precision.

Conclusion

The available evidence is not sufficient to answer the research question on whether one specific strategy in lung cancer screening is favourable compared to other screening strategies.

Research question 4

Information retrieval

Information retrieval identified 15 studies — five randomised trials (10 documents) [177-186], three controlled observational studies (3 documents) [187-189] and seven uncontrolled pre–post-intervention (PPI) studies (10 documents) [190-199] — as relevant for the research question on the effectiveness of different strategies to inform individuals in the target group about lung cancer screening. The last search was performed on 24th July 2020.

Characteristics of the studies included in the assessment

Two RCTs and one nonrandomised comparative study compared different information or invitation materials/strategies for lung cancer screening in general, and the remaining 12 studies assessed the effect of different shared decision-making strategies or tools for individuals invited for lung cancer screening.

Interventions assessed in the studies were rather heterogeneous and included sending of information leaflets or brochures on lung cancer screening, educational programmes informing about the benefit and harm of lung cancer screening, telephone counselling and the use of different types of decision aids. Twelve studies were conducted in the USA, two in the UK and one in Japan. Participants in the majority of the studies were men and women eligible for lung cancer screening, that is, current or former smokers aged 45–55 years and older. The percentage of women in the studies ranged from 40% to 65%. The mean age of participants in the studies was 59–65 years.

Overview of outcomes relevant for the assessment

All but four studies reported data on participants' change in knowledge about lung cancer screening. Participant empowerment was evaluated in nine studies, all focusing on the decisional conflict experienced by the participants, while five studies also investigated whether the participants were prepared to make a decision about lung cancer screening (informed decision-making). Participants' satisfaction with the information was evaluated in three studies. The participation rate was defined as an outcome in eight of the studies.

RoB assessment and quality of the evidence

RoB at the study level was rated as low for two RCTs and as high for three. The main reasons for high RoB were unclear randomisation sequence generation and missing information regarding adequate allocation concealment.

RoB at the outcome level was rated as low for two RCTs. For the other three RCTs in which RoB at the study level was already classified as high, there was consequently high RoB at the outcome level.

Depending on the outcome assessed, the quality of the evidence ranged from very low to moderate.

Results on clinical effectiveness and safety

Increased knowledge

Data on the change in knowledge about lung cancer screening were available from two RCTs with low RoB, two RCTs with high RoB, four other studies with low RoB and four other studies with high RoB.

When compared to standard information material on cancer screening, the use of decision aids or information films in the shared decision-making process before lung cancer screening increased knowledge about the benefits and risks of lung cancer screening among screening-eligible individuals.

No difference in knowledge was reported for different screening invitation strategies (targeted vs standard invitation material) for lung cancer screening.

Informed decision-making

Data on informed decision-making was available from one RCT with low RoB, one RCT with high RoB, one single-arm study with low RoB, and one single-arm and one comparative study with high RoB.

One RCT and one observational study, both comparing the use of decision aids in the information process for lung cancer screening compared to standard information materials for cancer screening, reported significantly better rates of shared decision-making scores for the decision aid group.

No difference in shared decision-making scores was reported in one RCT comparing different decision-making strategies/tools (option grid vs decision aid). In addition, two single-arm studies reported that the majority of participants felt well informed about lung cancer screening after the intervention.

Participant empowerment

Data on participant empowerment was available from two RCTs with low RoB, two RCTs with high RoB, three single-arm studies with low RoB, and one single-arm and one comparative study with high RoB.

In comparisons of the use of decision aids or information films in the information process for lung cancer screening to written standard information materials for lung cancer screening, there was significantly less decisional regret regarding screening participation in the decision aid/information film groups. In addition, all single-arm studies investigating the use of decision aids reported low scores on the Decisional Conflict Scale after the intervention. In comparisons of different decision-making strategies/tools, the use of option grids resulted in less decisional regret when compared to the use of decision aids.

No difference in participant empowerment was reported for different screening invitation strategies (targeted vs standard invitation material) for lung cancer screening.

Participant satisfaction

Data on participant satisfaction were available from one RCT with low RoB and two comparative studies with high RoB.

Different screening invitation strategies (targeted vs standard invitation material), different screening information materials (decision aid vs standard information material) or different information delivery modes (in-person vs telephone) did not result in any difference in the satisfaction of participants with their decision regarding screening or their satisfaction with the information process.

Screening participation rate

Data on the screening participation rate were available from two RCTs with low RoB, two RCTs with high RoB, one single-arm study with low RoB and three comparative studies with high RoB.

In all controlled studies (RCTs and non-RCTs), no differences in lung cancer screening participation rates were reported between study groups for different invitation or information strategies. In addition, one single-arm study showed no change in intention to undergo screening after the information intervention compared to before the intervention.

Conclusion

Overall, the current evidence is not sufficient to assess the effectiveness of a particular information or invitation strategy for lung cancer screening. The use of decision aids in the lung cancer screening process probably has a beneficial effect on participants' knowledge about the benefit and harm of lung cancer screening and therefore probably increases decisional certainty on whether to participate in a screening programme or not.

The following table gives an overview of the main results for all research questions.

Summary of findings – Research question 1

Table 0.5: Summary-of-findings table for lung cancer screening in individuals with a history of smoking or current smokers without suspected lung cancer

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk without screening [b]	Risk with LDCT screening [c]				
Mortality						
Overall mortality	8–11 years after randomisation: 5 (–3 to 12) less 101 per 1,000	96 per 1000	IRR 0.95 (0.88–1.03); *p* = 0.164	I: 17,234 C: 16,469 (6 studies)	High ++++	Screening for lung cancer with LDCT results in little or no difference in overall mortality compared with no screening.
Lung cancer mortality	8–11 years after randomisation: 5 (3–8) less 28 per 1,000	23 per 1000	IRR 0.81 (0.72–0.91); *p* = 0.004	I: 17,234 C: 16,469 (6 studies)	Moderate [d] +++0	Screening for lung cancer with LDCT probably reduces lung cancer mortality compared with no screening. Without LDCT screening, 28 out of 1000 people probably die of lung cancer. With LDCT screening, 23 out of 1,000 people probably die of lung cancer. LDCT screening probably saves ~5 out of 1000 people from dying of lung cancer within ~10 years. [e]
Morbidity						
Overdiagnosis	–	0 [f] (0–1.1) to 22 (1–42) [g] per 1,000 [h]	Range (minimum–maximum) of point estimates for the risk of overdiagnosis of the individual studies in relation to persons invited for screening: 0%–2.2%	I: 15,917 C: 15,189 (6 studies)	High ++++	Screening for lung cancer with LDCT is liable to lead to harm compared to no screening owing to the higher risk of overdiagnosis, i.e. from the resulting invasive clarification diagnostics and treatment including associated complications and side effects. In the studies included, screening detects lung cancer in 0–22 out of 1000 screening participants that would not have caused any symptoms for the rest of the person's life. The risk of overdiagnosis calculated from the individual studies in relation to persons diagnosed with lung cancer during the screening phase is between 0% and 63%.
Consequences of false-negative screening results	–	–	–	–	–	Not reported in the studies.

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk without screening [b]	Risk with LDCT screening [c]				
Consequences of false-positive screening results	1–15 per 1000 –	– –	See Table 4.15	I: 17,234 C: – (6 studies)	High ++++	Screening for lung cancer with LDCT might lead to harm due to consequences of false-positive screening results. In the studies included, 1–15 persons per 1000 receive an invasive diagnostic test or an operation with subsequent benign findings. [i]
AEs after surgery for suspicious findings [j]	Maximum 8 years: 12 (2–37) more 5 per 1,000	17 per 1,000	OR 3.48 (1.41–8.62); p = 0.004	I: 1264 C: 1186 (1 study)	Low [k] ++00	Screening for lung cancer with LDCT may increase AEs compared with no screening. Without LDCT screening, 5 of every 1000 persons may suffer an AE after surgery, 2 of them an AE of severity ≥ 3. With LDCT screening, 17 of 1000 persons may have an AE after surgery, 8 of them an AE of severity ≥ 3.
AEs after surgery of severity ≥ 3 [j]	Maximum 8 years: 6 (0–36) more 2 per 1,000	8 per 1,000	OR 4.25 (0.92–19.69); p = 0.046	I: 1264 C: 1186 (1 study)	Low ++00	LDCT screening may lead to an additional AE after surgery in 12 persons, 6 of them an EA of severity ≥ 3.
Health-related quality of life						
HRQoL	–	–	–	–	–	Not reported in the studies or not usable for the assessment.

Abbreviations: C=control group; CI=confidence interval; HRQoL=health-related quality of life; I=intervention group; IRR=incidence rate ratio; LDCT=low-dose computed tomography; OR=odds ratio; AE=adverse event.[a] To calculate the absolute effects, the IRR from the meta-analysis was applied to the median risk in the control group (baseline risk).

[b] Median risk of the control group per 1000 persons.

[c] Median risk of the intervention group per 1000 invited screening participants.

[d] Downgraded by one level because the evaluation of the studies with a low risk of bias alone showed no statistically significant difference between the groups.

[e] Mean value of the observation time since randomisation.

[f] Based on the results of the ITALUNG study. Fewer lung cancer cases were diagnosed in the intervention group than in the control group. Thus, no overdiagnosis is detectable.

[g] Based on the results of the DANTE study.

[h] Using the total number of lung cancer diagnoses in the intervention group as the denominator.

[i] Among all participants invited to the screening, 0.1%–0.3% (0.04%) suffered a (severe) complication after surgery for benign findings.

[j] Results of the DANTE study, the only study to report usable data on this outcome.

[k] Downgraded by 2 levels because of high risk of bias at the study level and a wide CI.

Research question 2

No relevant studies available.

Research question 3

Table 0.6: Summary-of-findings table for biennial compared to annual LDCT lung cancer screening in individuals with a history of smoking or current smokers without suspected lung cancer

Outcome	Anticipated absolute effects [a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with biennial screening	Risk with annual screening				
Mortality						
Overall mortality	10 years after randomisation: 13 (–8 to 28) less 51 per 1000	64 per 1000	HR 0.80 (0.57–1.12); *p* = 0.191	I: 1,186 C: 1,190 (1 study)	Very low [b] +000	The evidence is very uncertain about the effect of biennial compared to annual LDCT screening on overall mortality.
Lung cancer mortality	10 years after randomisation: 2 (–7 to 17) more 18 per 1000	16 per 1000	HR 1.10 (0.59–2.05); *p* = 0.760	I: 1,186 C: 1,190 (1 study)	Very low [b] +000	The evidence is very uncertain about the effect of biennial compared to annual LDCT screening on lung cancer mortality.
All other outcomes	–		–	–	–	For this intervention, the results for other outcomes were considered irrelevant, as mortality results had very low quality. In addition, results for other outcomes were seriously imprecise.

Abbreviations: C=control group; CI=confidence interval; FR = hazard ratio; I=intervention group; LDCT=low-dose computed tomography.

[a] To calculate the absolute effects, the HR was applied to the risk in the control group with annual screening.

[b] Downgraded by 3 levels because of (i) a high risk of bias at the study level, (ii) serious imprecision because independent replication by a second study is lacking and (iii) serious statistical imprecision.

Research question 4

Table 0.7: Summary-of-findings table for different screening information strategies for individuals with a history of smoking or current smokers without suspected lung cancer

Outcome	Anticipated absolute effect (95% CI)	*N* (%) unless otherwise stated	Number of participants (studies)	Quality	Comments
Information leaflets for screening awareness					
Increased knowledge	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Informed decision-making	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant empowerment	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant satisfaction	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Screening participation rate	–	93 (38.8) vs 92 (37.7), *p* = n.r.	I: 240 C: 244 (1 non-RCT)	Very low +000	We are uncertain whether information leaflets improve the screening participation rate.
Targeted screening invitation					
Increased knowledge	–	5.7 (2.3) vs 5.5 (2.3) [a], *p* = ns	I: 388 C: 415 (1 RCT)	Low ++00	Targeted screening invitations may result in little to no difference in participant knowledge regarding lung cancer screening compared to standard invitation materials.
Informed decision-making	–	–	–	–	For this intervention, no studies were found that looked at this outcome.
Participant empowerment	–	≥ 83.2% vs ≥ 76.2% [b], *p* = ns	I: 388 C: 415 (1 RCT)	Low ++00	Targeted screening invitations may result in little to no difference in participant empowerment regarding the decision on lung cancer screening participation compared to standard invitation materials.
Participant satisfaction	–	≥ 98.7% vs ≥ 97.3% [c], *p* = n.r.	I: 388 C: 415 (1 RCT)	Low ++00	Targeted screening invitations may result in little to no difference in participant satisfaction compared to standard invitation materials.

Outcome	Anticipated absolute effect (95% CI)	*N* (%) unless otherwise stated	Number of participants (studies)	Quality	Comments
Screening participation rate	–	OR 1.47 (0.91–2.40), $p = 0.177$	I: 416 C: 429 (1 RCT)	Low ++00	Targeted screening invitations may result in little to no difference in the screening participation rate compared to standard invitation materials.
Telephone counselling for screening invitation					
Increased knowledge	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Informed decision-making	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant empowerment	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant satisfaction	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Screening participation rate	–	OR 1.10 (0.70–1.72), $p = 0.98$	I: 213 C: 218 (1 non-RCT)	Very low +000	We are uncertain whether telephone counselling in addition to an information brochure improves the screening participation rate compared to an information brochure alone.
Decision aids for screening information					
Increased knowledge	–	Significant difference in favour of decision aid (see Table 4.29)	I: 265 C: 284 (1 RCT, 1 non-RCT)	Moderate +++0	The use of decision aids probably increases knowledge about lung cancer screening compared to standard information materials.
Informed decision-making	–	Significant difference in favour of decision aid (see Table 4.31)	I: 257 C: 275 (1 RCT, 1 non-RCT)	Moderate +++0	The use of decision aids probably increases informed decision-making compared to standard information materials.
Participant empowerment	–	−14.9 (−20.1 to −9.7) [d], $p < 0.001$	I: 234 C: 233 (1 RCT)	Moderate +++0	The use of decision aids probably increases participant empowerment regarding the decision on lung cancer screening participation compared to standard information materials.
Participant satisfaction	–	4.8 (0.8) vs 4.7 (0.6) [e], $p < 0.001$	I: 30 C: 51 (1 RCT)	Very low +000	We are uncertain whether the use of decision aids improves participant satisfaction compared to standard information materials.

Outcome	Anticipated absolute effect (95% CI)	*N* (%) unless otherwise stated	Number of participants (studies)	Quality	Comments
Screening participation rate	–	OR 0.70 (0.47–1.03) [f], *p* = 0.07	I: 237 C: 238 (1 RCT)	Moderate +++0	The use of decision aids probably leads to little or no difference in the screening participation rate compared to standard information materials.
Option grid versus online decision aid for screening information					
Increased knowledge	–	64.7% vs 62.4% [g], *p* = 0.43	I: 128 C: 109 (1 RCT)	Low ++00	The use of an option grid may result in little to no difference in participant knowledge regarding lung cancer screening compared to an online decision aid.
Informed decision-making	–	97.4 vs 98.6 [h], *p* = 0.60	I: 128 C: 109 (1 RCT)	Low ++00	The use of an option grid may result in little to no difference in informed decision making compared to an online decision aid.
Participant empowerment	–	6.0 vs 10.2 [i], *p* = 0.0198	I: 128 C: 109 (1 RCT)	Low ++00	The use of an option grid may improve participant empowerment regarding the decision on lung cancer screening participation compared to an online decision aid.
Participant satisfaction	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Screening participation rate	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Screening information film					
Increased knowledge	–	MD 0.62 (0.17–1.08) [j], *p* = 0.007	I: 120 C: 109 (1 RCT)	Low ++00	The use of an information film in addition to a booklet may improve participant knowledge regarding lung cancer screening compared to an information booklet alone.
Informed decision-making	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant empowerment	–	8.5 (1.25) vs 8.24 (1.49) [k], *p* = 0.007 [l]	I: 120 C: 109 (1 RCT)	Low ++00	The use of an information film in addition to a booklet may improve participant empowerment regarding the decision on lung cancer screening participation compared to an information booklet alone.
Participant satisfaction	–	–	–	--	For this intervention, no studies that looked at this outcome were found.

Outcome	Anticipated absolute effect (95% CI)	*N* (%) unless otherwise stated	Number of participants (studies)	Quality	Comments
Screening participation rate	--	76.7% vs 78.9% [m], *p* = 0.66	I: 120 C: 109 (1 RCT)	Low ++00	An information film in addition to a booklet may result in little to no difference in the screening participation rate compared to an information booklet alone.
Delivery mode for SDM counselling					
Increased knowledge	–	–	–	–	For this intervention, no studies were found that looked at this outcome.
Informed decision-making	–	–	–	–	For this intervention, no studies that looked at this outcome were found.
Participant empowerment	–	11.3 (3.4) vs 12.1 (3.4) [k], *p* = n.r.	I: 69 C: 68 (1 non-RCT)	Very low +000	We are uncertain whether in-person SDM counselling improves participant empowerment compared to telephone counselling.
Participant satisfaction	–	26.7 (2.8) vs 24.6 (5.6) [n], *p* = n.r.	I: 69 C: 68 (1 non-RCT)	Very low +000	We are uncertain whether in-person SDM counselling improves participant satisfaction compared to telephone counselling.
Screening participation rate	–	88.4% vs 88.2% [o], *p* = n.r.	I: 69 C: 68 (1 non-RCT)	Very low +000	We are uncertain whether in-person SDM making counselling improves the screening participation rate compared to telephone counselling.

Abbreviations: C=control group; CI=confidence interval; I=intervention group; LDCT=low-dose computed tomography; MD=mean difference; n.r.=not reported; ns=not significant; OR=odds ratio; RCT=randomised controlled trial; SD=standard deviation; SDM=shared decision-making.

[a] Knowledge score; mean (SD).

[b] Percentage of participants with low decisional conflict.

[c] Percentage of participants satisfied with their decision.

[d] Decisional Conflict Scale; MD (95% CI).

[e] Satisfaction score; mean (SD).

[f] Scheduled for screening within 1 year.

[g] Percentage of participants with correct answers.

[h] Mean CollaboRATE SDM score.

[i] Mean score for the Decisional Conflict Scale.

[j] Objective knowledge score; MD (95% CI).

[k] Decisional Conflict Scale; mean (SD).

[l] Multivariable analysis using multiple linear regression (which assumes that residuals, not the raw scores, are normally distributed) adjusted for baseline scores, age, educational level, ethnicity, Index of Multiple Deprivation score and smoking duration.

[m] Percentage of participants with LDCT completion.

[n] Decisional satisfaction score; mean (SD).

[o] Percentage of participants with LDCT completion.

Discussion

Every screening strategy causes harm through false screening results and overdiagnosis. Screening is only justified if the harm is more than outweighed by the benefit. When weighing up the benefits and harms, it must also be taken into account that the results are weighted differently for the various outcomes.

Benefit

The studies have shown that LDCT screening probably reduces the risk of lung cancer death in (formerly) heavy smokers. LDCT screening prevents approximately 5 out of 1000 individuals (95% CI 3–8) from dying of lung cancer within approximately 10 years. On the basis of the study results, however, it cannot be statistically proven that overall mortality is also improved by screening. It is conceivable that, owing to competing causes of death, in particular other tobacco-related diseases such as other cancers and cardiovascular diseases, some of the screening participants saved from lung cancer death might die at a comparable time and thus the life span of these individuals might not be significantly extended.

The recently published NELSON study in particular highlighted this problem [54] Despite a statistically significant reduction in lung cancer mortality (IRR 0.76, 95% CI 0.61–0.94), no detectable change in overall mortality was found in the main analysis (IRR 1.01, 95% CI 0.92–1.11). Instead, the study found that other causes of death tended to occur more frequently. Critics have thus argued that LDCT screening might only lead to “an exchange of death from lung cancer for death from another cause” [200], without conveying an overall mortality benefit [201]. However, the figures quoted by the authors for the NELSON study refer to men alone, whereas in the meta-analysis in this report, a numerical reduction in overall mortality among women was quite visible (Figure 4.4). In this report, the NELSON study was included with data for both men and women (16% of the study population).

Overall, the results for overall mortality do not contradict the results for lung cancer mortality. Thus, the two estimators of the respective meta-analyses point in the same direction. Moreover, the absolute effect estimate and its corresponding CI for overall mortality are similar to the effect for lung cancer mortality: The estimate for the absolute effect is 5 per 1,000 persons (95% CI –3 to 12) for overall mortality and 5 per 1,000 persons (95% CI 3–8) for lung cancer mortality within approximately 10 years. It is therefore considered likely that the effect of LDCT screening on lung cancer mortality is also reflected in overall survival. In conclusion, screening for lung cancer with LDCT may reduce mortality compared when with no screening.

Harm

Results for adverse events after surgery indicate harm in itself. However, very few data were available on adverse events (all forms of treatment) for the intervention and comparison groups, so the actual harm based on these data is unclear (see Section 5.7). However, it can be assumed that the effect of screening on the rate of adverse events is essentially represented by the overdiagnosis. Harms resulting from radiation exposure are specifically described in Section 5.9.

No data were available on consequences of false-negative screening results. In the case of false-negative screening results, individuals falsely believe that they have no lung cancer. The most significant consequence would be to ignore symptoms, which could delay diagnosis and subsequent

treatment. However, should this result in an increase in mortality, this would be reflected in the lung cancer mortality outcome. Overall, the influence of the lack of specific data on consequences of false-negative screening results on the balancing of benefit and harm is estimated to be small. In the case of false-positive screening results, individuals suffer harm through the reporting of a worrying finding, through the subsequent diagnostic workup and through the complications associated with this. According to the results of this assessment, 1–15 of every 1,000 participants invited for lung cancer screening will receive an invasive diagnostic workup or lung resection with subsequent benign findings. The most common complication of lung biopsy is pneumothorax [202]. The risk of developing pneumothorax varies, depending on the biopsy procedure and the location of the pulmonary nodule. Some of these individuals will require thoracic drainage.

It is conceivable that removal of a benign pulmonary nodule could also provide information about other diagnoses and prevent future complications (e.g., retention pneumonia). For example, the NELSON study documented incidental findings in the screening group [72]. A systematic investigation of incidental findings on LDCT screening was not performed for the present assessment, as information on such events and their consequences is only available for the screening groups. It therefore remains unclear whether these findings benefit or harm individuals. Although the NLST study considered random findings in both groups, chest X-ray screening is again not an adequate comparator for investigating the effect compared to no screening. For example, Loomans-Kropp et al. [168] investigated whether random findings can lead to an increase in the incidence and overdiagnosis of thyroid carcinoma. In the authors' view, the data could indicate this. After a median observation period of 6.6 years and 6.5 years in the intervention and control groups, respectively, 35 thyroid carcinomas were diagnosed in the LDCT screening group (n = 26 457) and 25 in the chest X-ray screening group (n = 26 238). In total, seven of the 60 individuals with thyroid cancer died, six of them from the LDCT screening group, with malignant neoplasia of the thyroid gland being the cause of death in only three. Other causes of death were other diagnoses of cancer and heart disease.

The risk of overdiagnosis related to those with a lung cancer diagnosis during the screening phase varied greatly between studies, ranging from 0% (no overdiagnosis in the ITALUNG study) to 63% (in the DLCST study). The studies showed that an estimated 0–22 out of every 1,000 individuals invited for lung cancer screening were diagnosed with lung cancer that would not have caused symptoms for the rest of their lives.

No usable data were available for the HRQoL outcome. It can be assumed that the reporting of a suspicious finding for screening participants impairs their HRQoL. Since this effect is likely to be only short-term in the case of false-positive results, only the screening participants with true-positive results can be expected to be significantly impaired. The effect of screening on HRQoL is therefore likely to be partly reflected by the effect on the overdiagnosis outcome.

Other risk groups

In addition to tobacco smoking, which is considered the main risk factor for lung cancer, many other factors increase the risk of developing lung cancer. For this rapid effectiveness assessment, only RCTs that reported results on screening for lung cancer in current or former smokers could be identified. There is currently no direct evidence from RCTs of lung cancer screening in individuals with risk factors for lung cancer other than tobacco smoking. It is not possible to transfer the results to individuals with other risk factors for lung cancer because of (possible) differences in lung cancer risk, disease course, the diagnostic accuracy of screening or diagnostic tests, and treatment effectiveness.

Biomarkers

The use of biomarkers is expected to improve the accuracy of screening for lung cancer and to reduce false-positive results and associated unnecessary further diagnostic procedures. Studies using data from the LDCT arms of lung cancer screening RCTs showed the potential for higher specificity and positive predictive value of multimodal screening using biomarkers and LDCT when compared to LDCT alone. Nevertheless, no comparative studies investigating such a multimodal lung cancer screening strategy with LDCT and additional biomarkers compared to a strategy using LDCT alone is currently available.

Screening strategies

In terms of organisational variations in screening with and without invitation, approaches in the studies could not be assigned to any clear categories. In some studies (e.g., NELSON and LUSI) a sample was identified from population registries and questionnaires on smoking history were sent out. The recruitment in other studies (e.g., MILD and DLCST) was based on public announcements or campaigns to attract candidates to screening. As a third option, potentially eligible individuals were identified and invited by general practitioners (e.g., ITALUNG). Different recruitment strategies were also combined in some trials. However, with regard to screening intervals, the RCTs included were largely comparable and used mostly annual screening. Nevertheless, one of the RCTs, MILD, was a three-arm study in which participants in the intervention groups were screened either annually or biennially. According to the 10-year data from that study, biennial as compared to annual LDCT screening results in similar overall mortality and similar lung cancer mortality. Taking into account the very low quality of the available evidence, the evidence is very uncertain about the effect of biennial compared to annual LDCT screening on mortality. However, questions concerning the implementation of screening are being examined in a recently launched European study (4-IN THE LUNG RUN) [203].

Information strategies

Screening for lung cancer differs from other cancer screenings in that the target group cannot be clearly defined by age or sex, but includes individuals with different risk factors. One challenge is therefore to identify and invite suitable candidates for screening. Another important aspect of screening programmes is to inform potential participants about the potential benefits and harms of the test. The current evidence for general information or invitations to screening for lung cancer is generally weak and does not allow a clear statement regarding a suitable strategy. Within a lung cancer screening programme, the use of decision aids for shared decision-making might be beneficial, since this increases participants' knowledge regarding benefits and harms and reduces their decisional conflict. However, shared decision-making requires appropriate training of physicians, the provision of suitable evidence-based tools such as decision aids, and time and personnel resources.

Concluding summary

High-quality evidence shows that screening for lung cancer with LDCT in (former) heavy smokers results in little or no differences in overall mortality when compared with no screening. For lung cancer mortality, moderate-quality evidence shows that screening for lung cancer with LDCT probably reduces lung cancer mortality when compared with no screening. Since the absolute effects and

corresponding CIs are of a similar order of magnitude for overall and lung cancer mortality, the assumption that screening also has a positive effect on overall mortality seems justified. Taking together the considerations for the two suboutcomes for mortality, we can conclude that screening for lung cancer with LDCT may have a mortality benefit.

However, screening for lung cancer with LDCT may increase adverse events and lead to harm due to the consequences of false-positive screening results. In addition, it leads to harm in terms of overdiagnosis. The consequences of false-negative screening results were not reported in the studies. Their influence on the balancing of benefit and harm is estimated to be small. Data from only one study were available for the adverse events outcome and no usable data were available for the HRQoL outcome. However, the effect of screening on the rate of adverse events and on HRQoL is likely to be partly covered by the effect on the overdiagnosis outcome.

LDCT screening probably saves approximately 5 out of 1,000 individuals (95% CI 3–8) from dying of lung cancer within approximately 10 years and may potentially extend the life of some of these screening participants compared to no screening. The benefit in terms of mortality is mainly opposed by the harm resulting from false-positive screening results and overdiagnosis. False-positive screening results lead to invasive procedures that would not have been performed without the screening in at least 1 in 1,000, but at most 15 in 1,000 individuals. These procedures can cause complications such as the occurrence of pneumothorax. Overdiagnosis is considered as harm because of the unnecessary subsequent diagnostic procedures and therapy, including the resulting complications. The risk of overdiagnosis in the individual studies is between 0 and 22 per 1,000 individuals invited for screening. The risk of overdiagnosis in the presence of screening-detected lung cancer is between 0% and 63% in the individual studies. This underlines how important it is for a positive benefit-to-harm ratio to keep the risk of overdiagnosis low in optimal screening strategies.

For risk groups other than (former) heavy smokers, no studies investigating lung cancer screening using LDCT compared to no screening could be identified. It is not possible to transfer the potential benefit of screening for lung cancer by LDCT in (former) heavy smokers to individuals with other risk factors for lung cancer because of (possible) differences in lung cancer risk, disease course, the diagnostic accuracy of screening or diagnostic tests, and treatment effectiveness.

For the use of biomarkers as an adjunct to LDCT in lung cancer screening, no evidence from RCTs is currently available.

No conclusion can be drawn on how best to reach individuals eligible for screening, because the studies currently available used different recruitment strategies without obvious differences in effectiveness between the strategies. With regard to screening interval, the overall evidence is insufficient to use a screening interval other than 1 year.

Current evidence is insufficient to conclude whether there is an appropriate information strategy to reach the target groups for lung cancer screening. Moderate-quality evidence shows that the use of decision aids before LDCT for participants eligible for lung cancer screening probably increases their knowledge about the benefits and harms of lung cancer screening and probably reduces their decisional conflict for or against screening participation.

1 BACKGROUND

1.1 Overview of the disease, health condition and target population

HTA CORE MODEL DOMAIN: CUR[3]

1.1.1 Description of the health condition: lung cancer

Lung cancer is a malignant growth of cells in the lung or bronchial system [2]. Some 95% of lung malignancies can be classified as non–small-cell carcinoma (79%) or small-cell carcinoma (16%). Rarely occurring tumours such as carcinoid tumours account for the remaining 5% of primary lung cancers. Non–small-cell carcinomas are further classified as adenocarcinoma, large-cell carcinoma, squamous cell carcinoma or undifferentiated carcinoma. Individual tumours can have characteristics of several of these subgroups. Of the above, adenocarcinoma is the most common subtype [204]. The occurrence of small-cell lung cancer (SCLC) has decreased [205].

According to the tumour node metastasis (TNM) staging system developed by the International Association for the Study of Lung Cancer, four disease stages (stage I, II, III and IV) can be determined, for which the primary tumour characteristics (T) and the presence or absence of regional lymph node involvement (N) and distant metastases (M) are taken into account [206]. Determination of the stage of a lung cancer is based on a combination of these factors.

- Stage I lung cancer is a small tumour that has not spread to any lymph nodes. There is no bronchoscopic evidence of invasion in the main bronchus. Depending on tumour size, stage I is divided into substages. In principle, a stage I tumour is ≤ 3 cm in greatest dimension.
- Stage II tumours, which are also divided into substages, are > 3 cm and ≤ 5 cm in size or have one of the following features: the main bronchus is involved without involvement of the carina, the tumour invades the visceral pleura, or the tumour is associated with atelectasis or obstructive pneumonitis either involving part of or the entire lung.
- Stage III tumours are > 5 cm but not > 7 cm in size or have already directly affected one or more of the following: the parietal pleura, phrenic nerve, parietal pericardium or chest wall, or there are associated separate tumour nodules in the same lobe as the primary tumour.
- Stage IV tumours are > 7 cm in size and affect one or more of the following: the mediastinum, diaphragm, heart, great vessels, trachea, vertebral body, recurrent laryngeal nerve, oesophagus or carina, or there are separate tumour nodules in an ipsilateral lobe to the primary tumour [207-209].

The symptoms of lung cancer are rather nonspecific and usually appear when the disease has already spread to other parts of the body. The following symptoms and clinical signs are characteristic for lung cancer: cough (8%–75%), weight loss (0%–68%), shortness of breath (3%–60%), chest pain (20%–49%), haemoptysis (6%–35%), bone pain (6%–25%), fever (0%–20%) and a feeling of weakness (0%–10%). Approximately one-third of the symptoms are caused by the primary tumour. In a further one-third of cases, systemic symptoms such as anorexia, weight loss or weakness (asthenia) occur; in another one-third of cases, specific symptoms are present for a defined metastasis site. The most common symptom of primary lung carcinoma is cough, followed by dyspnoea, chest pain and haemoptysis or expectoration of bloody sputum. Other manifestations such

[3] This section addresses the following elements in the CUR domain of the HTA core model: A0002, A0003, A0004, A0005, A0007 and A0023.

as vena cava-superior syndrome, dysphagia and stridor are rather rare [210]. At the time of diagnosis, patients rarely have only one symptom of lung cancer, and the positive predictive value is higher when two or more symptoms occur [211].

Lung cancer can be triggered by certain diseases such as human immunodeficiency virus infection, idiopathic pulmonary fibrosis, COPD and tuberculosis, or may be associated with a family history of lung cancer [211].

Prevalence

Lung cancer is the fourth most frequently diagnosed cancer in the EU, affecting more than 312,000 individuals. Only breast, colorectal and prostate cancers have higher incidence rates. Europe, along with North America, has the world's highest age-standardised rate of lung cancer incidence. With an age-standardised rate of 51.6 per 100,000, which is 20 points higher than the EU average, Hungary is the country with the highest incidence of lung cancer. The probability of developing lung cancer is approximately 11 times higher for smokers than for nonsmokers. Moreover, lung cancer is the second and third most common cancer diagnosis among men and women, respectively. Approximately 213,663 men and 98,982 women in Europe develop lung cancer annually. The data show that more men worldwide develop lung cancer, but the incidence among women is rising. The highest smoking rates among women were found in Austria, Bulgaria and Greece, but the risk of lung cancer is still higher among women in northern countries. This is probably because of the 20-year lag in the correlation between smoking prevalence and lung cancer incidence. Denmark and the Netherlands currently have the highest incidence rates among women (4 in every 100 women will develop lung cancer), followed by the UK, Ireland and Norway (3 in 100). Hungary, Poland, Romania, Croatia and Latvia have the highest incidence of lung cancer among men [212].

1.1.2 Risk factors for lung cancer

1.1.2.1 Tobacco smoking

Smoking is by far the most important cause of lung cancer, accounting for 90% of cases among men and 80% among women [213, 214]. It is estimated that individuals who smoke are 11 times more likely to develop lung cancer compared to those who have never smoked (pooled relative risk ratio 10.92, 95% CI 8.28–14.40). The risk is similar for men (ninefold higher) and women (12-fold higher). The risk increases with smoking duration and the number of cigarettes smoked. A pooled analysis of 13 studies reporting pack-years found that cigarette consumption of < 20 pack-years resulted in a significant threefold increase in the risk of developing lung cancer; the increase in risk was sevenfold for 20–40 pack-years, 11-fold for 40–60 pack-years and 12-fold for > 60 pack-years [215]. At 15–20 years after stopping smoking, the risk of lung cancer was reduced by 90% in comparison to people who continue to smoke. The number of life years added by stopping tobacco smoking was higher for cessation at a younger age: cessation in the 30s added 10 years to life, while cessation at approximately 60 years of age added only 4 years [216].

Passive smoking, also known as second-hand smoke or environmental tobacco smoke, is also associated with a higher risk of lung cancer. People who are exposed to passive smoke during adulthood are 1.41 times more likely to develop lung cancer compared to never-smokers unexposed to passive smoke (relative risk ratio 1.41, 95% CI 1.21–1.65) [217]. Passive smoke is classed as cancer-causing by the World Health Organization and there are no safe levels of exposure (categorised as a Class A carcinogen by the International Agency for Research on Cancer) [218].

According to the World Health Organization, all forms of tobacco use are harmful, including e-cigarettes, heat-not-burn products and smokeless tobacco. However, no long-term studies have yet investigated the impact of these types of product across an individual's lifetime [219].

Prevalence

Tobacco consumption in the EU countries is registered in the Eurostat databases, in which current smokers are defined as individuals who smoke manufactured or hand-rolled cigarettes daily or occasionally. Daily smoking includes two levels of consumption: < 20 cigarettes per day and > 20 cigarettes per day [220]. According to the 2014 data set, among the 28 EU member states for which data were available, the proportion of daily smokers was 19.2% (men: 23.0%; women: 15.6%). In 2014, 5.9% of the population aged > 15 years consumed at least 20 cigarettes per day and approximately 12.6 % consumed < 20 per day. Among men, the proportion of heavy smokers in the adult population was ≤ 10.7% in most countries, while it exceeded one-fifth in Cyprus and Greece. Among women, this proportion did not exceed 10.0 % in any member state, with proportions of ≤ 1.2% in Romania, Sweden, Lithuania and Finland, and ≥ 6.5 % in Bulgaria, Croatia and Austria, with a peak of 9.4% in Greece [220].

The prevalence of occasional smokers in the 28 EU member states reached 4.7% in 2014. Hungary was the country with the lowest level (1.6%) and Ireland had the highest percentage of individuals who smoke less than daily (7.4%). By sex, the percentage of occasional smokers was similar, at 5.5% (range 1.8%–8.4%) for males and 4.0% (range 1.5%–6.8%) for females. In addition, the distribution of rates by country was similar, apart from the proportion of female occasional smokers, which was the highest in Czechia. The proportion of occasional smokers decreased stepwise in by age group, varying from 7.8% for those aged 15–24 years to 2.2% for the group aged 65–74 years [220].

Data on smoking rates including other tobacco products such as cigars, cigarillos and pipes were reported in the 2017 Eurobarometer database. According to this report, the proportion of individuals currently smoking cigarettes, cigars, cigarillos or a pipe daily or occasionally among the 28 EU member states was 26% (men: 30%; women: 22%). Among those who smoke, approximately 70% used boxed cigarettes at least once daily, while 23% consumed hand-rolled cigarettes daily. Consumptions of cigars, cigarillos or a pipe on a daily basis each accounted for 1% of the smokers. Among occasional smokers, the proportion of cigar or cigarillo smokers was 8% and of pipe smokers was 4% [221].

According to the 2017 Eurobarometer database, the proportion of former smokers among the 28 EU member states was approximately 20%. In addition, 31% of former smokers stopped smoking more than 20 years previously, similar proportions stopped 11–20 years or ≤ 5 years previously (26%) and 16% gave up the habit between 6 and 10 years previously [221].

Table 1.1, Table 1.2 and Table 1.3 show tobacco smoking prevalence by country, sex, age, level of cigarette consumption (> 20 vs < 20 pack-years), former or current smoker and years of smoking cessation in the case of ex-smokers (> 20 vs < 20 years since quitting).

Table 1.1: Prevalence of current smokers in the 28 EU member states (percentage of the population)

		<45 years of age [a]		>45 years of age		<45 years of age [a]		>45 years of age	
		Daily	Occasional	Daily	Occasional	Daily	Occasional	Daily	Occasional
Country	BE [b]	23.4	6.4	36.9	6.1	17.8	4.5	28.8	4.2
	BG	41.1	8.0	56.3	11.5	29.8	9.6	26.9	6.9
	CZ	29.5	8.9	46.9	12.3	16.2	9.4	29.1	8.8
	DK	12.3	11.2	32.7	10.4	11.1	11.1	25.4	6.5
	DE	20.1	10.4	28.4	7.5	16.2	7.8	27.2	5.6
	EE	23.9	6.1	61.4	5.2	18.2	4.8	25.9	6.2
	IE	16.5	12.2	26	8	15.6	9.3	22.9	7
	EL	38.5	7.3	55.4	8.8	26.0	6.3	34.4	7.8
	SP	31.8	3.6	44.1	2.8	23.9	3.2	28.8	1.7
	FR	32.2	9.3	34.6	8.4	27.8	7.6	25.9	6.4
	HR	32.4	3.6	46.9	4.9	24.8	5.5	33.1	6.1
	IT	26.2	8.9	35.5	7.8	14.8	6.0	25.1	5
	CY	41.0	4.2	59.7	4.3	15.8	3.7	15.6	4.0
	LV	39.4	8.7	61.7	5.9	18.5	6.8	23.7	4.2
	LT	33.1	8.0	61.5	8.6	13.4	4.0	11.1	4.5
	LU	18.1	8.2	24.3	9.4	14.5	7.9	19.7	3.5
	HU	36.5	2.4	49.1	2.1	23.3	2.6	34.5	1.2
	MT	23.8	5.8	40.8	4.1	19.3	5.2	24.8	3.7
	NL	23.1	10.0	34.1	9.2	16.5	7.9	31.2	6.2
	AT	31.0	9.1	35.3	7.5	25.4	6.7	31.3	6.7
	PL	27.3	4.7	54.1	4.8	15.3	3.8	34.5	4.4
	PT	28.3	5.9	35.7	4.9	15.9	4.0	13	1.8
	RO	35.0	9.2	51.1	10.4	11.7	6.1	9.9	4.8
	SI	23.2	8.4	31.4	6.5	19.3	7.4	24.3	5.6
	SK	32.9	8.4	47.7	11.3	18.8	8.2	22.3	6.2
	FI	14.1	12.1	26.7	8.5	13.0	9.5	18.3	5.8
	SE	6.1	11.4	17.5	7.9	7.4	7.9	23.1	6.8
	UK	17.7	4.8	24.1	4.4	15.6	3.7	23.3	2.9

Source: European Commission. Eurostat. Smoking of tobacco products by sex, age and country of birth. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_sk1b&lang=en

Abbreviations: BE=Belgium; BG=Bulgaria; CZ=Czechia; DK=Denmark; DE=Germany; EE=Estonia; IE=Ireland; EL=Greece; SP=Spain; FR=France; HR=Croatia; IT=Italy; CY=Cyprus; LV=Latvia; LT=Lithuania; LU=Luxembourg; HU=Hungary; MT=Malta; NL=Netherlands; AT=Austria; PL=Poland; PT=Portugal; RO=Romania; SI=Slovenia; SK=Slovakia; FI=Finland; SE=Sweden; UK=United Kingdom.

[a] This range includes the population aged from 15 to 44 years.

[b] According to the database, these data have low reliability.

Table 1.2: Prevalence of the level of consumption of current smokers in the 28 EU Member states (percentage of the population)

		Male				Female			
		<45 years of age [a]		>45 years of age		<45 years of age [a]		>45 years of age	
		<20 cigarettes/ day	>20 cigarettes/ day	<20 cigarettes/ day	>20 cigarettes/ day	<20 cigarettes/ day	>20 cigarettes/ day	<20 cigarettes/ day	>20 cigarettes/ day
Country	BE [b]	14.1	7.8	22.7	16.8	11.8	4.0	20.1	14.3
	BG	18.9	21.4	30.2	33.9	19.7	9.0	18.9	9.7
	CZ	19.4	10.3	38.1	21.3	14.3	1.9	28.7	6.1
	DK	8.3	4.0	19.3	14	7.9	2.6	25.9	6.7
	DE	13.3	6.5	19.2	15.5	12.3	3.2	21.2	6.8
	EE	19.7	11.7	28.6	13.5	15.6	1.8	24.4	5.5
	IE	9.6	4.0	10.9	9.8	11.6	2.4	19.8	9.2
	EL	15.8	23.0	23.5	44.8	15.3	10.4	22	19.1
	SP	21.4	8.5	29.7	20.3	17.6	4.7	18.6	9.2
	FR	23.0	7.8	22.8	10.8	21.7	2.7	22.2	6.3
	HR	15.0	16.5	20.6	34.5	17.4	7.3	25.6	13.5
	IT	17.8	8.1	25	19.6	11.9	2.7	24.2	7.5
	CY	21.8	19.6	26	48.4	12.5	4.8	12	9.4
	LV	23.6	15.6	46.1	28.2	16.2	2.0	23	5.6
	LT	20.4	12.8	45.6	28.5	11.9	1.5	11.5	1.3
	LU	11.1	6.3	15.9	14.5	10.4	2.6	14.1	8.1
	HU	26.9	9.6	41.5	22.1	20.0	3.0	35.2	5.7
	MT	14.3	9.1	19	27.9	13.3	5.3	17.7	11.7
	NL	16.7	5.1	26.1	11	14.0	2.2	29.2	9.4
	AT	19.4	12.9	21.1	21.9	19.8	7.9	26.1	11.3
	PL	13.4	13.0	30	37.6	10.7	4.0	27.1	13.4
	PT	17.0	9.7	20	19.8	12.3	3.2	10.7	4.8
	RO	25.0	10.0	47.7	15.2	10.1	1.6	9.3	2.1
	SI	13.6	9.3	17.3	22.2	15.3	3.3	20.7	7.5
	SK	24.2	8.3	41.9	6.8	16.2	2.2	23.4	2.6
	FI	13.2	0	27.6	0	12.3	0	22.1	0
	SE	6.7	0.9	15.7	4.2	6.9	0.8	27.6	3.2
	UK	13.1	4.3	17.4	9.8	12.3	2.4	21.8	7.5

Source: European Commission. Eurostat. Smoking of tobacco products by sex, age and country of birth. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_sk1b&lang=en

Abbreviations: BE=Belgium; BG=Bulgaria; CZ=Czechia; DK=Denmark; DE=Germany; EE=Estonia; IE=Ireland; EL=Greece; SP=Spain; FR=France; HR=Croatia; IT=Italy; CY=Cyprus; LV=Latvia; LT=Lithuania; LU=Luxembourg; HU=Hungary; MT=Malta; NL=Netherlands; AT=Austria; PL=Poland; PT=Portugal; RO=Romania; SI=Slovenia; SK=Slovakia; FI=Finland; SE=Sweden; UK=United Kingdom.

[a] This range includes the population aged from 15 to 44 years.

[b] According to the database, these data have low reliability.

Table 1.3: Prevalence of former smokers in the 28 EU Member states (percentage of the population)

Country (number of former smokers)		Male		Female		<45 years of age [a]		>45 years of age	
		<20 years of quitting	>20 years of quitting	<20 years of quitting	>20 years of quitting	<20 years of quitting	>20 years of quitting	<20 years of quitting	>20 years of quitting
	BE (245)	64	34	73	27	100	0	53.1	46.9
	BG (129)	97	23	95	5	100	0	48.1	51.9
	CZ (197)	76	24	74	26	99	1	94.4	5.6
	DK (329)	69	31	64	36	98.2	1.8	68.7	31.3
	DE (318)	63	37	68	32	99.7	0.3	65.4	34.6
	EE (243)	66	34	70	30	98.8	1.2	68.8	31.2
	IE (185)	64	36	75	25	99.5	0.5	69.2	30.8
	EL (193)	77	23	84	16	99.5	0.5	79.8	20.2
	SP (228)	74	26	76	24	100	0	74.6	25.4
	FR (216)	57	43	73	27	99.5	0.5	64.4	35.6
	HR (162)	70	30	78	22	100	0	72.8	27.2
	IT (139)	82	18	80	20	100	0	81.3	18.7
	CY (87)	64	36	77	23	100	0	66.7	33.3
	LV (228)	74	26	68	32	99.6	0.4	71.9	28.1
	LT (180)	80	20	71	29	99.5	0.5	97.2	22.8
	LU (113)	63	37	70	30	100	0	66.4	33.6
	HU (153)	68	32	74	26	100	0	69.9	30.1
	MT (95)	61	39	74	26	100	0	67.4	32.6
	NL (322)	57	43	53	47	99.7	0.3	55	45
	AT (187)	78	22	77	23	99.5	0.5	78.1	21.9
	PL (177)	71	29	76	24	100	0	72.9	27.1
	PT (149)	59	41	77	23	99.3	0.7	63.8	36.2
	RO (162)	68	32	87	13	100	0	72.4	27.6
	SI (199)	57	43	74	26	99.0	1.0	64.3	35.7
	SK (169)	86	14	72	28	99.4	0.6	81.1	18.9
	FI (294)	59	41	67	33	99.3	0.7	63.6	36.4
	SE (409)	64	36	56	44	99.8	0.2	60.2	39.8
	UK (300)	69	31	70	30	100	0	69.7	30.3

Source: European Commission. Eurostat. Smoking of tobacco products by sex, age and country of birth. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_sk1b&lang=en

Abbreviations: BE=Belgium; BG=Bulgaria; CZ=Czechia; DK=Denmark; DE=Germany; EE=Estonia; IE=Ireland; EL=Greece; SP=Spain; FR=France; HR=Croatia; IT=Italy; CY=Cyprus; LV=Latvia; LT=Lithuania; LU=Luxembourg; HU=Hungary; MT=Malta; NL=Netherlands; AT=Austria; PL=Poland; PT=Portugal; RO=Romania; SI=Slovenia; SK=Slovakia; FI=Finland; SE=Sweden; UK=United Kingdom.

[a] This range includes the population aged from 15 to 44 years.

1.1.2.2 Chronic obstructive pulmonary disease

COPD and lung cancer are caused by cigarette smoking but there is increasing evidence that COPD is an independent risk factor for lung carcinoma, particularly for squamous cell carcinoma, and lung cancer is more likely to occur in smokers with airflow obstruction than those with normal lung function. A recent meta-analysis involving 12,442 lung cancer cases with median follow-up of 5 years concluded that a history of COPD conferred a relative risk of 2.06 (95% CI 1.50–2.85) for the development of lung cancer [222]. Stratification by COPD severity yielded risk of 1.46 for mild, 2.05 for moderate and 2.44 for severe COPD. There were similar risk estimations for never- and ever-smokers. The risk was significantly higher for squamous cell cancer than for adenocarcinoma and for small cell cancer of the lung ($p < 0.05$).

Prevalence

The precise prevalence of COPD in Europe is unknown. The Global Burden of Disease Study 2017 [223], a comprehensive study based on the literature, survey data, surveillance data, inpatient admission records, outpatient visit records and health insurance, estimates that COPD prevalence ranges from 5.17% to 11.03% among the EU 28 member states [224]. The lowest prevalence rates were in Italy (5.17%), Finland (5.41%) and France and Cyprus (5.46%), while the highest was in Hungary (11.02%), followed by Bulgaria (10.39%) and Austria (9.69%).

Estimates from several population-based studies identified in a 2012 SR that assessed all spirometry-defined COPD varied from 2.1% to 26.1% [225]. The countries with the highest prevalence rates were Austria, Denmark, Poland and Sweden, but estimates differed widely between geographical areas. The reasons for these variations include sex, age, survey methods, diagnostic criteria, analytical approaches and age distribution. The international population-based Burden of Obstructive Lung Disease (BOLD) study aimed to use standardised survey methods and a spirometric criterion for COPD to allow direct comparison between study populations. The overall prevalence of spirometry-defined COPD (forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] < 0.7; FEV1 < 80% of predicted value) calculated using data from nine countries was approximately 10% (range 3.9%–18.1%). A recent meta-analysis that included all population-based studies published between 2014 and 2015 that used the Global Initiative for Chronic Obstructive Lung Disease definition (FEV1/FVC < 0.7) estimated that the overall prevalence of COPD in these European countries (22 studies; 11 countries) was 13.29% (11.22%–15.31%) and 18.03% among males (15.66%–20.39%) and 11.06% among females (9.23%–12.89%) [226]. By stage, the COPD prevalence was 7.74% (5.79%–9.64%) for stage I, 8.14% (6.95%–9.33%) for stage II and 1.89% (1.40%–2.37%) for stage III/IV. Prevalence increased with age and was more than twice as high among individuals who smoked in comparison to nonsmokers. The results of the main COPD studies are reported in Table 1.4.

Table 1.4: Prevalence (%) of COPD in Europe

Country	GBDS (2017) [224]		SR of population-based studies [225]		BOLD study [227]
	Prevalence	Limits	Study period	Prevalence range	
Austria	9.69	8.44–11.10	2005–2009	16.6–26.1	15.8
Belgium	8.67	7.64–9.80			
Bulgaria	10.39	9.00–11.96			
Croatia	9.41	8.13–10.71			
Cyprus	5.46	4.48–6.20	2012	4.9	

Country	GBDS (2017) [224]		SR of population-based studies [225]		BOLD study [227]
	Prevalence	Limits	Study period	Prevalence range	
Czechia	9.26	7.99–10.57			
Denmark	6.75	5.80–7.67	2003–2009	11.9–25.4	
Finland	5.41	4.71–6.19	1991–2004	5.2–9.4	
France	5.46	4.72–6.19	2007	7.5	
Germany	8.98	7.70–10.29	1994–2009	9.3–18.4	8.9
Greece	7.49	6.56–8.56	2001–2008	5.6–18.4	
Hungary	11.02	9.53–12.61			
Ireland	6.69	5.86–7.65			
Italy	5.17	4.42–5.89	1990	15.1	
Latvia	6.41	5.60–7.35			
Lithuania	6.49	5.67–7.39			
Luxemburg	6.55	5.72–7.46			
Malta	6.02	5.29–6.88			
Netherlands	6.50	5.72–7.37	2003–2008	3.9–18.7	18.1
Norway	6.28	5.58–7.02	1990–2005	4.6–18.8	12.5
Poland	8.67	5.72-7.46	2000–2009	6.0–22.1	13.7
Portugal	5.73	5.00–6.52	1995–2008	5.3–14.2	11.5
Romania	8.62	7.54–9.93			
Slovakia	6.94	6.00–8.01			
Slovenia	8.20	7.09–9.44	2005	10.3	
Spain	6.37	5.63–7.17	1997–2012	7.3–10.2	3.9–11.0
Sweden	7.66	6.88–8.53	1991–2009	2.1–20.1	9.3
United Kingdom	8.68	7.74–9.66	1993–2009	9.0–25	16

Abbreviations: GBDS=Global Burden of Disease Study; SR=systematic review; BOLD=Burden of Obstructive Lung Disease.

1.1.2.3 Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a rare, chronic, progressive form of fibrosing interstitial pneumonia of unknown cause that occurs primarily in older adults. It has been reported that the condition is associated with a higher risk of lung cancer. However, few studies have explored the specific risk associated with this disease. The prevalence of lung cancer among patients suffering from this condition ranges from 2.7% to 48% [228].

Prevalence

It is estimated that idiopathic pulmonary fibrosis affects approximately 80,000–111,000 people in Europe [229]. The real prevalence is difficult to establish because of the use of different case definitions, diagnostic criteria and study populations. In the literature, the prevalence ranges from 1.25–3.4 per 100,000 in Belgium and Greece [230, 231] to 35.5–39 per 100,000 in the UK, but specific comparisons between data sets are not possible. Table 1.5 summarises the literature data on prevalence.

Table 1.5: Prevalence of idiopathic pulmonary fibrosis in Europe

Country	Study period	Information source	Prevalence per 100,000 (95% CI)
Belgium [230, 231]]	1992–1996	Population-based ILD registry	1.25
Czechia [230, 231]	1981–1996	Retrospective observational study	12.1
Finland [230, 231]]	1997–1998	Pulmonary clinics and hospital databases	16–18 (2000 ATS/ERS criteria)
France [232]	2011–2012	national survey to pulmonologists	8.7
Greece [230, 231]	2004	Survey to pulmonologists	3.38 (2000 ATS/ERS criteria)
Italy (Lazio) [233]	2005–2009	Regional hospital discharge, population and cause of death databases	31.6
Italy (Lombardy) [234]	2005–2010	Health Care Administrative database	35.5 (general definition) 22.4 (broad definition) 12.6 (narrow case definition)
Norway	1984–1988	Hospital records	23.4 (14.9–33.0)
United Kingdom [235]	2000–2012	Clinical Practice Research Datalink GOLD primary database	19.94 (18.48–21.47) in 2010 38.82 (37.04–40.66) in 2012

Abbreviations: CI=confidence interval; ATS=American Thoracic Society; ERS=European Respiratory Society.

1.1.2.4 Family history of lung cancer

Even after adjusting for age, sex and smoking habits, several studies indicate an elevated risk of lung cancer for first-degree relatives of individuals with lung cancer. A family history of lung cancer has also been associated with a higher risk of the disease [214]. This risk is higher for individuals with several affected family members and for those who were diagnosed with cancer at a young age. If family members have classic cancer susceptibility syndromes (such as retinoblastoma and Li–Fraumeni syndrome), there is a significantly higher risk of lung cancer if the person also smokes tobacco [236].

A meta-analysis that included 24 case–control studies showed that individuals with a family history of lung cancer are two- to threefold more susceptible to lung cancer development than those without such a history. Subjects with a first-degree relative with lung cancer have a 1.51-fold higher risk of lung cancer after adjustment for smoking and other potential confounders (95% CI 1.39–1.63); this association is strongest for those whose siblings have been affected by lung cancer (OR 1.82, 95% CI 1.62–2.05) [237]. Moreover, genome-wide association studies independently revealed that the chromosomal region 15q24–25.1 is associated with a higher risk of nicotine dependence and lung cancer development [238].

Prevalence

Studies on the prevalence of a family history of lung cancer in European countries are not available. However, a population-based telephone survey from the USA reported data on the risk of lung cancer due to family history. According to this study, 6.4% (95% CI 4.9%–8.3%) of respondents reported a family history of lung cancer among first-degree relatives, 18.3% (95% CI 15.7%–21.2%) among second-degree relatives and 22.9% (95% CI 20.4%–25.7%) among first- and second-degree relatives. Subgroup analyses of the prevalence of a family history of lung cancer were performed for different confounders including race, ethnicity, sex, income or education level and personal history of any cancer, but differences between the subgroups were not statistically significant.

There was an inverse correlation between increasing age and reported prevalence of a family history of lung cancer among second-degree relatives (p = 0.006) but not first-degree relatives [239].

1.1.2.5 Environmental or occupational exposures to harmful substances

Radon is a natural radioactive gas produced by the decay of radium (^{226}Ra) and uranium (^{238}U) that emanates from rocks and soils in amounts that depend on the geological characteristics of the ground. Radon was classified as a human Group I carcinogen by the International Agency for Research on Cancer in 1988. The US Environmental Protection Agency recognised indoor exposure to radon as the second leading risk factor for lung cancer after smoking, and the first risk factor for nonsmokers.

It is estimated that between 3% and 14% of all lung cancers are linked to radon, depending on the average radon concentration in individual countries and the methods used for estimating radon levels [240, 241]. The results of a pooled analysis of 13 European studies (9 countries; 7148 cases and 14,208 controls) showed a linear dose–response relationship and the estimated adjusted excess relative risk of lung cancer was 0.16 (95% CI 0.05–0.31) for a 100-Bq/m^3 increase in the time-weighted average radon concentration observed. For lifelong nonsmokers, the risk of lung cancer at corrected radon concentrations of 100 and 400Bq/m^3 was estimated to be 1.2 and 1.6, respectively, relative to the risk for lifelong nonsmokers exposed to 0 Bq/m^3. The combined excess relative risk for radon and smoking status was estimated to be 25.8, 29.9 and 42.3 at radon concentrations of 0, 100 and 400 Bq/m^3, respectively, for smokers of 15–24 cigarettes per day, relative to lifelong nonsmokers at 0 Bq/m^3 [242, 243].

There is no evidence for a possible threshold concentration below which radon exposure presents no risk. Even low concentrations can result in a small increase in the risk of lung cancer. The majority of radon-induced lung cancers are assumed to be caused by low and moderate radon concentrations, because in general few people are exposed to high indoor concentrations [241].

In the general population, most radon exposure occurs indoors in small buildings such as houses. According to studies on indoor radon concentrations, the worldwide average is approximately 39 Bq/m^3, while levels in Europe range between 21 Bq/m^3 and > 110 Bq/m^3 (Table 1.6).

Table 1.6: Average indoor concentration of radon at the EU level

Country	Radon concentration (Bq/m^3)		
	Arithmetic mean	Geometric mean	Geometric standard deviation
Luxembourg	110	70	2
Sweden	108	56	-
Spain	90	46	2.9
Ireland	89	57	2.4
Norway	89	40	-
Slovakia	87	-	-
Italy	70	52	2.1
Portugal	62	45	2.2
Poland	49	31	2.3
Netherlands	23	18	1.6
United Kingdom	20	14	3.2
Worldwide average	39	–	–

The World Health Organization data set, which is based on surveys carried out by the Joint Research Centre of the European Commission to map radon concentrations, shows that the estimated percentage of dwellings with annual mean levels of radon > 200 Bq/m^3 ranges from 0.5% to 18%, while the percentage of dwellings with levels > 400 Bq/m^3 ranges from 0.0001% to 3.6%. Data are only available for 11 EU countries (https://gateway.euro.who.int/) and are presented in Table 1.7.

Table 1.7: Percentage of dwellings with high radon dose levels

Country	Dwellings with ≥200 Bq/m^3 (%)	Dwellings with ≥ 400 Bq/m^3 (%)
Austria	12	4
Belgium	2.2	0.5
Czechia	18	3
Finland	12.3	3.6
France	8.5	2
Germany	3.5	1
Hungary	5.9	0.8
Netherlands	0.3	0.0001
Poland	2	0.4
Spain	6	2
United Kingdom	0.5	0.1

1.1.2.6 Occupational exposures

Occupational exposures also play a role as risk factors for lung cancer. It has been estimated that at a European level, 7%–15% of lung cancer deaths among men and 2%–9% among women in 2000 were attributable to occupational exposures to carcinogens. A 2008 literature review found that the population-attributable proportion of lung cancers associated with occupational exposure varied from 3% to 40% [244].

According to the estimates of the Global Burden of Disease Study 2016, 86% (300,000) of the global occupation-attributable deaths due to carcinogens were related to lung cancer; asbestos was the main workplace carcinogen, accounting for 60.5% (181,450) of the total deaths due to lung cancers [245]. It is estimated that asbestos exposure is linked to lung cancer in 20%–25% of workers heavily exposed to asbestos [214]. Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series [246]. An EU directive mandated that all member states ban asbestos from 2005.

Other occupational exposures associated with a burden of cancer mortality are silica (16%), second-hand smoke (14.7%), diesel engine exhaust fumes (5%), nickel (2.7%) and arsenic (2.69%) [245]

The estimated occupational-attributable percentages of deaths due to carcinogens for all cancer types by risk factor for Europe according to the Global Burden of Disease Study 2016 are shown in Table 1.8 [245].

Table 1.8: Occupational-attributable percentage of deaths due to carcinogens for all cancer types by risk factor

	Number	Asbestos	Silica	SHS	DEE	Nickel	Arsenic
Western Europe	92,443	88.1%	5.5%	6.9%	0.7%	0.8%	1%
Eastern Europe	10,462	62.6%	15.5%	15.7%	1.9%	2.1%	2.2%
Central Europe	10,478	59.7%	17.4%	17.3%	1.9%	2.6%	3.0%
Global	348,741	62.7%	13.8%	14.1%	5.0%	2.3%	2.3%

Abbreviations: DEE=diesel engine exhaust; SHS=second-hand smoke.

1.1.3 Target population in this assessment

According to current clinical guidelines, individuals at high risk of lung cancer should be screened; those at medium or low risk should not be screened [210, 236, 247, 248].

Therefore, the target population in this assessment is adults aged ≥ 18 years without lung cancer at the time of screening (confirmed or suspected) and at elevated risk of lung cancer: individuals with a history of smoking or current smokers and those with other potential risk factors, including occupational or environmental exposures (e.g., radon, asbestos or fine particles), COPD, idiopathic pulmonary fibrosis or a family history of lung cancer.

1.2 Current clinical practice

HTA CORE MODEL DOMAIN: CUR[4]

1.2.1 Diagnosis

The following examination programme can be regarded as the basic diagnosis schedule for lung cancer [210, 211]:

- Anamnesis, clinical examination;
- Laboratory tests;
- Chest X-ray;
- Spiral CT of the thorax
  (including the upper abdominal area up to and including the adrenal glands);
- Bronchoscopy; and
- Abdominal sonography.

Initial suspicion of lung carcinoma is confirmed on the basis of corresponding symptoms (clinical examination) and a conspicuous finding on an X-ray of the thoracic organs. In addition, the medical history, concomitant diseases and the family history must be taken into account, as well as smoking habit and occupational exposure to pollutants (e.g., asbestos, arsenic compounds, chromium and nickel). The physical examination mainly includes an assessment of the thoracic organs

[4] This section addresses the following assessment elements of the CUR domain of the HTA core model A0024, A0025.

and lymph nodes. Basic laboratory tests include a differential blood count, electrolytes, liver and kidney parameters, and coagulation values. Owing to limited specificity and sensitivity, routine determination of tumour markers such as carcinoembryonic antigen, neuron-specific enolase and cytokeratin fragment 21–1 is not recommended for diagnosis of primary or recurrent lung cancer [210]. The diagnostic test most widely used for lung cancer is fibre-optic bronchoscopy. This also involves an assessment of the regional lymph nodes using endobronchial and/or endoscopic ultrasonography. In the majority of cases this will be adequate to make a diagnosis of non–small-cell lung cancer (NSCLC), even though the amount of material obtained is often insufficient to classify the tumour in more detail [249].

According to current guidelines, clinical pathways for further diagnosis of suspected lung cancer include contrast-enhanced chest CT to support the diagnosis and contribute to determining the stage. Positron emission tomography (PET)-CT is recommended for patients potentially eligible for curative treatment. Depending on the localisation and spread of the lung cancer, further examinations, many of them invasive and including endoscopy and biopsy, are recommended [210, 236, 250].

1.2.2 Treatment

Guideline recommendations on therapy depend on the type of lung cancer and the stage of development. Primarily, an individual should stop smoking as soon as a lung cancer diagnosis is suspected. When assessing whether surgery is necessary, a global risk score such as the Thoracoscore should be considered for individuals with NSCLC to estimate their mortality risk [251]. In early tumour stages of NSCLC, surgery is the most important treatment. If the cancer is more advanced, radiotherapy and chemotherapy are common modalities [210, 249, 250].

Surgical resection is the cornerstone in the first two stages of treatment for potentially resectable lung cancer if a patient is willing to accept the procedural risks [249]. For patients with NSCLC who are well enough and for whom curative treatment is appropriate, lobectomy is recommended [249, 250]. More extensive operations (bronchoangioplastic surgery, bilobectomy and pneumonectomy) should only be offered if necessary to obtain clear margins. For patients who refuse lobectomy or for whom contraindications exist, radical radiotherapy using stereotactic ablative radiotherapy (SABR) and sublobar resection are suitable options [250]. Moreover, for stage I cancer, SABR is the nonsurgical treatment of choice and is associated with low toxicity in patients suffering from COPD and elderly patients [249]. Chemoradiotherapy should be considered for individuals with stage II or III NSCLC who are unsuitable for or refuse surgery [250]. Adjuvant chemotherapy is beneficial for patients with tumour stage II or III and may also be included for patients with resected disease at stage IB and if the primary tumour is larger than 4 cm [249]. Under defined conditions, postoperative chemotherapy can also be considered [250]. Patients with stage III disease should receive a combination of radiotherapy and chemotherapy if their general condition and tumour spread allow this. Chemotherapy simultaneous to radiotherapy improves quality of life when compared to radiotherapy alone [210].

The central therapeutic measure for individuals with SCLC is combination chemotherapy. Depending on the stage, this is supplemented by local treatments such as radiotherapy. In the absence of remote metastasis and irradiatable tumour spread, primary tumour irradiation increases the rate of cure. At an early stage, surgical intervention is a treatment option [210, 250]. In all stages, prophylactic cranial irradiation also lowers the intracerebral recurrence rate for responsive patients and prolongs survival. Surgical or radiotherapeutic measures alone are not suitable for long-term control of the disease [210].

1.3 Features of the intervention

HTA CORE MODEL DOMAIN: TEC[5]

1.3.1 Lung cancer screening

Lung cancer screening is a programme for the detection and treatment of lung cancer at an early stage and has a major impact on the high mortality rate of lung cancer. A good lung cancer screening test is sensitive, specific, acceptable to individuals and providers, and cost-effective [204].

1.3.1.1 Claimed benefit of lung cancer screening

The claimed benefits of lung cancer screening over no screening are as follows:

- *Lower lung cancer mortality or an improvement in other oncological outcomes*
  According to a US national health survey, more than 12,000 premature lung cancer deaths per year may be prevented by lung cancer screening in the USA. Patients with the earliest stage (IA) of lung cancer may have a 5-year survival rate of approximately 75% with surgery. However, this rate decreases rapidly with increasing stage [252].

- *Quality-of-life benefits from screening and early detection of cancer*
  The claimed benefits of lung cancer screening in terms of quality of life are a reduction in disease-related morbidity, a decrease in treatment-related morbidity, changes in lifestyle that affect health (e.g., smoking cessation) and a reduction in anxiety and mental stress [204].

- *Detection of disease, other than lung cancer, that requires treatment*
  Other clinical conditions may be identified in a lung cancer screen that are unrelated to lung cancer and require follow-up (e.g., COPD, coronary artery calcification and other cancers). It is likely that treatment of these other diseases will reduce the overall burden of disease [204].

1.3.2 Guidelines on lung cancer screening

Since the publication of results from the NLST [253], several international scientific societies have published guidelines recommending annual LDCT for screening in asymptomatic, high-risk individuals. The US Preventive Services Task Force (USPSTF) has issued a grade B recommendation for lung cancer screening with annual LDCT for patients at high risk [254] and the Centers for Medicare and Medicaid Services and private insurers now cover the screening cost under certain conditions [255]. Major American, European and Asian health organisations also endorse LDCT screening, including the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, the American Lung Association, the American Thoracic Society (ATS), the National Comprehensive Cancer Network (NCCN), the Canadian Task Force on Preventive Health Care, Cancer Care Ontario, the European Society of Radiology (ESR), the European Respiratory Society (ERS), the European Society of Thoracic Surgeons and the European Society for Medical Oncology, among others [236, 247, 256-265].

[5] This section addresses the following assessment elements of the TEC domain of the HTA core model: B0001, A0020, B0002, B0003, B0004, B0008, B0009, B0013, A0024, A0025.

Recommendations regarding individuals eligible for screening adopted by major health organisations have mainly followed the NLST criteria regarding age, smoking history and time since quitting, as follows: current and former smokers aged 55–80 years, smoking history of at least 30 pack-years and a maximum time since quitting of 15 years for former smokers. However, some have also included individuals with lower or higher lung cancer risks, such as the ATS, NCCN, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften/Deutsche Krebsgesellschaft and the Canadian Association of Radiologists, which also recommended screening individuals aged 50 years with a smoking history of ≥ 20 pack-years if they have a cumulative 5-year cancer incidence risk of ≥ 1.5% or an additional risk factor for lung cancer.

In Europe, lung cancer screening is yet to be implemented at the population level. To the best of our knowledge, no European national funding body has supported implementation of lung cancer screening. While the white paper published by the European Society of Radiology and the European Respiratory Society (ERS) recommends screening within comprehensive, quality-assured programmes, within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres [263], there is considerable variability in the recommendations issued by national authorities and scientific societies. Germany, Spain and the Nordic countries have issued recommendations in favour of LDCT screening, but France does not support it [210, 248, 265-268].

Existing guidelines agree that patients undergoing screening should have access to high-quality, high-volume centres similar to those enrolling patients in the NLST; screening is not considered appropriate for individuals with substantial comorbidity, such as severe emphysema or cardiovascular disease that would preclude an attempt at curative therapy or limit life expectancy. Lung cancer screening does not replace smoking cessation, and screening programmes should provide support for smoking cessation and prevention of relapse. Guidelines encourage providers to ensure that patients are making informed decisions.

An overview of the current international guidelines on lung cancer screenings is presented in Appendix 6.

1.3.3 Screening technologies

1.3.3.1 Selection of screening participants

Current guidelines recommend lung cancer screening for individuals at high risk of lung cancer. According to the NCCN there are two groups that qualify as having high risk:

1) Individuals aged 55–74 years who currently smoke tobacco or stopped smoking within the previous 15 years and have a smoking history of ≥ 30 pack-years.
2) Individuals aged 50 years who currently smoke tobacco or stopped smoking within the previous 15 years and have a smoking history of ≥ 20 pack-years and have an additional risk factor for lung cancer (i.e., family history of lung cancer, personal history of cancer or lung disease, or exposure to occupational or environmental toxins).

The selection of individuals eligible for lung cancer screening can be based on these concise inclusion criteria. As an alternative, several risk prediction models have been developed to calculate the individual risk for lung cancer [269, 270]. These calculations take into account the individual's age and detailed smoking history, the presence of pulmonary disease (e.g., COPD), a family or personal history of cancer, body mass index and background socioeconomic indicators. In addition to correct selection strategies, several biomarkers are currently under development that might refine the screening selection criteria independent of age and tobacco exposure [271].

1.3.3.2 Imaging technologies

Imaging technologies are used for lung cancer screening. The use of ionising radiation for diagnostic purposes is only indicated if the health benefit outweighs the radiation risk [210]. Chest X-ray was initially proposed for lung cancer screening, but after negative trial results [272] it is no longer recommended. Currently LDCT is the only technology recommended in guidelines for lung cancer screening. Further technologies such as biomarkers are under evaluation, but are beyond the scope of this assessment because they are not yet mature.

- Chest X-ray

  A thoracic overview image in two planes is the initial radiological procedure most frequently used for the thoracic area and is often performed before or when lung cancer is suspected. A thoracic overview is recommended as an initial radiological procedure in the clarification of lung cancer. In the case of positive and negative findings and discrepancy in the clinic, further diagnostic tests should be carried out [210].

- Computed tomography

  CT should be carried out as a contrast-enhanced examination of the thorax and upper abdomen (adrenal glands and liver). Since CT provides exact information about the location of lesions, it should always be performed before invasive measures, in particular before bronchoscopy or mediastinoscopy. In patients with suspected lung carcinoma and with a foreseeable therapy option, a CT examination of the thoracic organs should be performed, since the potential benefit outweighs the relatively low risk of radiation-induced damage [210].

1.3.3.3 Biomarkers

Lung cancer biomarkers can also be used for early detection of the disease. A biomarker is a biological characteristic that can be measured and evaluated [271]. The diagnostic performance of EarlyCDT-Lung (an antibody-based biomarker screening panel), a microRNA (miRNA) signature classifier (a plasma-based 24 miRNA risk score) and miR test (a serum-based 13-miRNA signature) and their influence on mortality was evaluated but there was insufficient evidence to justify implementation in clinical practice [265]. Although the existing candidates and methods have enormous potential, no single molecular biomarker for lung cancer is currently used in routine medical practice. Much improvement is still needed and studies should be promoted for promising biomarkers (molecular and image-based) and technologies to facilitate selection of the most appropriate combinations [271]. Thus, biomarkers for lung cancer are still at an early stage of development.

1.3.4 Setting and requirements

Lung cancer screening is offered in cancer centres, academic medical centres and outpatient radiology clinics, for example [236, 273]. Certain quality parameters required for lung cancer screening include minimum equipment standards, a standard screening protocol and suitable personnel such as radiologists and technologists who have received training in image acquisition and interpretation [273]. In addition, continuous monitoring of false-negative biopsy rates is recommendable.

There should be a medical director or medical advocate for the screening programme who takes overall control of the safety of patients participating in the programme. Moreover, an assessor should manage the procedure and a radiologist should be responsible for LDCT in individual cas-

es. The responsible clinician manages transfers to a rapid-access pulmonary clinic [251, 274]. The multidisciplinary team responsible for diagnostic evaluation should consist of a medical oncologist, a radio-oncologist, a pathologist, a radiologist, a thoracic surgeon and a pulmonologist [211].

Lung cancer screening is best carried out in a certified lung cancer centre. For example, screening in Germany is carried out in a lung cancer centre certified by the German Hospital Association [275].

Lung cancer screening options are outlined above. The equipment required for lung cancer screening depends on which technology is used. For example, LDCT uses sophisticated X-ray equipment and less ionising radiation in comparison to normal CT while maintaining good diagnostic quality. LDCT can be performed with single-slice spiral CT, but the use of multidetector row CT scanners is currently preferred [276]. The minimum requirement is a 16-slice CT device with multiple detectors (fixed or mobile) capable of providing low-dose protocols. Volumetric software is used to assess pulmonary nodules [251].

2 OBJECTIVES AND SCOPE

The aim of this EUnetHTA assessment is to provide a reliable synthesis of the available evidence on lung cancer screening in risk groups (individuals with a history of smoking or current smokers, those with occupational or environmental exposure to radon, asbestos or fine particles, patients with COPD or idiopathic pulmonary fibrosis, and individuals with a family history of lung cancer). For this purpose, four research questions were defined:

- **Research question 1:** What is the benefit/harm of screening for lung cancer using LDCT compared to no (or no systematic) screening in individuals at elevated risk of lung cancer? As there is reason to assume comparability of no screening and screening using chest X-ray, screening for lung cancer using chest X-ray will also be taken into account as a comparator, if reasonable.
- **Research question 2:** What is the benefit/harm of screening for lung cancer using biomarkers in addition to LDCT compared to screening using LDCT alone in individuals at elevated risk of lung cancer?
- **Research question 3:** What is the benefit/harm of organisational variations of systematic screening for lung cancer using LDCT (e.g., screening using different intervals, with/without invitation) for individuals at elevated risk of lung cancer?
- **Research question 4:** What is the best strategy to inform individuals in the target group about a lung cancer screening programme to optimise an informed choice regarding participation?

The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) for assessment of the effectiveness (EFF) and safety (SAF) domains are defined in the project scope below.

Table 2.1: Scope of the assessment: PICO 1

Description	Project scope
Population	Adults (age ≥ 18 years) without lung cancer (confirmed or suspected) (ICD-10 code C34) at elevated risk of lung cancer. • Population 1: Persons with a history of smoking or current smokers • Population 2: Persons with other potential risk factors: occupational or environmental toxins (e.g., radon, asbestos or fine particle exposure), COPD (ICD-10 code J44), idiopathic pulmonary fibrosis (ICD-10 code J84.1) or a family history of lung cancer (ICD-10 code C34)
Intervention	Systematic screening for lung cancer using low-dose computed tomography
Comparison	No (systematic) screening (usual care). In a sensitivity analysis, screening for lung cancer using chest X-ray was also taken into account as an additional comparator for mortality and consequences resulting from overdiagnoses as outcomes. Rationale: Results from the PLCO study [1] give reason to assume comparability of no screening and screening using chest X-ray, at least in terms of their effect on lung cancer specific mortality.
Outcomes	• Mortality (overall mortality, lung cancer mortality) • Morbidity • Health-related quality of life

Description	Project scope
Outcomes *(continuation)*	• Harms resulting from screening itself (e.g., consequences from radiation exposure) or from subsequent diagnostic interventions (e.g., invasive biopsy) including overdiagnoses,[6] consequences resulting from false screening results (false positive and false negative) • (Serious) adverse events
Study design	Randomised controlled trials

Table 2.2: Scope of the assessment: PICO 2

Description	Project scope
Population	See PICO 1 (Table 2.1)
Intervention	Screening for lung cancer using biomarkers in addition to low-dose computed tomography (LDCT) • Biomarkers can be used as a test for selection of individuals undergoing screening • Biomarkers can be used as a test for characterisation of undetermined nodules found during the CT-based screening.
Comparison	Screening for lung cancer using LDCT alone Rationale: LDCT alone is the recommended screening intervention according to current guidelines.
Outcomes	See PICO 1 (Table 2.1)
Study design	See PICO 1 (Table 2.1)

Table 2.3: Scope of the assessment: PICO 3

Description	Project scope
Population	See PICO 1 (Table 2.1)
Intervention	Annual systematic screening for lung cancer using LDCT as recommended in guidelines
Comparison	Systematic screening for lung cancer using LDCT different in screening interval (shorter or longer) or type of systematic screening (organisational variants, e.g. with invitation)
Outcomes	See PICO 1 (Table 2.1)
Study design	See PICO 1 (Table 2.1)

[6] Defined as the number of diagnoses (true-positive findings) that would not have become clinically relevant during a person's lifetime.

Table 2.4: Scope of the assessment: PICO 4

Description	Project scope
Population	See PICO 1 (Table 2.1)
Intervention	Specific information strategy for lung cancer screening (e.g., content, mode of distribution)
Comparison	A specific information strategy for lung cancer screening different from the one used in the intervention group (e.g., different content, different mode of distribution) No specific information strategy for lung cancer screening
Outcomes	• Screening participation rate • Participant satisfaction • Participant empowerment • Increased knowledge • Informed decision-making
Study design	Randomised controlled trials; nonrandomised controlled trials; prospective observational studies; qualitative studies

3 METHODS

The assessment methods and processes adhere to the EUnetHTA Methodological Guidelines and EUnetHTA standard operating procedures.

3.1 Clinical effectiveness and safety

3.1.1 Information retrieval

For **research question 1**, the results from the German national benefit–harm assessment report on screening for lung cancer using LDCT in individuals with a history of smoking or current smokers conducted by one of the co-authors (IQWiG; report number S19-02 [1]) were used.

3.1.1.1 Information retrieval in the IQWiG report

A systematic literature search for relevant SRs was conducted in the bibliographic databases MEDLINE, Cochrane Database for Systematic Reviews and the Health Technology Assessment Database. The search was restricted to the last 6 years before 2019. The aim was to select one or more high-quality and up-to-date SRs from which primary studies were identified and then selected according to the specific inclusion criteria of the report.

In addition, for time periods not covered by a chosen up-to-date and high-quality relevant SR [2], systematic literature searches for RCTs were conducted in the following databases:

- MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials

Furthermore, a search for ongoing or unpublished studies was carried out in the following study registries:

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform

In addition, references from the SRs on lung cancer screening were checked and documents made available from consultation procedures were considered. Authors of potentially relevant studies were also contacted (via e-mail, if the e-mail address was available in the publication). Queries were only sent out if the questions were likely to have a direct impact on the conclusion of the assessment. The contents of the requests can be found in Appendix 9.

3.1.1.2 Additional information retrieval for the EUnetHTA rapid assessment report

The inclusion criteria for research question 1 were extended to other risk factors for lung cancer (occupational or environmental exposure to harmful substances, COPD, idiopathic pulmonary fibrosis and a family history of lung cancer). Therefore, the list of studies excluded from the IQWiG report was rescreened to identify studies on these risk factors. In addition, all studies already included for research question 1 were checked regarding the proportion of individuals reporting other exposures and results for these subgroups were extracted, if possible.

For **research question 2**, a systematic literature search was performed for biomarkers in lung cancer screening in the following bibliographic databases:

- MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials
- Cochrane Database for Systematic Reviews

Furthermore, a search was performed for ongoing or unpublished studies in the following clinical trial registries:

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform

For **research question 3**, no separate information retrieval was carried out, but all studies already included for research question 1 and research question 2 were used for evaluations regarding different screening strategies.

For research question 4, we performed independent systematic literature searches in the bibliographic databases MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews.

In addition to the electronic search, we checked reference lists from the primary studies and reviews included.

The search strategies for bibliographic databases (research questions 1, 2 and 4) and study registries (research questions 1 and 2) are displayed in Appendix 1.

3.1.2 Selection of relevant studies and documents

3.1.2.1 Selection of SRs (focused)

The studies and documents identified in bibliographic databases were reviewed and assessed with regard to their relevance by one reviewer. A second reviewer checked the whole selection process.

3.1.2.2 Selection of relevant studies and documents

Bibliographic databases: In a two-step procedure, the titles and abstracts of the references were first screened against the inclusion and exclusion criteria, followed by screening of the full texts of potentially relevant publications identified in the first step.

Study registries: In a one-step procedure, registry entries were screened against the inclusion and exclusion criteria.

Selection of studies retrieved from the searches in bibliographic databases and study registries was performed by two reviewers independently of each other. Discrepancies were resolved via discussion.

3.1.2.3 Inclusion criteria

The inclusion criteria are detailed in PICO questions 1–4 summarised in Table 2.1 to Table 2.4.

The exclusion criteria were as follows:

- Languages other than English or German as per the IQWiG report for questions 1–3.
- Languages other than English, German or Spanish for question 4.
- Publications of clinical trials not meeting the Consolidated Standards of Reporting Trials (CONSORT) criteria [277].
- For research questions 1–3, study designs other than RCTs were excluded.

3.1.2.4 Data management

- Endnote X9 was used for citation management.
- Study selection was performed using the IQWiG internal web-based trial selection database (webTSDB).

3.1.3 Data extraction

All necessary information for the assessment was extracted from documents for the studies included into standardised tables. The data extracted included:

- Characteristics of the studies
- Characteristics of the interventions
- Study inclusion and exclusion criteria
- Baseline characteristics of the study population
- Outcomes reported

For research question 1, information from the corresponding tables in the IQWiG report was used. If discrepancies arose in the comparison of information from different documents for a study (but also from multiple data on an aspect within a document itself) that could have a considerable influence on the interpretation of the results, this is identified in the relevant place in the results section of the report.

Results for patient-relevant endpoints reported in the studies are described in a comparative manner in the report.

If possible, the data analyses and syntheses described in Section 3.1.5 were performed in addition to comparisons of results from the individual studies. A final summary assessment of the information was carried out in any case.

Data for outcomes were generally not included in the benefit assessment if they were based on < 70% of the participants to be included in the evaluation, that is, if the proportion of participants who are not included in the evaluation was > 30%.

Furthermore, the results were not included in the benefit assessment if the difference in the proportion of not-considered participants between the study groups was > 15 percentage points.

3.1.3.1 Determination of the risk of overdiagnosis

The risk of overdiagnosis was calculated using two different approaches.

Individuals diagnosed with lung cancer during the screening phase: The proportion of overdiagnoses was calculated as the number of participants with a lung cancer diagnosis from randomisation to the end of the observation period for both the intervention and control groups and the number of participants diagnosed with lung cancer at the end of the screening phase in the intervention group. This value represents the frequency of overdiagnoses as a proportion of the total number of lung cancer diagnoses in the intervention group during the screening phase.

Individuals invited to screening: The number of lung cancer diagnoses was compared between the intervention group and the control group from randomisation to the end of the observation period. The difference was used to estimate the number of additional lung cancer diagnoses resulting from screening. The additional lung cancer diagnoses (at the end of the observation period) were related to the number of invited participants.

In principle, diagnoses made via screening may be overdiagnoses. When quantifying the proportion of overdiagnoses and determining the standard errors, mathematical estimation can lead to negative values. Such estimates were set to 0.

3.1.4 Quality rating and RoB assessment

Assessment of the study and outcomes validity and the level of evidence followed the criteria described in the two EUnetHTA guidelines on the internal validity of RCTs and nonrandomised studies on interventions. As recommended in these guidelines, RoB was assessed for the RCTs included according to the Cochrane RoB tool [278] at study and outcome levels. RoB for nonrandomised studies on interventions was assessed according to the ROBINS-I tool [279].

Two independent assessors judged the RoB (low risk or high risk) on the basis of the information retrieved from the selected documents.

The RoB for the results from each study included was described separately for each patient-relevant outcome. For this purpose, the following domains across (A) outcomes and (B) outcome-specific domains were systematically extracted:

RCTs

A: RoB for results at the study level

- Generation of the randomisation sequence
- Concealment of the allocation to groups
- Blinding of participants and personnel
- Selective outcome reporting
- Other sources of bias

B: RoB of results at the outcome level

- Blinding of the outcome assessors
- Implementation of the intention-to-treat principle

- Selective reporting
- Other potential sources of bias

Other studies

A: RoB for results at the study level

- Bias due to confounding
- Bias in the selection of participants for the study
- Bias in the classification of interventions
- Bias due to deviations from intended interventions

B: RoB for results at the outcome level

- Bias due to missing data
- Bias in the measurement of outcomes
- Bias in the selection of the results reported

The RoB was then categorised as low or high. If the results had low RoB at the study level, an RoB assessment at the outcome level was performed. If the results had high RoB at the study level, the outcome-specific RoB of the results was not assessed because the high RoB at study level was directly transferred to the outcome-specific RoB for the results. Classifying RoB as high does not lead to exclusion of the corresponding study or outcome data. Rather, the RoB classification informs the discussion on heterogeneous study results.

To rate the quality of the overall evidence available for a given outcome, the GRADE approach was applied [280]. In general, the certainty of evidence was evaluated at the outcome level (possible levels: high, moderate, low and very low), as detailed in the section on Certainty of the evidence.

3.1.5 Data analyses and synthesis

The information on study design, study methods, populations, endpoints and study results in the documents included was evaluated. The results of this evaluation are presented and were used to identify relevant analyses and were considered for the conclusions of the assessment report.

One current SR was used [2] that met our inclusion criteria and guarantees high quality for information retrieval. The quality of information retrieval was checked using point 3 of the AMSTAR checklist [281].

3.1.5.1 Meta-analyses

When studies were comparable with regard to the research question and relevant characteristics and no significant heterogeneity was observed, the individual study results were summarised quantitatively by means of meta-analyses.

The estimated effects and CIs from the studies were summarised using forest plots. The study pool was then examined for the presence of heterogeneity using statistical tests [282]. If the heterogeneity test yielded a statistically nonsignificant result ($p \geq 0.05$), it was assumed that estimating a common (pooled) effect usually made sense, as long as no reasons (clinical/design) existed against

applying this approach. The meta-analyses were conducted on the basis of the random-effects model according to the Knapp and Hartung method; estimation of heterogeneity was conducted according to the Paule–Mandel method [283]. Results are presented as the pooled effect together with the 95% CI. Because heterogeneity cannot be reliably estimated when only a few studies are available, fixed-effect models were used in the event of four or fewer studies, as long as no other reasons existed against applying this approach; for instance, the studies had to be sufficiently similar.

Since the studies considered for research question 1 did not have sufficiently comparable study designs to be able to use a fixed-effect model for a meta-analysis, it was assumed that a model with random effects is appropriate in the meta-analyses. We first checked whether the CI for the Knapp and Hartung estimate was narrower than the estimate using the DerSimonian–Laird method. If this was the case, the Knapp and Hartung estimate with variance correction was further considered. Furthermore, we checked whether the 95% CI for the Knapp and Hartung estimate (possibly with a variance correction) was completely included in the union of the 95% CIs for the individual studies. If this was the case, the Knapp and Hartung estimate was used to derive a benefit statement if the result was statistically significant. If the Knapp and Hartung estimate (possibly with a variance correction) is not shown or provided a statistically nonsignificant result, we checked whether the DerSimonian–Laird estimate delivered a significant result. If this was the case, a benefit statement was made about rectification of the effects in the meta-analysis studies. If the DerSimonian–Laird estimate was not statistically significant, consideration of the rectification was omitted and it was concluded that there is no evidence of an effect.

If the heterogeneity test yielded a statistically significant result ($p < 0.05$), the prediction interval was shown only if at least five studies were covered. A qualitative summary was provided if four or fewer studies were covered. In both cases, we also examined which factors might be the cause this heterogeneity. This includes methodological factors (see Section 3.1.5.2) and clinical factors, so-called effect modifiers (see Section 3.1.5.3). If unexplained heterogeneity was present, the quality of the evidence was lowered, depending on the magnitude of the heterogeneity according to the GRADE approach.

Meta-analyses were calculated using SAS, version 9.4.

For research question 4 no meta-analyses were planned or performed.

3.1.5.2 Sensitivity analyses

To evaluate the robustness of the results, an assessment may include sensitivity analyses with regard to methodological factors. These factors arise from decisions made within the framework for the retrieval and assessment of information, for example, the specification of cut-offs for the time points for data collection or the choice of effect measures. The sensitivity analysis should in particular consider the classification of the RoB for study results. The result of the sensitivity analysis can affect assessment of the certainty of the results.

The assessment focuses on the comparison of LDCT screening versus no screening. In addition, for the mortality (overall mortality and lung cancer mortality) and consequences of overdiagnosis outcomes, studies with screening by chest X-ray as a comparative intervention were also considered. A meta-analytical summary of both comparative interventions in comparison to LDCT screening was carried out as a sensitivity analysis to check whether these studies can provide additional information on the question addressed in the report. For other outcomes, such a sensitivity analysis was considered to be not useful.

3.1.5.3 Subgroup characteristics and other effect modifiers

The results were examined with regard to potential effect modifiers, that is, clinical factors influencing the effects. The aim was to uncover possible differences in effects between person groups and screening characteristics. Statistical significance based on a homogeneity or interaction test is a prerequisite for the detection of different effects. If potential effect modifiers are identified, then the conclusions inferred from the effects observed in the whole study group can possibly be formulated more precisely. Subgroup analyses were only performed if each subgroup comprised at least 10 persons and, in the case of binary data, at least 10 events had occurred in one of the subgroups. In particular, the following possible effect modifiers were considered for investigation:

- Sex
- Age
- Strength of exposure to tobacco or occupational toxins
- Screening strategy (e.g., screening interval)

If further possible effect modifiers arose from the available information, these were also included if reasonable and corresponding conclusions on the effects observed were adapted, if applicable.

3.1.5.4 Certainty of the evidence

To rate the quality of the evidence, the GRADE method was applied [280].

3.1.6 Patient involvement

Patient involvement was planned and patient organisations for COPD from Germany and Ireland were contacted to provide input on the draft research questions. However, it was not possible to arrange participation.

3.1.7 External expert involvement

To guarantee quality assurance throughout the whole assessment process, external experts in the field of epidemiology, oncology, radiology and screening programmes were involved by reviewing the project plan and the assessment draft.

No manufacturers were included in the preparation of this rapid relative effectiveness assessment. This is because the technology under assessment is the screening process itself. Therefore, the focus was not on the evaluation of a single diagnostic or therapeutic product or technology.

3.2 Division of work within the project

IAMEV (author)

- Develop the first draft of the project plan.
- Develop the first draft for the TEC/CUR domains of the assessment.
- Perform literature searches for research question 4 and study selection for research questions 1 (other risk factors), 2 and 4.
- Carry out the assessment for research question 1 on other risk factors (study selection, data extraction, analysis, synthesis and interpretation of findings). Quality-check the steps of the assessment for research question 1 on current and previous smokers.
- Carry out the assessment for research question 3 for LDCT versus no (systematic) screening for individuals with other risk factors and support the production of data for all domains and quality-check the steps for this process for the remaining research question 3.
- Carry out the assessments for research question 2 and 4 (data extraction, analysis, synthesis and interpretation of findings).
- Send draft versions to dedicated reviewers and external experts for comments, compile feedback from reviewers and experts, and incorporate relevant changes to the draft.
- Prepare the final assessment, including an executive summary.

IQWiG (co-author)

- Review the project plan draft.
- Perform a literature search for research questions 1 and 2; provide lists of excluded references for research question 1 (other risk factors).
- Carry out the assessment for research question 1 on current and previous smokers (study selection, data extraction, analysis, synthesis and interpretation of findings). Quality-check the steps of the assessment for research question 1 on other risk factors.
- Carry out the assessment for research question 3 for LDCT versus no (systematic) screening for current and previous smokers and support the production of data for all domains and quality-check the steps of this process for the remaining research question 3.
- Collaborate on writing of the discussion and conclusions in direct connection with research question 1 and research question 3, and endorse these sections.
- Review drafts of the assessment, including the executive summary, in connection with research question 1 and research question 3.

Avalia-t; ACIS (co-author)

- Review the draft project plant.
- Collect data on the European epidemiology of risk factors
- Perform a literature search on international guidelines regarding lung cancer screening.
- Support the production of data for all domains and quality-check the steps of this process for research question 2 and 4 (data extraction, analysis, synthesis, and interpretation of findings).
- Check, provide input and endorse the content for all domains. Collaborate on writing of the discussion and conclusions.
- Approve/endorse conclusions drawn and all draft versions and the final assessment, including the executive summary.

RER and UMIT (dedicated reviewers)

- Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts.
- Review the methods, results, and conclusions based on the original studies included.
- Provide constructive comments in all the project phases.

UTA (observer)

- Review the draft project plan, propose amendments where necessary and provide written feedback.
- Review the assessments, propose amendments where necessary and provide written feedback.

3.3 Deviations from the project plan

Information retrieval for research questions 1 and 2

For research question 1, no references from the studies included were reviewed, but documents from the consultation process for IQWiG report S19-02 were taken into account.

For research question 2, the list of studies excluded from the IQWiG report were not re-screened, but separate systematic literature searches in bibliographic databases and study registries were performed.

Inclusion criteria for research question 4

SRs were not included, but were used as sources for potentially relevant studies.

Outcomes for research question 1:

The outcomes “Stage distribution of lung cancer” and “Consequences resulting from unclear findings” were not assessed.

4 RESULTS: CLINICAL EFFECTIVENESS AND SAFETY

4.1 Research question 1

4.1.1 Information retrieval

Focused search for SRs

Of the 11 SRs included (Appendix 2), one (Snowsill 2018 [2]) was evaluated as up-to-date and of high quality and was included for the purpose of identifying primary studies.

The assessment of the quality of information retrieval for this SR is presented in Appendix 3. From this SR, 12 primary studies could be extracted and were reviewed to determine the extent to which they meet the inclusion criteria of report S19-02 (see Section 2). The Lung Search study did not meet the inclusion criteria for the intervention [284]. Two studies (Depiscan 2007 [285] and Garg 2002 [286]) had no reported results or relevant publications of results (see Section 4.1.2).

Study selection

Figure 4.1 shows the results for information retrieval adopted from IQWiG report S19-02. In addition, the references excluded in report S19-02 with E1 (population) were rescreened with regard to further risk factors. References for the documents that were excluded after checking the full text are presented in Appendix 4 with the reasons for exclusion.

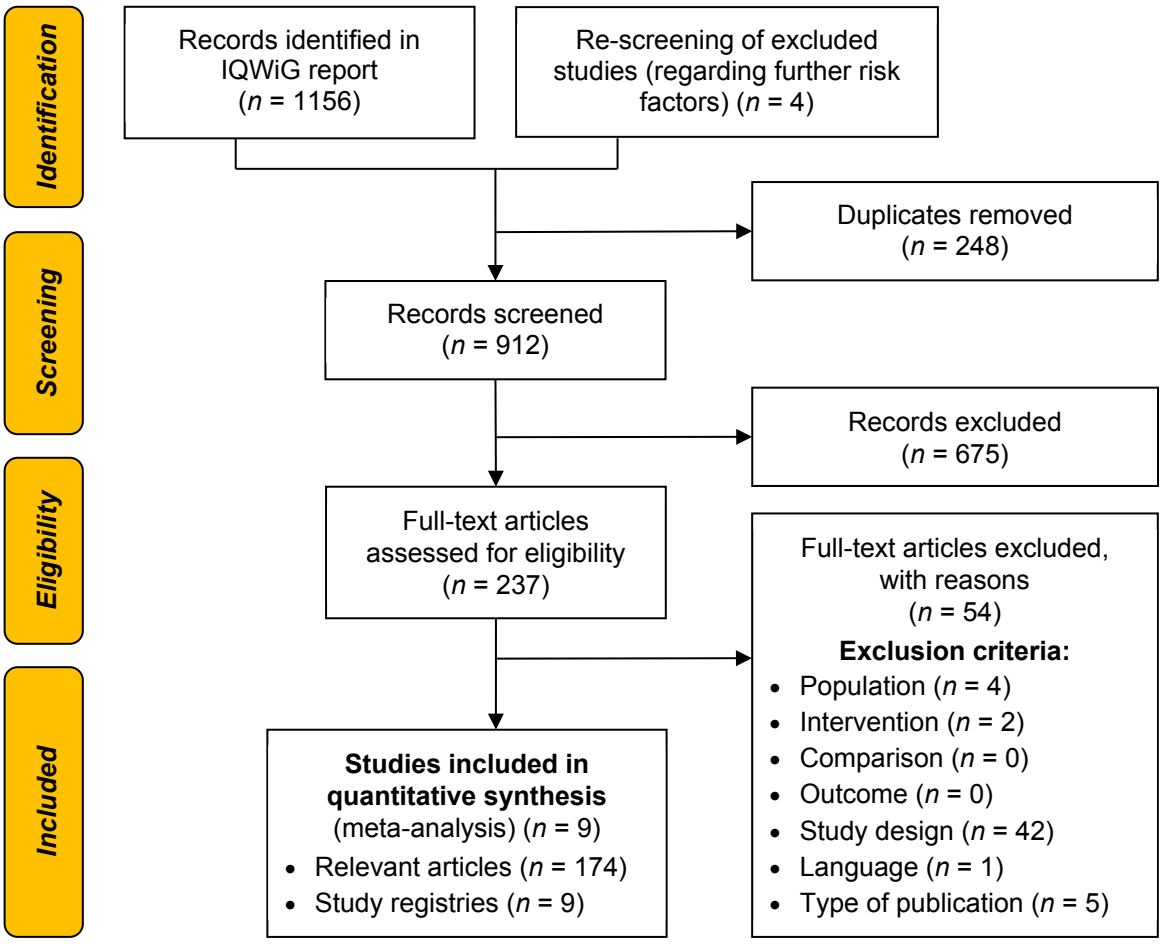


Figure 4.1: Flow chart of information retrieval for clinical effectiveness and safety

Information retrieval identified nine randomised trials (184 documents) as relevant for research question. Two ongoing studies and one planned study were also identified. In addition, one completed study without reported results was identified and four studies with unclear status. The last search was performed on 12th June 2020.

4.1.2 Studies included in the assessment

The studies listed in Table 4.1 were included in the assessment.

Table 4.1: Study pool: list of relevant studies used for the assessment

Study	Documents available	Study registry entries	Result report from study registries
DANTE	Yes [93-97]	Yes [287]	No
DLCST	Yes [13-28]	Yes [288]	No
ITALUNG	Yes [29-39]	Yes [289]	No
LSS	Yes [98-101]	Yes [290]	No
LUSI	Yes [40-44]	Yes [291]	No
MILD	Yes [45-52]	Yes [292]	No
NELSON	Yes [53-92]	Yes [293]	No
NLST	Yes [102-176]	Yes [294]	Yes [295]
UKLS [a]	Yes [3-12]	Yes [296]	No

[a] This is a feasibility study in which morbidity and mortality data are to be collected over a follow-up period of 10 years. This study was not used for clinical effectiveness assessment because no usable results have been reported so far. The following tables therefore do not provide a more detailed presentation of the UKLS trial.

Table 4.2 lists all planned, ongoing, withdrawn and completed studies without results on the intervention.

Table 4.2: List of planned, ongoing, withdrawn and completed studies without results on lung cancer screening in individuals with a history of smoking or current smokers without suspected lung cancer

Study	Document type, register ID (if applicable)	Status (estimated completion date)	Study type	Number of patients
CHANCES	Study register, ChiCTR1900025257 [297]	Planned (12/2028)	RCT	115,200
Depiscan 2007	Publication [285]	Unclear	RCT	1000/year
Garg 2002	Publication [286]	Unclear	RCT	400
JECS	Study register, JPRN-UMIN000005909 [298] [a]	Ongoing (03/2034)	RCT	27,000
LUCAS	Study register, ISRCTN58557945 [299]	Completed	RCT	2000 [b]
NCT00006087	Study register, NCT00006087 [300]	Unclear [c]	RCT	1000
NCT02898441	Study register, NCT02898441 [301]	Unclear [c] (12/2018)	RCT	6000
Yorkshire Lung Screening Trial	Study register, ISRCTN42704678 [302]	Ongoing (07/2024)	RCT	6892

Abbreviations: n.r.=not reported; RCT=randomised controlled trial.

[a] Further information on the study type in reference [303].

[b] Information from reference [304].

[c] The classification “unclear” is based on the following: (1) the study is marked as ongoing according to the register entry, but the planned end of the study was already in the past at the time of the search; (2) the study was suspended according to the register entry and may be continued; or (3) the status of the study is marked as “unknown” in the register.

4.1.3 Description of the evidence used

Table 4.3, Table 4.4 and Table 4.5 describe the studies used for the assessment.

One study, UKLS [3-12], is a feasibility study that basically fulfils the inclusion criteria of the report, but no results that could be used for the benefit assessment were reported. A more detailed presentation of the UKLS trial is therefore not given in what follows.

The remaining eight studies (number of randomised subjects: 90,836) differed with regard to the screening strategies applied. In six studies the subjects were assigned to either screening by LDCT or no screening. In DLCST [13-28], ITALUNG [29-39], LUSI [40-44], MILD [45-52] and NELSON [53-92], participants in the control group were not offered any imaging procedures at baseline or during follow-up unless lung cancer was suspected. In the DANTE study [93-97], a baseline examination using chest X-ray was performed. Since this examination was performed in both the intervention group and the control group and no further screening was performed in the control group during the course of the study, the study was also classified as a study comparing LDCT versus no screening. By contrast, the LSS [98-101] and NLST [102-176] studies represent a comparison between LDCT screening and screening using chest X-ray. Both studies are US-American RCTs.

In the study groups without screening, the endpoint-specific data were all collected via registers. In addition, depending on the study, postal or telephone inquiries and clinical examinations were also used. All studies were conducted within Europe (Italy, Denmark, Germany, Netherlands and Belgium).

The number of participants in six of the studies ranged from 3,000 to 4,000 participants, while the NELSON and NLST studies included approximately 16,000 and 53,500 participants, respectively. The duration of the screening phase ranged from 1 to 6 years, and the planned follow-up period ranged from 5 to 10 years (in LSS, no information was available on the follow-up duration). With the exception of the MILD and NELSON studies, the screening interval was 1 year throughout all screening rounds. MILD was the only three-arm study in which participants in the intervention group were screened either annually or every 2 years (biennially). At the beginning of the study, participants were randomised to annual or biennial screening. Randomisation to an additional control group started later, resulting in different group sizes. In the NELSON study, the screening interval after each screening round was extended from 1 year to 2 years and then to 2.5 years.

Table 4.3: Characteristics of the studies included

Study name	Study type	Number of individuals randomised	Intervention	Comparator	Location and recruitment period	Duration of screening-phase/ planned duration of follow-up (since randomisation)	Primary endpoint and patient-relevant secondary endpoints [a]
LDCT screening versus no screening							
DANTE	RCT, multi-centre	2811 • I: 1403 [b] • C: 1408 [b]	• Annual LDCT screening • Chest-X-ray and sputum cytology at baseline	• No screening • Annual medical examination • Chest X-ray and sputum cytology at baseline	Italy, March 2001 to February 2006	4 years/≥ 7 years	Primary: lung cancer mortality; overall mortality Secondary: incidence of lung cancer, resection rate
DLCST	RCT, single-centre	4104 • I: 2052 • C: 2052	• Annual LDCT screening • Annual pulmonary function test	• No screening • Annual pulmonary function test	Denmark, October 2004 to March 2006	4 years/10 years	Primary: lung cancer mortality Secondary: overall mortality, incidence of lung cancer, false-positive screening results, health-related quality of life
ITALUNG	RCT, multi-centre	3206 • I: 1613 • C: 1593	• Annual LDCT screening • Invitation to smoking prevention programme	• No screening • Invitation to smoking prevention programme	Italy, 2004 to 2006	3 years/10 years	Primary: lung cancer mortality Secondary: overall mortality, overdiagnoses
LUSI	RCT, single-centre	4052 • I: 2029 • C: 2023	• Annual LDCT screening • Invitation to smoking cessation counselling	• No screening • Invitation to smoking cessation counselling	Germany, October 2007 to April 2011	4 years/9 years	Primary: lung cancer mortality Secondary: undefined
MILD	RCT, single-centre [c]	4099 [d] • I: 2376 Annual: 1190 Biannual: 1186 • C: 1723	• LDCT screening with two study arms: • Annual and • Biannual screening • Pulmonary function test at baseline • Invitation to smoking prevention programme	• No screening • Pulmonary function test at baseline • Invitation to smoking prevention programme	Italy, September 2005 to January 2011	6.2 years [e]/ 10 years [f]	Primary: lung cancer mortality, overall mortality Secondary: incidence of lung cancer, procedures for benign lung disease

Study name	Study type	Number of individuals randomised	Intervention	Comparator	Location and recruitment period	Duration of screening-phase/ planned duration of follow-up (since randomisation)	Primary endpoint and patient-relevant secondary endpoints [a]
NELSON	RCT, multi-centre	15 792 • I: 7900 • C: 7892	• LDCT screening at intervals of 1, 2 and 2.5 years • Pulmonary function test at baseline • Invitation to smoking cessation counselling	• No screening • Pulmonary function test at baseline in a sample • Invitation tom smoking cessation counselling	The Netherlands and Belgium, 2003 (1st wave) and 2005 (2nd wave)	5.5 years/ 10 years	Primary: lung cancer mortality Secondary: health-related quality of life
LDCT versus chest X-ray							
LSS	RCT, multi-centre	3318 • I: 1660 • C: 1658	• Annual LDCT screening	• Annual chest X-ray screening	USA, September 2000 to November 2000	1 year/ n.r.	Primary: Feasibility of conducting a lung cancer study with regard to recruitment, implementation of interventions and contamination, prevalence of abnormal findings, extent of diagnostic follow-up subsequent to abnormal screening findings
NLST	RCT, multi-centre	53 454 • I: 26 722 • C: 26 732	• Annual LDCT screening	• Annual chest X-ray screening	USA, September 2002 to April 2004	2 years/ at least 5 years	Primary: lung cancer mortality Secondary: overall mortality, incidence of lung cancer

Abbreviations: C=control group; I=intervention group; LDCT=low-dose computed tomography; n.r.=not reported; RCT=randomised controlled trial.

[a] Primary endpoints contain information without consideration of its relevance for this assessment. Secondary endpoints contain exclusively information on the relevant available outcomes for this assessment.

[b] Numbers differ from those in the result tables. After randomisation, some of the subjects of the I and C groups were excluded for registration errors, the absence of consent or ineligibility.

c: Originally designed as a multicentre study but carried out as a single-centre study owing to financial and organisational restrictions.

[d] Originally planned to enrol 10,000 subjects.

[e] The study was originally designed with a screening-phase of 10 years.

[f] Actual duration of follow-up; the planned duration of follow-up is unclear.

Table 4.4: Characterisation of the intervention: part 1

Study	Method of recruitment	Follow-up
LDCT screening versus no screening		
DANTE	Recruitment of volunteers via medical doctors, large-scale mailings, advertising papers and local media. Acquisition of smoking habits, occupational history, past medical history and present condition via questionnaire.	For 4 additional years, annual follow-up was a clinical examination for the intervention and control groups; follow-up was by telephone interviews thereafter. Linkage with local health registries for acquisition of mortality data after active follow-up and verification using medical records.
DLCST	Recruitment of volunteers via advertisement in free newspapers. Acquisitions of smoking habits via questionnaire.	Annual collection of data for the intervention and control groups by questionnaire regarding health, lifestyle, smoking habits and psychosocial consequences of screening. Mortality information was obtained annually from the Danish Civil Registration System. In the case of death, cause-of-death information was extracted from the Danish Causes of Death Registry. In addition to the registry inquiries, the medical history of the deceased was obtained, if possible, from general practitioners, hospital medical records and autopsy reports. For lung cancer data, annual inquiries to the Danish Lung Cancer Registry were made. Active participants and dropouts were followed up for 10 years (since randomisation) or until death. At 5 years after the latest CT scan in the intervention group, inquiries were made to the Danish Lung Cancer Registry, the Danish Cancer Registry, the Danish Causes of Death Registry, and the Danish Pathology Registry.
ITALUNG	Recruitment of volunteers via cooperating family doctors. Acquisition of smoking habits via questionnaire.	After 4 years, each enrolled subject or his/her general practitioner was interviewed via telephone. In addition, data collection for incidence of lung cancer and mortality was done by linkage to the local cancer registry.
LUSI	Sample identified through population registries. Acquisition of smoking habits via a questionnaire sent by mail.	After five annual screening examinations in the intervention group, follow-up of the intervention and control groups for a further 5 years via annual questionnaire sent by mail. In addition, repeated linkage of the cancer registry to the local population registers was made.
MILD	Recruitment via advertisement and articles in the media and on television. Eligibility check by questionnaire via telephone, fax, e-mail or Internet. In both groups, retrieval of information on smoking habits, personal and family medical history and smoking cessation efforts.	Active telephone follow-up and record linkage with the cancer registry of Lombardy. For deceased participants, death certificates were obtained from Istituto Nazionale di Statistica.
NELSON	Sample identified through population registries. Acquisition of smoking habits via a questionnaire sent via mail.	Follow-up data after 5, 7, 10 and 11 years were obtained via national registries. In addition, linkage to a population-based database was made to obtain data regarding, inter alia, date of death and cause of death for participants from Belgium.

Study	Method of recruitment	Follow-up
LDCT screening versus chest X-ray screening		
LSS	Recruitment of volunteers via large-scale mailings, media adverts and posters and medical doctors' recommendations. Acquisition of smoking habits not reported.	Study participants completed a study update form at the 2nd screening to identify any cases of lung cancer identified after negative or missing 1st screening results (baseline screening). After a negative screening result in the 2nd screening round, subjects did not receive any further follow-up. In 2007, linkage of all participant records with mortality registry (National Death Index) until 2005.
NLST	Recruitment via targeted mailings, advertisements on radio, television and the internet, targeted address of local groups and associations via information channels of the National Cancer Institutes and the American Cancer Society, institutional websites, targeted recruitment of minority groups.	Vital status of participants was obtained via annual (LSS) or half-yearly (ACRIN) questionnaires to 31st December 2009. Vital status of participants lost to follow-up was obtained by matching with mortality registries. Cases of death were compared with data from death certificates.

Abbreviations: ACRIN=American College of Radiology Imaging Network; C=control group; I=intervention group; CT=computed tomography; LDCT=low-dose CT

Table 4.5: Characterisation of the intervention: part 2

Study	Screening strategy as reported
LDCT screening versus no screening	
DANTE	**Intervention:** **Information on performance/implementation of screening:** Screening strategy: • Number of screening rounds: 5 • Screening interval: 1 year • Additional chest X-ray examination by radiologists blinded to CT results and 3-day sputum cytology at baseline CT technology: • Single-slice and (since 2003) multislice CT scanner CT parameters: • Slice thickness: 5 mm (reconstruction interval: 3 mm); in the case of follow-up examinations for abnormalities suggestive of malignancy, high-resolution CT (reconstruction interval: 1 mm) • Dosage: n.r. Imaging evaluation/interpretation: • Independent reading of images by two radiologists. In cases of disagreement, consensus reading was obtained with the local coordinator. **Definitions and consequences:** Negative screening result: • Pulmonary nodule < 5 mm in diameter, pleural plaques, diffuse emphysema, bullae, widespread ground-glass opacities, bronchiectasis, pulmonary fibrosis or other minor abnormalities o Diagnostic follow-up: continuation of regular screening Suspicious screening result: • Abnormalities of the heart, aorta or mediastinal structures, not suggestive of lung malignancy but requiring further evaluation, were documented. • Pulmonary nodule < 10 mm in diameter with smooth surface • Diagnostic follow-up: LDCT at 3, 6 and then 12 months Positive screening result: • Noncalcified pulmonary nodules ≥ 10 mm in diameter, or smaller but showing speculated margins • Non-nodular lesions such as a hilar mass, focal ground-glass opacities, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses

Study	Screening strategy as reported
	Diagnostic workup of positive screening results by high-resolution CT: • Pulmonary nodule ≥ 6 mm but ≤ 10 mm in diameter: oral antibiotics and repeat high-resolution CT after 6–8 weeks; if no regression, follow the lesion or perform invasive procedures to obtain a tissue diagnosis (bronchoscopy, fine-needle aspiration biopsy or VATS) • Pulmonary nodule > 10 mm but ≤ 20 mm in diameter: oral antibiotics and repeat high-resolution CT after 6–8 weeks; if no regression; PET scan for solid lesions or follow the lesion or perform invasive procedures to obtain a tissue diagnosis (bronchoscopy, fine-needle aspiration biopsy, VATS or thoracotomy) • Pulmonary nodule > 20 mm in diameter: discretional oral antibiotics and high-resolution CT or standard contrast-enhanced CT and PET scan; if PET scan positive, tissue diagnosis by bronchoscopy, percutaneous fine-needle aspiration biopsy, VATS or thoracotomy; if PET scan negative, close follow-up and biopsy in cases of lesion progression
	Confirmation of diagnosis: • The workup protocol was not rigid but only served as a guide for clinicians, and could be adjusted on the basis of personal preferences, experience and availability of facilities.
	Comparator: • Chest X-ray examination and 3-day sputum cytology at baseline • Afterwards, annual invitation for medical telephone interviews and follow-up clinical examination for 4 years Diagnostic follow-up: • Chest X-ray in addition to medical interview in cases of abnormality or difficulties in breathing
DLCST	**Intervention:** **Information on performance/implementation of screening:** Screening strategy: • Number of screening rounds: 5 • Screening interval: 1 year CT technology: • Multislice CT scanner: 16-slice scanner CT parameters: • Slice thickness: 1,5 mm • Estimated effective dose of approximately 1 mSv[a] Imaging evaluation/interpretation: • Independent reading of images by two certified radiologists. In cases of disagreement, consensus was obtained. Weekly conferences on diagnostic findings between a radiologist, pulmonologist and surgeon. Definition and consequences: • All pulmonary nodules were classified into four categories according to location, size and shape. • At incidence screenings, nodules were characterised as new or pre-existing, as solid, nonsolid, or part-solid. Evaluation of size was based on linear measurement of the maximal diameter and computer-based volume calculations. • Growth was defined as an increase in volume of at least 25%. VDT was used to measure the growth rate and was considered a supplement in decision-making. • VDT < 400 days: rapid growth; increased suspicion of malignancy • VDT > 400 days: slow growth, decreased suspicion of malignancy Negative screening result: *Category 1* • Pulmonary nodule with benign characteristics ≤ 15 mm in diameter • Calcified pulmonary nodules ≤ 20 mm in diameter • Diagnostic follow-up: documentation, continuation of the planned screening *Category 2* • No pulmonary nodule • Pulmonary nodule < 5 mm in diameter • Diagnostic follow-up: documentation, continuation of the planned screening

Study	Screening strategy as reported
	Positive screening result: *Category 3* • Pulmonary nodule 5–15 mm in diameter not classified as benign, confirmed by repeat LDCT after 3 months *Category 4* • Pulmonary nodule > 15 mm in diameter *Category 5* • Rapidly growing pulmonary nodules (> 25% increase in volume): **Diagnostic workup of positive screening results:** • Referral of participants for diagnostic evaluation was decided at weekly follow-up conferences between a pulmonologist and the radiologists. Indeterminate nodules were often evaluated using FDG-PET-CT. CT with contrast was performed before invasive procedures. Depending on the results of these initial procedures, an individual diagnostic plan was made involving a variety of invasive procedures such as bronchoscopy, transthoracic needle-aspiration biopsy, endoscopic ultrasound, endobronchial ultrasound and/or mediastinoscopy or VATS. Confirmation of diagnosis: • FDG-PET, VATS and other procedures had to be performed for staging of the disease. Final staging was determined according to the cytology/histology of the cancers and the recommendations of the International Association for the Study of Lung Cancer seventh edition.
	Comparator: • No screening • In cases of clinical suspicion of lung cancer, the Danish national guidelines for lung cancer management were followed.
ITALUNG	**Intervention:** **Information on performance/implementation of screening:** Screening strategy • Number of screening rounds: 4 • Screening interval: 1 year CT technology: • Single-slice and multislice CT scanner CT parameters: • Slice thickness: ≤ 3 mm • Mean annual effective dose: o Multislice CT: 0.83 mSv/participant o Single-slice CT: 1.46 mSv/participant (3 mm collimation) or 1.78 mSv/participant (10 mm collimation) • Mean effective dose across all screening rounds: o CT scans and clarifying diagnostics: 6.2–6.8 mSv/participant o CT-guided fine-needle aspiration biopsy, per scan: 0.9 mSv for multislice CT; 2.1 mSv for single-slice CT Imaging evaluation/interpretation: • Independent reading of images by two radiologists
	Definitions and consequences: Negative screening result: • No pulmonary nodule/no focal abnormalities • Solid, noncalcified pulmonary nodule < 5 mm in diameter • Pure, nonsolid pulmonary nodule < 10 mm in diameter • Diagnostic follow-up: continuation of planned screening Suspicious screening result: • New pulmonary nodule ≤ 3 mm: diagnostic follow-up LDCT after 6 months • New pulmonary nodule between 3 and 5 mm: diagnostic follow-up LDCT after 3 months Positive screening result: • Solid, noncalcified pulmonary nodule ≥ 5 mm in diameter • Nonsolid pulmonary nodule ≥ 10 mm in diameter • Part-solid pulmonary nodule

Study	Screening strategy as reported
	Diagnostic workup of positive screening results at baseline screening: • Solid, noncalcified pulmonary nodule ≥ 8 mm in diameter and nonsolid, noncalcified pulmonary nodule > 10 mm in diameter, persistent after antibiotic therapy: FDG-PET, in some cases for large lesions, CT-guided fine-needle aspiration biopsy or fibre optic bronchoscopy o PET-positive pulmonary nodule: fine-needle aspiration biopsy; negative or intermediate finding: follow-up LDCT after 3 months o PET-negative pulmonary nodule: follow-up LDCT after 3 months; negative finding: continuation of planned screening • Solid or part-solid noncalcified pulmonary nodule between 5 and 7 mm in diameter: LDCT after 3 months o In cases of significant growth: FDG-PET or CT-guided fine-needle aspiration biopsy for peripheral pulmonary nodule or fibre optic bronchoscopy for nonperipheral pulmonary nodule • Focal abnormalities consistent with inflammatory disease: antibiotic therapy and follow-up LDCT after 1 month o Complete resolution of the abnormality: continuation of planned screening o Partial or no resolution of the abnormality: antibiotic therapy and follow-up LDCT after 2 months **Diagnostic workup of positive screening results at incidence screening rounds:** • Pulmonary nodule ≥ 5 mm in diameter or in cases of multiple focal solid or nonsolid abnormalities, consistent with inflammatory disease: antibiotic therapy and follow-up LDCT after 1 month o Complete resolution of the abnormality: continuation of planned screening o Partial or no resolution of the abnormality: antibiotic therapy and follow-up LDCT after 2 months • Solid, noncalcified pulmonary nodule ≥ 8 mm in diameter, persistent after antibiotic therapy: FDG-PET; in cases with larger lesions, direct CT-guided fine-needle aspiration biopsy or fibre optic bronchoscopy o PET-positive pulmonary nodule: fine-needle aspiration biopsy; negative or intermediate finding: follow-up LDCT after 3 months o PET-negative pulmonary nodule: follow-up LDCT after 3 months; negative finding: continuation of planned screening • New or growing nonsolid or part-solid noncalcified pulmonary nodule ≥ 8 mm in diameter, persistent after antibiotic therapy: CT-guided fine-needle aspiration biopsy
	Confirmation of diagnosis: • Management of positive screening results according to a shared protocol basically similar to that of the I-ELCAP study. • All surgically removed lesions were evaluated according to WHO criteria [305]. Staging of screen-detected lung cancer was based on the pathology report when available, or on contrast-enhanced CT or FDG-PET findings in cases not amenable to surgical resection.
	Comparator: No screening
LUSI	**Intervention:** **Information on performance/implementation of screening:** Screening strategy: • Number of screening rounds: 5 • Screening interval: 1 year CT technology: • Multislice CT scanner: initially 16-slice scanner, since 2010 128-slice scanner CT parameters: • Slice thickness: 1 mm, reconstruction interval: 0.8 and 0.7 mm • Estimated effective dose: 1.6–2 mSv per scan maximally Imaging evaluation/interpretation: • Multislice CT data were evaluated by specially trained radiologists. • Initial nodule evaluation was done using 2D image representation and subsequent evaluation with 3D representation using CAD (MEDIAN) with volumetric software.

Study	Screening strategy as reported
	Definitions and consequences: Negative screening result (baseline screening/primary screening): • No pulmonary nodule: continuation of planned screening • Pulmonary nodule < 5 mm in diameter: continuation of planned screening Suspicious screening result (baseline screening/primary screening): • Largest observed pulmonary nodule between 5 and 7 mm in diameter: LDCT after 6 months • Largest observed pulmonary nodule between 8 and 10 mm in diameter: LDCT after 3 months • Largest observed pulmonary nodule > 10 mm in diameter: immediate recall Negative screening result (repeat LDCT): • Disappearance of pulmonary nodule: continuation of planned screening • VDT > 600 days: continuation of planned screening Suspicious screening result (repeat LDCT): • Pulmonary nodule with VDT between 400 and 600 days: LDCT after 3 or 6 months according to nodule diameter (< 7.5 mm in diameter; 7.5–10 mm in diameter) • Pulmonary nodule with VDT < 400 days or > 10 mm in diameter: immediate recall (recommendation of individual assessment by an office-based pulmonologist, which could involve X-ray examination, full-dose CT, PET, bronchoscopy, VATS, biopsy, antibiotic treatment) **Diagnostic workup and confirmation of diagnosis:** • Clinical workup for malignancies followed respective guidelines and was not affected by the trialists.
	Comparator: • No screening • Collection of data for incidence of lung cancer by annual inquiries and information from office-based physicians, as well as record linkages to the local population registers and cancer registries.
MILD	**Intervention:** **Information on performance/implementation of screening:** • Randomised allocation to two LDCT screening groups: annual or biennial Screening strategy: • Number of screening rounds: 7 for participants with annual screening, 4 for those with biennial screening • Screening interval: 1 year or 2 years
	CT technology: • Multislice CT scanner: 16-slice scanner CT parameters: • Slice thickness: 1 mm • Dosage: n.r. Imaging evaluation/interpretation: • Independent reading of images by two radiologists, of whom one took a software-automated volume measurement. In the event of disagreement, a third radiologist was consulted. **Definitions and consequences:** Negative screening result: • Solid pulmonary nodule with a volume < 60 mm³ (≤ 4.8 mm in diameter) • Pulmonary nodule with benign characterisation • Diagnostic follow-up: continuation of planned screening Indeterminate screening result: • Pulmonary nodule with a volume between 60 and 250 mm^3 (between 5 and 8 mm in diameter) • Diagnostic follow-up: repeat LDCT after 3 months ○ Positive screening result in cases of noncalcified pulmonary nodule, otherwise annual screening (in both screening interval groups) Positive screening result: • Pulmonary nodule with a volume > 250 mm³

Study	Screening strategy as reported

	• Follow-up: PET or contrast-enhanced CT, in cases of positive FDG uptake, biopsy or lung surgery
	  o Threshold indicative of malignant growth: volumetric growth of ≥ 25%
	  o Nodules showing no volumetric growth: continuation of planned screening
	Confirmation of diagnosis:
	• Final staging of disease was according to the histology (pTNM) and the recommendations in the seventh edition of the International Association for the Study of Lung Cancer.

	Comparator: No screening

NELSON	**Intervention:**
	Information on performance/implementation of screening:
	Screening strategy:
	• Number of screening rounds: 4 rounds over 5.5 years
	• Screening interval: 1 year, 2 years and 2.5 years
	CT technology:
	• Multislice CT scanner
	• Initially 16-slice, later 64-slice scanner
	CT parameters:
	• Slice thickness: 1 mm
	• Estimated effective dose: < 0.4 mSv up to < 1.6 mSv (depending on body weight)
	Imaging evaluation/interpretation:
	• Independent reading of images by two radiologists in the first two screening rounds. In cases of discrepancy, a third experienced radiologist made the final decision.
	• Images from the last two screening rounds were read by a single radiologist with 6 years of experience in thoracic imaging.
	• Images were read using semi-automated software.
	Definitions and consequences:
	New pulmonary nodules evaluated according to size and characteristics. For pulmonary nodules that were present previously, the growth rate is calculated via comparison of CT scans:
	• Negative screening result: change of volume < 25%
	• Calculation of VDT in cases with an increase in volume of ≥ 25%
	Categories of new pulmonary nodules:
	NODCAT 1:
	• Benign pulmonary nodule (with fat/benign calcifications) or other benign abnormalities
	NODCAT 2:
	• Pulmonary nodule smaller than NODCAT 3, not belonging to NODCAT 1
	NODCAT 3:
	• Solid pulmonary nodule: volume ≥ 50 mm^3 and ≤ 500 mm^3
	• Solid pleural-based pulmonary nodule: minimal diameter ≥ 5 mm and ≤ 10 mm
	• Partial solid pulmonary nodule
	  o With solid component: volume ≥ 50 mm^3 and ≤ 500 mm^3
	  o With nonsolid component: mean diameter ≥ 8 mm
	• Nonsolid pulmonary nodule: mean diameter ≥ 8 mm
	NODCAT 4:
	• Solid pulmonary nodule: volume > 500 mm^3
	• Solid pleural-based pulmonary nodule: minimal diameter > 10 mm
	• Partial solid pulmonary nodule with solid component: volume > 500 mm^3
	Categories of existing pulmonary nodules:
	• GROWCAT A: VDT > 600 days
	• GROWCAT B: VDT ≤ 400 days and ≤ 600 days
	• GROWCAT C: VDT < 400 days, or new solid component in nonsolid lesion

	Definitions baseline screening/primary screening Negative screening result: • NODCAT 1 and NODCAT 2 • GROWCAT A and GROWCAT B (result of LDCT follow-up after 3–4 months for indeterminate result) • Diagnostic follow-up: continuation of planned screening

Study	Screening strategy as reported
	Indeterminate screening result: • NODCAT 3 • Diagnostic follow-up: LDCT follow-up after 3–4 months Positive screening result: • NODCAT 4 • GROWCAT C (result of LDCT follow-up after 3–4 months for indeterminate result) • Diagnostic follow-up: Referral to pulmonologist for workup and diagnosis: If lung cancer was diagnosed, the participant was treated and left the screening trial; otherwise (benign result) the regular next-round CT was scheduled. **Definitions subsequent screening rounds:** Negative screening result: • NODCAT 1, GROWCAT A • Diagnostic follow-up: continuation of planned screening Indeterminate screening result: • NODCAT 2, NODCAT 3, GROWCAT B • Diagnostic follow-up: LDCT follow-up after 1 year (NODCAT 2 and GROWCAT B) or after 6–8 weeks (NODCAT 3) Positive screening result: • NODCAT 4, GROWCAT C • Diagnostic follow-up: referral to pulmonologist for workup and diagnosis: If lung cancer was diagnosed, the participant was treated and left the screening trial; otherwise (benign result) the regular next-round CT was scheduled.
	Confirmation of diagnosis: Workup, staging and treatment were standardised across all screening sites to national or international guidelines. Diagnostic workup included physical examination, bronchoscopy, FDG-PET scan and contrast-enhanced standard-dose CT of the chest and upper abdomen. Participants with a positive nonsurgical diagnostic workup were referred for surgery for histological workup of the pulmonary nodule. All cases of suspected lung cancer were discussed in a multidisciplinary tumour board.
	Comparator: No screening
LDCT screening versus chest X-ray screening	
LSS	**Intervention:** **Information on performance/implementation of screening:** Screening strategy: • Number of screening rounds: 5 • Screening interval: 1 year • Additional chest X-ray examination by radiologists blinded to CT results and 3-day sputum cytology at baseline CT technology: • Single-slice and (since 2003) multi-slice CT scanner CT parameters: • Slice thickness: 5 mm (reconstruction interval: 3 mm); for follow-up examinations for abnormalities suggestive of malignancy, high-resolution CT (reconstruction interval: 1 mm) • Dosage: n.r. Imaging evaluation/interpretation: • Independent reading of images by two radiologists. In cases of disagreement, consensus reading was obtained with the local coordinator. **Definitions and consequences:** Negative screening result: • Pulmonary nodule < 5 mm in diameter, pleural plaques, diffuse emphysema, bullae, widespread ground-glass opacities, bronchiectasis, pulmonary fibrosis or other minor abnormalities • Diagnostic follow-up: continuation of regular screening Suspicious screening result: • Abnormalities of the heart, aorta or mediastinal structures, not suggestive of lung malignancy but requiring further evaluation, were documented.

Study	Screening strategy as reported
	• Pulmonary nodule < 10 mm in diameter with smooth surface • Diagnostic follow-up: LDCT at 3, 6 and then 12 months Positive screening result: • Noncalcified pulmonary nodules ≥ 10 mm in diameter, or smaller but showing speculated margins • Non-nodular lesions such as a hilar mass, focal ground-glass opacities, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses
	Diagnostic workup of positive screening results by high-resolution CT: • Pulmonary nodule ≥ 6 mm but ≤ 10 mm in diameter: oral antibiotics and repeat high-resolution CT after 6–8 weeks; if no regression, follow the lesion or perform invasive procedures to obtain a tissue diagnosis (bronchoscopy, fine-needle aspiration biopsy or VATS) • Pulmonary nodule > 10 mm but ≤ 20 mm in diameter: oral antibiotics and repeat high-resolution CT after 6–8 weeks; if no regression, PET scan for solid lesions or follow the lesion or perform invasive procedures to obtain a tissue diagnosis (bronchoscopy, fine-needle aspiration biopsy, VATS or thoracotomy) • Pulmonary nodule > 20 mm in diameter: discretional oral antibiotics and high-resolution CT or standard contrast-enhanced CT and PET scan; if PET scan positive, tissue diagnosis by bronchoscopy, percutaneous fine-needle aspiration biopsy, VATS or thoracotomy; if PET scan negative, close follow-up and biopsy in cases of lesion progression
	Confirmation of diagnosis: The workup protocol was not rigid but only served as a guide for clinicians, and could be adjusted on the basis of personal preferences, experience and availability of facilities
	Comparator: • Chest X-ray examination and 3-day sputum cytology at baseline • Afterwards, annual invitation for medical telephone interviews and follow-up clinical examination for 4 years Diagnostic follow-up: • Chest X-ray in addition to medical interview in cases of abnormality or difficulties in breathing
	Intervention: **Information on performance/implementation of screening:** Screening strategy: • Number of screening rounds: 5 • Screening interval: 1 year CT technology: • Multislice CT scanner: 16-slice scanner CT parameters: • Slice thickness: 1,5 mm • Estimated effective dose of around 1 mSv[a] Imaging evaluation/interpretation: • Independent reading of images by two certified radiologists. In cases of disagreement, consensus was obtained. Weekly conferences on diagnostic findings between a radiologist, pulmonologist and surgeon. **Definition and consequences:** • All pulmonary nodules were classified into four categories according to location, size and shape. • At incidence screenings, nodules were characterised as new or pre-existing, as solid, nonsolid, or part-solid. Evaluation of size was based on linear measurement of the maximal diameter and computer-based volume calculations. • Growth was defined as an increase in volume of at least 25%. VDT was used to measure the growth rate and was considered a supplement in decision-making. • VDT < 400 days: rapid growth; increased suspicion of malignancy • VDT > 400 days: slow growth, decreased suspicion of malignancy Negative screening result: *Category 1* • Pulmonary nodule with benign characteristics ≤ 15 mm in diameter • Calcified pulmonary nodules ≤ 20 mm in diameter • Diagnostic follow-up: documentation, continuation of the planned screening

Study	Screening strategy as reported
	Category 2 • No pulmonary nodule • Pulmonary nodule < 5 mm in diameter • Diagnostic follow-up: documentation, continuation of the planned screening
NLST	Positive screening result: *Category 3* • Pulmonary nodule 5–15 mm in diameter not classified as benign, confirmed by repeat LDCT scan after 3 months *Category 4* • Pulmonary nodule > 15 mm in diameter *Category 5* • Rapidly growing pulmonary nodules (> 25% increase in volume): Diagnostic workup for positive screening results: • Referral of participants for diagnostic evaluation was decided at weekly follow-up conferences between a pulmonologist and the radiologists. Indeterminate nodules were often evaluated using FDG-PET-CT. CT with contrast was performed before invasive procedures. Depending on the results of these initial procedures an individual diagnostic plan was made involving a variety of invasive procedures such as bronchoscopy, transthoracic needle-aspiration biopsy, endoscopic ultrasound, endobronchial ultrasound and/or mediastinoscopy or VATS. **Confirmation of diagnosis:** • FDG-PET, VATS and other procedures had to be performed for staging of the disease. Final staging was according to the cytology/histology of the cancers and the recommendations of the International Association for the Study of Lung Cancer seventh edition.
	Comparator: • No screening • In cases of clinical suspicion of lung cancer, the Danish national guidelines for lung cancer management were followed.

	Intervention:
	Information on performance/implementation of screening:
	Screening strategy
	• Number of screening rounds: 4
	• Screening interval: 1 year
	CT technology:
	• Single-slice and multi-slice CT-scanner
	CT parameters:
	• Slice thickness: ≤ 3 mm
	• Mean annual effective dose:
	  ○ Multi-slice CT: 0.83 mSv/participant
	  ○ Single-slice CT: 1.46 mSv/participant (3 mm collimation) or 1.78 mSv/participant (10 mm collimation)
	• Mean effective dose across all screening rounds:
	  ○ CT scans and clarifying diagnostics: 6.2–6.8 mSv/participant
	  ○ CT-guided fine-needle aspiration biopsy, per scan: 0.9 mSv for multislice CT; 2.1 mSv for single-slice CT
	Imaging evaluation/interpretation:
	• Independent reading of images by two radiologists

Abbreviations: ACRIN=American College of Radiology Imaging Network; CAD=computer-aided detection; CT=computed tomography; FDG=fluorodeoxyglucose; GROWCAT=nodule category based on volume doubling time (growth); I-ELCAP= International Early Lung Cancer Action Program; NODCAT=nodule category based on volume; n.r.=not reported; PET=positron emission tomography LDCT=low-dose CT; VATS=video-assisted thoracoscopic surgery; VDT=volume doubling time.

[a] Information is derived from CT parameters given in the publication.

[b] Information is based on 2002 European guidelines on quality criteria for computed tomography, EUR 16262 EN.

[c] Information is based on 2007 recommendations of the International Commission on Radiological Protection (http://www.icrp.org/publication.asp?id=ICRP%20Publication%20103).

Table 4.6 and Table 4.7 show the characteristics of the patients in the studies included in the review.

The studies included men and women who smoked at baseline (at least 20 or 30 pack-years) or stopped smoking less than 10 years ago (15 years in the NLST). Exceptions are the DANTE study, which only examined men, and the NELSON study. In the latter, only men were recruited initially, with women recruited only later in the course of the study. The authors justify this with a lower proportion of women with long-term exposure to cigarette consumption in the Dutch population and an associated increased effort to recruit the desired number of cases. The percentage of women in the NELSON study is therefore only approximately 16%, while in the other studies it is at least 31%. The age of participants in the studies was set in a range from ≥ 49 years to 75 years, whereby the MILD study was the only study not to set an upper age limit.

Table 4.6: Inclusion and exclusion criteria

Study	Essential inclusion criteria	Essential exclusion criteria
LDCT screening versus no screening		
DANTE	• Age: 60–74 years • Male sex • Smokers • Former smokers (quit < 10 years before recruitment) • ≥ 20 pack-years	• Severe comorbidity with life expectancy ≤ 5 years • Severe heart failure • Chronic respiratory insufficiency • O_2 saturation levels < 94% at rest • Uncontrolled hypertension • Severe vascular disease in active smokers • Uncompensated diabetes • Other severe metabolic disturbances • Renal disease • Inability to comply with the follow-up protocol • Dementia, schizophrenia or other severe psychiatric conditions • Drug or alcohol addiction • Conditions carrying severe disability • Previous malignancy (except nonmelanoma skin cancer) • Cancer of any organ site, if treated < 10 years before accrual • Early squamous cancer of the larynx/oral cavity, < 5 years
DLCST	• Age: 50–70 years • Male and female sex • Smokers • Former smokers (quit < 10 years before recruitment and after the age of 50 years) • ≥ 20 pack-years	• Not able to climb two flights of stairs (36 steps) without pausing • Body weight > 130 kg • Symptoms of lung cancer • FEV1 ≥ 30% of predicted normal at baseline • Previous treatment of lung cancer, breast cancer, malignant melanoma or hypernephroma • History of any other cancer within 5 years or tuberculosis within 2 years or any serious illness that would shorten life expectancy to < 10 years • Chest CT within the last year before recruitment
ITALUNG	• Age: 55–69 years • Male and female sex • Smokers • Former smokers (quit < 10 years before recruitment) • ≥ 20 pack-years within the last 10 years	• History of previous cancer other than nonmelanoma skin cancer • General condition precluding thoracic surgery

Study	Essential inclusion criteria	Essential exclusion criteria
LUSI	• Age: 50–69 years • Male and female sex • Smokers • former smokers (quit < 10 years before recruitment) • > 15 cigarettes per day for ≥ 25 years or > 10 cigarettes per day for ≥ 30 years	• Cancer diagnosis ≤ 5 years ago • Medical circumstances preventing surgical treatment in the case of a lung cancer diagnosis • Serious illness shortening life expectancy to < 10 years
MILD	• Age: ≥ 49 years • Male and female sex • Smokers • Former smokers (quit < 10 years before recruitment) • ≥ 20 pack-years	• Cancer diagnosis ≤ 5 years ago
NELSON	• Age:50–75 years (1928–1952) • Initially only male sex, with female sex later too • Smokers • Former smokers (quit < 10 years before recruitment) • > 15 cigarettes per day for ≥ 25 years or > 10 cigarettes per day for ≥ 30 years	• Moderate or bad self-reported health • Unable to climb two flights of stairs • Body weight ≥ 140 kg • Enough cardiopulmonary reserve to undergo surgery • Current or past renal cancer, melanoma or breast cancer • Lung cancer diagnosed < 5 years ago • Lung cancer diagnosed ≥ 5 years ago but still under treatment • Chest CT < 1 year before filling in the first study questionnaire
LDCT screening versus chest X-ray screening		
LSS	• Age: 55–74 years • Male and female sex • Smokers • Former smokers (quit < 10 years before recruitment) • ≥ 30 pack-years	• Thoracic or lung CT ≤ 2 years ago • History of lung cancer • Current treatment for other cancer (except nonmelanoma skin cancer) • Removal of a portion of a lung or an entire lung • Participation in another cancer screening trial (including the PLCO cancer trial) or a primary cancer prevention trial other than a smoking cessation study
NLST	• Age: 55–74 years • Male and female sex • Smokers • Former smokers (quit < 15 years before recruitment) • ≥ 30 pack-years • Ability to lie on the back with arms raised over the head	• Metallic implants or devices in the chest or back, such as pacemakers • Treatment for or evidence of any cancer other than nonmelanoma skin cancer or carcinoma in situ (with the exception of transitional-cell carcinoma in situ or bladder carcinoma in situ) ≤ 5 years ago • History of lung cancer • History of removal of any portion of the lung, excluding needle biopsy • Requirement for home oxygen supplementation • Participation in another cancer screening trial • Participation in a cancer prevention study, other than a smoking cessation study • Unexplained weight loss of > 6.8 kg ≤ 12 months ago • Recent haemoptysis • Pneumonia or acute respiratory infection treated with antibiotics ≤ 12 weeks ago • Chest CT examination ≤ 18 months ago

Abbreviations: CT=computed tomography; FEV1=forced expiratory volume in 1 second; LDCT=low-dose CT.

Table 4.7: Baseline characteristics of the study population

Study group	N	Mean age, years (SD)	F/M sex (%)	Active smokers (%)	Median cigarette consumption, pack-years (IQR)
LDCT screening versus no screening					
DANTE					
Intervention	1264	64.6 (5.0 [a])	0/100	56.5	45.0 (28.5)
Comparator	1186	64.6 (4.1 [a])	0/100	57.4	45.0 (32.5)
DLCST					
Intervention	2052	57.9 (4.8)	44[a]/56	75.3	36.4 (13.4) [b]
Comparator	2052	57.8 (4.8)	45[a]/55	76.9	35.9 (13.4) [b]
ITALUNG					
Intervention	1613	60.9 (n.r.)	36/64	66	40 (n.r.)
Comparator	1593	60.7 (n.r.)	35/65	64	38 (n.r.)
LUSI					
Intervention	2029	55 [c] (n.r.)	35.1[a]/64.8[a]	62.1[a]	n.r.
Comparator	2023	55 [c] (n.r.)	35.4[a]/64.6[a]	61.7[a]	n.r.
MILD					
Intervention (annual)	1190	57 [c] (n.r.)	31.6/68.4	68.9	39 (n.r.)
Intervention (biennial)	1186	58 [c] (n.r.)	31.5/68.5	68.3	39 (n.r.)
Comparator	1723	57 [c] (n.r.)	36.7/63.3	89.7	38 (n.r.)
NELSON					
Intervention	7900	58.0 (8.0) [d]	16.7/83.3	56.0	38 (19.8)
Comparator	7892	58.0 (8.0) [d]	16.2/83.8	55.1	38 (19.8)
LDCT screening versus chest X-ray screening					
LSS		*N* (%)			*N* (%)
Intervention	1660	Aged 55–59: 616 (37.1) Aged 60–64: 514 (31.0) Aged 65–69: 337 (20.3) Aged 70–74: 193 (11.6)	41.9/58.1	57.9	< 40 pack-years: 300 (18.1) 44–55 [e] pack-years: 553 (33.3) 55–75 pack-years: 377 (22.7) > 75 pack-years: 430 (25.9)
Comparator	1658	Aged 55–59: 624 (37.6) Aged 60–64: 500 (30.2) Aged 65–69: 348 (21.0) Aged 70–74: 186 (11.2)	41.0/59.0	57.1	< 40 pack-years: 289 (17.4) 44–55 [e] pack-years: 559 (33.7) 55–75 pack-years: 384 (23.3) > 75 pack-years: 426 (25.7)
NLST					
Intervention	26,723[f]	61.4 (5.0)	41.0/59.0	48.2	48.0 (27.0)
Comparator	26,733[f,g]		41.0/59.0	48.3	48.0 (27.3)

Abbreviations: F=female; IQR=interquartile range; LDCT=low-dose computed tomography; M=male; N=number of individuals randomised (or included); n.r.=not reported; SD=standard deviation.

[a] Own calculation.

[b] Mean (SD).

[c] Median.

[d] Median (IQR).

[e] It remained unclear to which group individuals with consumption of 55 pack-years were assigned.

[f] Including one duplicate, therefore there is a deviation from Table 4.3 and Table 4.5 and the tables of results.

[g] Two further individuals were not included in the evaluation without giving reasons, therefore there is a deviation from the tables of results.

Table 4.8 shows the characterisation of the participant flow within the studies.

The participation rate in screening (adherence to screening) was between 81% and 96% in the respective intervention groups. Of the studies using no screening as the comparator, three reported contamination between 1% and 7%, although it is unclear how valid this information is. A study with chest X-ray screening as the comparator reported contamination of 4%. For the other four studies, no information on contamination was available.

Table 4.8: Characterisation of the participant flow within the studies included

Study	*N* included	*N* (%) adherence to screening	*N* (%) contamination	*N* (%) recall rate [a] for screened participants	*N* (%) invasive clarifying diagnostics for participants
LDCT screening versus no screening					
DANTE	*Screening round 1–5* I: 1264 [b] C: 1186 [b]	*Participation in all 5 screening rounds* I: 1184 (93.7)	n.r.	*Screening round 1–5* I: 355 [c] (30.0) [d] C: n.r.	*Screening round 1–5* I: 144 [e] (11.4) C: 64 [e] (5.4)
DLCST	*Screening round 1* I: 2052 *Screening round 2* I: n.r. *Screening round 3* I: n.r. *Screening round 4* I: n.r. *Screening round 5* I: n.r.	*Screening round 1* I: 2047 (99.8) *Screening round 2* I: 1976 (96.3) [g] *Screening round 3* I: 1944 (94.7) [g] *Screening round 4* I: 1982 (96.6) [g] *Screening round 5* I: 1851 (90.2) [g]	n.r.	*Screening round 1* I: 155 [f] (7.6) *Screening round 2* I: 20 [f] (1.0) *Screening round 3* I: 24 [f] (1.2) *Screening round 4* I: 18 [f] (0.9) *Screening round 5* I: 24 [f] (1.3)	n.r.
		Average participation in screening rounds 1–5 I: 1960 [d] (95.5) [g]	*Screening rounds 1–5* C: 152 (7.4 [h])	*Screening rounds 1–5* I: n.r.	*Screening rounds 1–5* n.r.
ITALUNG	*Screening round 1* I: 1613 *Screening round 2* I: 1593 *Screening round 3* I: 1589 *Screening round 4* I: 1581	*Screening round 1* I: 1406 (87.1) *Screening round 2* I: 1356 (85.1) *Screening round 3* I: 1308 (82.3) *Screening round 4* I: 1263 (79.8)	n.r.	*Screening round 1* I: 426 [i] (30.3) *Screening round 2* I: n.r. *Screening round 3* I: n.r. *Screening round 4* I: n.r.	n.r.
		Average participation in screening rounds 1–4 I: 1302 (81)	n.r.	*Screening round 1–4* I: 741 [j] (52.7) *Screening round 2–4* I: n.r. [i] (15.7)	*Screening round 1–4* CT-guided FNAB I: 34 (2.4) [d] C: n.r. Optical FBS I: 30 (2.1)

Study	*N* included	*N* (%) adherence to screening	*N* (%) contamination	*N* (%) recall rate [a] for screened participants	*N* (%) invasive clarifying diagnostics for participants
					C: n.r. Resections I: 38 (2.7) C: n.r.
LUSI	*Screening round 1* I: 2029 C: 2023	*Screening round 1* I: 2028 (99.9)	n.r.	*Screening round 1* I: immediately [k]: 53 (2.6) [d] I: after 3 or 6 months [j]: 398 (19.6) [d] I: total: 451 (22.2)	*Screening round 1* I: 52 (2.6) [d] C: n.r.
	Screening round 2 I: 2000	*Screening round 2* I: 1892 (94.6)		*Screening round 2* I: immediately [k]: 36 (1.9) [d] I: after 3 and 6 months [j]: 52 (2.7) [d] I: total: 88 (4.7)	*Screening round 2* I: 31 (1.6) [d] C: n.r.
	Screening round 3 I: 1978	*Screening round 3* I: 1849 (93.5)		*Screening round 3* I: immediately [k]: 25 (1.4) [d] I: after 3 and 6 months [j]: 49 (2.7) [d] I: total: 74 (4.0)	*Screening round 3* I: 23 (1.2) [d] C: n.r.
	Screening round 4 I: 1954	*Screening round 4* I: 1826 (93.4)		*Screening round 4* I: immediately [k]: 33 (1.8) [d] I: after 3 and 6 months [j]: 71 (3.8) [d] I: total: 104 [l] (5.7)	*Screening round 4* I: 26 (1.3 [d]) C: n.r.
	Screening round 5 I: 1925	*Screening round 5* I: 1810 (94.0)	n.r.	*Screening round 5* I: immediately [k]: 26 (1.5) [d] I: after 3 and 6 months [j]: 63 (4.0)[d] I: total: 89 (5.7)	*Screening round 5* I: 26 (1.4) [d] C: n.r.
		Participation in all 5 screening rounds I: 1706 (84.0)	*Screening rounds 1–5* I: 12 [m] (0.6) C: 98 [m] (4.8)	*Screening rounds 1–5* I: immediately [k]: 174[l]	*Screening rounds 1–5* n.r.
MILD	annual screening				
	Screening round 1 I: 1190 *Screening round 2* I: 1141 *Screening round 3* I: 1106	*Screening round 1* I: 1152 (96.8) *Screening round 2* I: 1111 (97.4) *Screening round 3* I: 1086 (98.2)	n.r.	*Screening round 1* I: 171 [d,n] (14.8) *Screening round 2* I: 36 [n] (3.2) *Screening round 3* I: 56 [n] (5.2)	n.r.

Study	*N* included	*N* (%) adherence to screening	*N* (%) contamination	*N* (%) recall rate [a] for screened participants	*N* (%) invasive clarifying diagnostics for participants
	Screening round 4 I: 1078 *Screening round 5* I: 1041 *Screening round 6* I: 1001 *Screening round 7* I: 793	*Screening round 4* I: 1045 (96.9) *Screening round 5* I: 1004 (96.5) *Screening round 6* I: 795 (79.4) *Screening round 7* I: 428 (54.0)		*Screening round 4* I: 29 [n] (2.8) *Screening round 5* I: 25 [n] (2.5) *Screening round 6* I: 7 [n] (0.9) *Screening round 7* I: 15 [n] (3.5)	
		Participation in ≥ 1 screening round I: 1052 (88.4)	*Screening rounds 1–7* C: 21 [o] (1.2)	*Screening round 1–7* n.r.	*Screening rounds 1–7* biopsies I: 5 [p] (0.4) [d] C: n.r.
	biennial screening				
	Screening round 1 I: 1186 *Screening round 2* I: 1138 *Screening round 3* I: 1070 *Screening round 4* I: 972	*Screening round 1* I: 1151 (97.0) *Screening round 2* I: 1086 (95.4) *Screening round 3* I: 983 (91.9) *Screening round 4* I: 751 (77.3)	n.r.	*Screening round 1* I: 158 (13.7) *Screening round 2* I: 51 (4.7) *Screening round 3* I: 31 (3.2) *Screening round 4* I: 34 (4.5)	n.r.
		Participation in ≥ 1 screening round I: 1151 (97.0)	n.r.	*Screening round 1–4* n.r.	*Screening round 1–4* biopsies I: 8 (0.7) [d] C: n.r.
	annual and biennial screening total				
	all screening rounds I: 2376 C: 1723	*Average participation in all screening rounds* I: 2303 [d] (96.9)	n.r.	*all screening rounds* n.r.	*10 years of follow-up:* resections I: total 67 [q] (2.9) [d] annual: 43 (4.1) [d] biennial: 24 (2.1) [d] C: 17 [q] (1.0) [d]

Study	*N* included	*N* (%) adherence to screening	*N* (%) contamination	*N* (%) recall rate [a] for screened participants	*N* (%) invasive clarifying diagnostics for participants
NELSON	*Screening round 1* I: 7915 *Screening round 2* I: 7482 *Screening round 3* I: 7221 *Screening round 4* I: 6735	*Screening round 1* I: 7557 (95.5) *Screening round 2* I: 7295 (97.5) [d] *Screening round 3* I: 6922 (95.9) [d] *Screening round 4* I: 5279 (78.4) [d]	n.r.	*Screening round 1* I: 1571 [c] (20.8) [d] *Screening round 2* I: 570 [c,d] (7.8) [d] *Screening round 3* I: 560 [c,d] (8.1) [d] *Screening round 4* I: n.r.	n.r.
LDCT screening versus chest X-ray screening					
LSS	*Screening round 1* I: 1660 C: 1658	*Screening round 1* I: 1586 (96) C: 1550 (93)	n.r.	*Screening round 1* I: 309 (19.5) C: 140 (9.0)	*Screening round 1* bronchoscopy I: 29 (1.8) C: 8 (0.5) Lung biopsy/resection I: 46 (2.9) C:12 (0.8) Invasive procedures [r] I: 53 (3.3) C: 15 (1.0)
	Screening round 2 I: 1629 C: 1648	*Screening round 2* I: 1398 (85.8) C: 1317 (79.9)		*Screening round 2* I: 332 [s] (23.7) C: 101 (7.7)	*Screening round 2* bronchoscopy I: 14 (1.0) C: 8 (0.6) Lung biopsy/resection I: 18 (1.3) C:10 (0.8)
		Screening rounds 1 + 2 I: 1374 (82.8) [d] C: 1287 (77.6) [d]	n.r.	*Screening rounds 1 + 2* n.r.	*Screening rounds 1 + 2* n.r.
NLST	*Screening round 1* I: 26,722 C: 26,732	*Screening round 1* I: 26,309 (98.5) C: 26,035 (97.4)	n.r.	*Screening round 1* I: 6369 [c] (24.2) V: 2176 [c] (8.4)	n.r.
	Screening round 2 I: 26,285 C: 26,410	*Screening round 2* I: 24,715 (94.0) C: 24,098 (91.2)	n.r.	*Screening round 2* I: 3866 [c] (15.6) V: 1078 [c] (4.5)	n.r.

Study	*N* included	*N* (%) adherence to screening	*N* (%) contamination	*N* (%) recall rate [a] for screened participants	*N* (%) invasive clarifying diagnostics for participants
	Screening round 3 I: 25,942 C: 26,110	*Screening round 3* I: 24,102 (92.9) C: 23,346 (89.4)		*Screening round 3* I: 2522 [c] (10.5) V: 957 [c] (4.1)	
		Average participation in screening rounds 1–3 I: n.r. (95) C: n.r. (93)	*Screening rounds 1–3* I: n.r. C: n.r. (4.3)	*Screening rounds 1–3* I: 8073 [t] (30.7) [u] C: 3510 [t] (13.1) [u]	*Screening rounds 1–3* I: 1106 (4.1) [v] C: 392 (1.5) [v]

Abbreviations: C=control group; CT=computed tomography; FBS=fibrobronchoscopy; FDG=fluorodeoxyglucose; FNAB=fine-needle aspiration biopsy; I=intervention group; LDCT=low dose CT; *N* included=number of participants randomised minus those who have since dropped out because of a lung cancer diagnosis or death; n.r.=not reported; PET=positron emission tomography; VATS=video-assisted thoracoscopic surgery.

[a] Number of participants who were called in again because of a suspicious finding. This includes additional LDCT scans as well as further diagnostic procedures.

[b] Number of participants who underwent the baseline examination.

[c] Number of participants who have undergone any further clarifying diagnostic tests, including imaging procedures.

[d] Own calculation.

[e] Number of participants who have undergone bronchoscopy, percutaneous biopsy, VATS, mediastinoscopy or thoracotomy.

[f] Number of participants who have undergone additional imaging procedures.

[g] The percentages refer to randomised participants. Therefore, the calculation also includes those who have since dropped out because of a lung cancer diagnosis or death.

[h] Percentage refers to 2052 participants in the comparison group at the time of baseline screening.

[i] Number of participants who tested positive and underwent further examination. Additional LDCT, FDG-PET scans and CT-guided fine-needle biopsies are mentioned.

[j] Number of participants who have participated in at least one additional LDCT examination.

[k] Information refers to direct referral to a lung specialist and associated further examinations such as bronchoscopy, VATS, thoracotomy, PET scans and antibiotic therapy.

[l] Discrepancy between publications; figures refer to the most recent publication.

[m] Number of participants with radiological imaging procedures of the lungs, mostly by X-ray. The procedure was performed without specific indication and outside the study protocol.

[n] Number of participants who underwent an additional LDCT examination after 3 months and/or an immediate clarifying diagnostic test after a positive LDCT result.

[o] The exact time frame for the data is not given.

[p] Number of participants who have undergone biopsies using transthoracic fine-needle puncture, fibrobronchoscopy and transbronchial fine-needle puncture.

[q] Sum of lung resection for benign findings and minor lung resection for malignant findings.

[r] Procedures include biopsy/resection, bronchoscopy, thoracotomy, thoracoscopy, mediastinotomy and mediastinoscopy.

[s] Number of participants who have undergone imaging procedures including pulmonary function tests, cytological procedures, surgical procedures or clinical examinations and comparisons with previous images.

[t] Number of participants who have undergone clarifying diagnostic tests including additional imaging procedures, biopsies, surgical procedures, pulmonary function tests, echocardiography or sputum cytology.

[u] Percentage in relation to participants screened at baseline.

[v] Number of participants who have undergone different types of biopsy and surgical procedures, such as mediastinoscopy, thoracotomy, lung resection, bronchoscopy or thoracocentesis.

4.1.4 Outcomes included

Data on patient-relevant outcomes could be extracted from eight studies. Table 4.9 provides an overview of the available evaluable data on patient-relevant outcomes from these studies. All studies reported evaluable data on the mortality endpoint (overall mortality and lung cancer mortality) and overdiagnosis. Chest X-ray screening is not considered an adequate comparator to investigate the effect of LDCT screening with regard to the consequences of false screening results, HRQoL or adverse events compared to no screening. Therefore, for the consequences of false screening results, HRQoL and adverse events as endpoints, only the six studies comparing LDCT screening versus no screening were considered. All six studies reported evaluable data on the consequences of false screening results. For adverse events, evaluable data from the DANTE study were available. For the HRQoL endpoint, either no data or no evaluable data were available in the studies.

Table 4.9: Matrix of outcomes in the studies included in the assessment

Study	Outcomes				
	Mortality	Morbidity			HRQoL
			Harms resulting from screening		
	Overall mortality and lung cancer mortality	Adverse events	Consequences of false screening results	Overdiagnosis	Health-related quality of life
LDCT screening versus no screening					
DANTE	●	●	●	●	–
DLCST	●	–	●	●	–
ITALUNG	●	–	●	●	–
LUSI	●	–	●	●	–
MILD	●	–	●	●	–
NELSON	●	–	●	●	–
LDCT screening versus chest X-ray screening					
LSS	●	x	x	●	x
NLST	●	x	x	●	x

Abbreviations: LDCT=low-dose computed tomography; HRQoL=health-related quality of life.

●: Data were reported and were evaluable.

–: No data were reported or the data were not evaluable for the benefit assessment.

x: For this endpoint, chest X-ray screening is not an adequate comparator to investigate the effect of LDCT screening compared to no screening.

4.1.5 RoB assessment and quality of the evidence

4.1.5.1 Study level

Table 4.10 describes RoB at the study level, which was rated as low for four studies (DLCST, ITALUNG LUSI and NELSON) and high for the remaining four studies. For the studies with high RoB at the study level, it was unclear whether the randomisation sequence was adequately generated (MILD and NLST) or whether the allocation concealment was adequate (DANTE, MILD and NLST). For the LSS study it was unclear whether reporting was independent of the results

(e.g., lack of information on the planned endpoints). For MILD, significant differences in baseline characteristics (age, sex, smoking status and pack-years) between the intervention and control groups also led to high RoB.

Table 4.10: Risk of bias in randomised studies at the study level

Study	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias at study level
			Participant	Treating person			
LDCT screening versus no screening							
DANTE	Yes	Unclear	No	No	Yes	Yes	High
DLCST	Yes	Yes	No	No	Yes	Yes	Low
ITALUNG	Yes	Yes	No	No	Yes	Yes	Low
LUSI	Yes	Yes	No	No	Yes	Yes	Low
MILD	Unclear	Unclear	No	No	Yes	No [a]	High
NELSON	Yes	Yes	No	No	Yes	Yes	Low
LDCT screening versus chest X-ray screening							
LSS	Yes	Yes	No	No	Unclear [b]	Yes	High
NLST	Unclear	Unclear	No	No	Yes	No [c]	High

Abbreviations: LDCT=low-dose computed tomography.

[a] Significant differences in baseline characteristics (age, sex, smoking status and pack-years) between the intervention and control groups. Inclusion of a control group only after the start of the study.

[b] No information on the planned endpoints and analyses, and no sample size estimation.

[c] For several endpoints there were discrepancies at the same evaluation time.

4.1.5.2 Outcome level

The RoB for the outcomes overall mortality and lung cancer mortality, consequences of false screening results and overdiagnosis was rated as low in the DLCST, ITALUNG and NELSON studies. Although the LUSI study shows low RoB at the study level, high RoB was found for all outcomes, partly because of discrepancies between publications regarding the results. The RoB for the adverse events outcome was rated as high for the DANTE study, which is the only study reporting results on adverse events.

For all studies for which RoB at the study level was already classified as high (DANTE, MILD, NLST and LSS), there is therefore high RoB at the outcome level, so no further outcome-specific RoB assessment was performed for these studies.

An overview is given in Tables A7–A11 in Appendix 7.

4.1.5.3 Quality of the evidence

The assessment of the outcome-specific quality of the evidence is presented in Tables A12–A17 in Appendix 8.

4.1.6 External validity

Since the majority of the studies used for the present report were conducted in European countries, the external validity of the evidence was considered to be high. Moreover, it can be expected that future screening programmes will be based on how screening was implemented in these studies. Therefore, no downgrading because of indirectness was required in the GRADE assessment of LDCT screening in (former) heavy smokers. No relevant studies were identified for risk groups for lung cancer other than smokers.

A summary characterising the applicability of studies can be found in Table 4.11.

Table 4.11: Summary table characterising the applicability of the body of studies

Domain	Description of the applicability of the evidence
Population	Possible differences between the underlying evidence and the potential implementation of LDCT screening in Europe include the following aspects: **Age and sex:** Although the inclusion criteria of the studies varied with regard to the lower (e.g., 50, 55 or 60 years) and upper (e.g., 70 or 75 years) age threshold, there is no reason to assume grossly different effects of screening within these age groups. Nevertheless, results cannot be extrapolated to younger or older age groups because baseline cancer risk and residual life expectancy have a strong influence on the risk/benefit ratio of screening measures. Sex also appears to be associated with slightly different effects. However, the test for interaction did not show statistical significance in any of the subgroup analyses with regard to the sex or age of participants as a potential effect modifier. Finally, the studies recruited both women and men, so the results (or subgroup results) allow for high applicability to European populations, even if the distribution of risk factors may change over the forthcoming years. **Smoking:** Valid estimation of the baseline risk of developing lung cancer is essential when designing a screening programme. However, it is certainly possible to transfer the screening strategy used in one of the existing trials to a nationwide screening programme. Thus, applicability is not a problem in this regard.
Intervention	Possible differences between the evidence and current real-world settings in Europe include the following aspects: **CT technology:** The CT scanners used in the current studies mostly represent the best available imaging technology. As such equipment is current standard in all European countries (at least in specialised centres), the trial results are transferable, but it still will be essential to restrict screening to adequately equipped centres. **Image analysis:** Automated image analysis systems were used in the more recent studies. Because recall rates can be reduced by using computerised volumetry [306], applicability may be negatively affected when implementing a screening programme that fails to include quality control measures for image analysis or false-positive recall rates. **Screening intervals:** A screening interval of 1 year has evolved as the standard and was well accepted in the trials. Applicability could only be compromised if the majority of eligible screening participants show a much lower attendance rate. **Duration of screening:** In the studies included, the duration of the screening phase was between 1 and 6 years, whereas future screening participants might attend annual screening over ~20 years. However, the effects are also considered to be transferable to long-term screening. The same holds true for the overall risk/benefit ratio of LDCT screening in (former) heavy smokers.
Comparators	In the majority of the studies, the comparator was no screening. Data from studies which compared LDCT and chest X-ray screening were considered partly transferable – at least for some outcomes, because previous studies had found no apparent effect of chest X-ray screening. In 4 studies, the contamination rate was recorded and found to be in the range between 1 and 7%. Such self-paid (or “grey”) screening is already taking place in most European countries. If a considerable proportion of the population would already get self-paid CT screening today, the effect observed in the studies would not be transferable to a routine setting any longer. However, as this appears unlikely, the results of the included studies seem transferable to the European context.

Domain	Description of the applicability of the evidence
Outcomes	No issue regarding applicability was identified, because lung cancer mortality was the key outcome in the present report and the underlying studies and is also a highly relevant outcome in the view of most potential screening participants. Even though considerable disadvantages are apparent for other outcomes (mainly over-diagnosis) and in some cases no usable data were available for other important outcomes (e.g., HRQoL), the applicability of the results seems not to be relevantly impaired.
Setting	All studies comparing LDCT screening with no screening were conducted in densely populated Western European countries (Italy, Denmark, Germany, Netherlands and Belgium). Furthermore, these countries have relatively well-organised and well-financed health care systems. Implementing a lung cancer screening programme in a remotely located population or a health care system with little resources could pose greater challenges, but the present results are nevertheless considered transferable to all European countries.

Abbreviations: CT=computed tomography; HRQoL=health-related quality of life; LDCT=low-dose CT.

4.1.7 Results on clinical effectiveness and safety

HTA CORE MODEL DOMAIN: EFF & SAF[7]

Table 4.12, Table 4.13, Table 4.14, Table 4.15, Table 4.16 and Table 4.17 summarise the results of the comparison of LDCT screening with no screening in risk groups.

4.1.7.1 Mortality

Overall mortality

For overall mortality, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, MILD and LUSI) were available for comparison against no screening. The data for the longest observation period were used for all studies. This was between 8 and 11 years since randomisation.

Since the studies considered did not have sufficiently comparable study designs (e.g., with regard to screening intervals, selection criteria for study participants and evaluation of the findings) to be able to base a meta-analysis on a fixed-effect model, meta-analyses with a random-effects model were used. The three studies with low RoB showed no statistically significant difference between the groups (IRR 0.93, 95% CI 0.69–1.26; p = 0.434). The combined analysis of studies with low and high RoB also showed no statistically significant effect in favour of screening (IRR 0.95, 95% CI 0.88–1.03; p = 0.164).

For the comparison of LDCT screening to chest X-ray screening, data from two studies (LSS and NLST) with high RoB were available for overall mortality. The sensitivity analysis considering these two studies with data for the longest observation period does not contradict the results for the comparison of LDCT screening versus no screening (IRR 0.97, 95% CI 0.92–1.02; p = 0.168).

The results are presented in Table 4.12, while Figure 4.2 and Figure 4.3 show forest plots.

[7] This section addresses the following elements in the EFF and SAF domains of the HTA core model: D0001, D0005, D0012, D0013, C0008, C0002, C0005, C0006.

Table 4.12: Results for overall mortality

Study	Observation time since randomisation	Intervention					Comparator					Intervention vs comparator		
		N	Persons with event		PYs	Events per 1000 PYs [a]	*N*	Persons with event		PYs	Events per 1000 PYs [a]	IRR	(95% CI)	*p* value
			n	%				*n*	%					
LDCT screening versus no screening														
DANTE	8.35 years (median)	1264	180	14.24	10,875	16.6 [b]	1186	176	14.84	10,104	17.4 [b]	0.95 [c]	(0.77–1.17)	n.r.
DLCST	10 years	2052	165	8.0 [b]	19,439	8.4 [b]	2052	163	7.9 [b]	19,547	8.3 [b]	1.02 [c]	(0.82–1.27)	0.867
ITALUNG	11.3 years (median)	1613	203	12.6 [b]	17,587	11.5 [b]	1593	246	15.4 [b]	17,051	14.4 [b]	0.80	(0.66–0.96)	0.018
LUSI	≥ 7 years; average 8.8 years	2029	148	7.3 [b]	n.r.	n.r.	2023	150	7.4 [b]	n.r.	n.r.	0.99 [d]	(0.79–1.25)	0.95
MILD														
Annual	10 years	1190	76	6.4 [b]	11,521	6.6 [b]	1723	106	6.2	16,210	6.5 [b]	n.r. [e]	n.r. [e]	n.r.
Biennial		1186	61	5.1 [b]	11,562	5.3 [b]						n.r. [e]	n.r. [e]	n.r.
NELSON	10 years	7900	959	12.1 [b]	75,099 [b]	12.77 [b]	7892	974	12.3 [b]	74,785[b]	13.02 [b]	n.r. [e]	n.r. [e]	n.r.
LDCT screening versus chest X-ray screening														
LSS	5.2 years (median)	1660	139	8.4 [b]	8339	16.7	1658	116	7.0 [b]	8384	13.8	1.20	(0.94–1.54)	n.r.
NLST	12.3 years (median)	26,722	5253	19.7 [b]	n.r.	n.r.	26,730	5366	20.1 [b]	n.r.	n.r.	0.97	(0.94–1.01)	n.r.

Abbreviations: CI=confidence interval; IRR=incidence rate ratio; LDCT=low-dose computed tomography; *n*=number of participants with event; *N*=number of participants analysed; n.r.=not reported; PYs=person-years.

[a] To calculate the absolute effects, the IRR from the meta-analysis was applied to the median risk in the control group (baseline risk).

[b] Own calculation.

[c] Hazard ratio from the Cox proportional hazards model.

[d] Hazard ratio from the Cox proportional hazards model adjusted for age.

[e] This figure was not reported in the documents, but could be calculated for use in the meta-analysis.

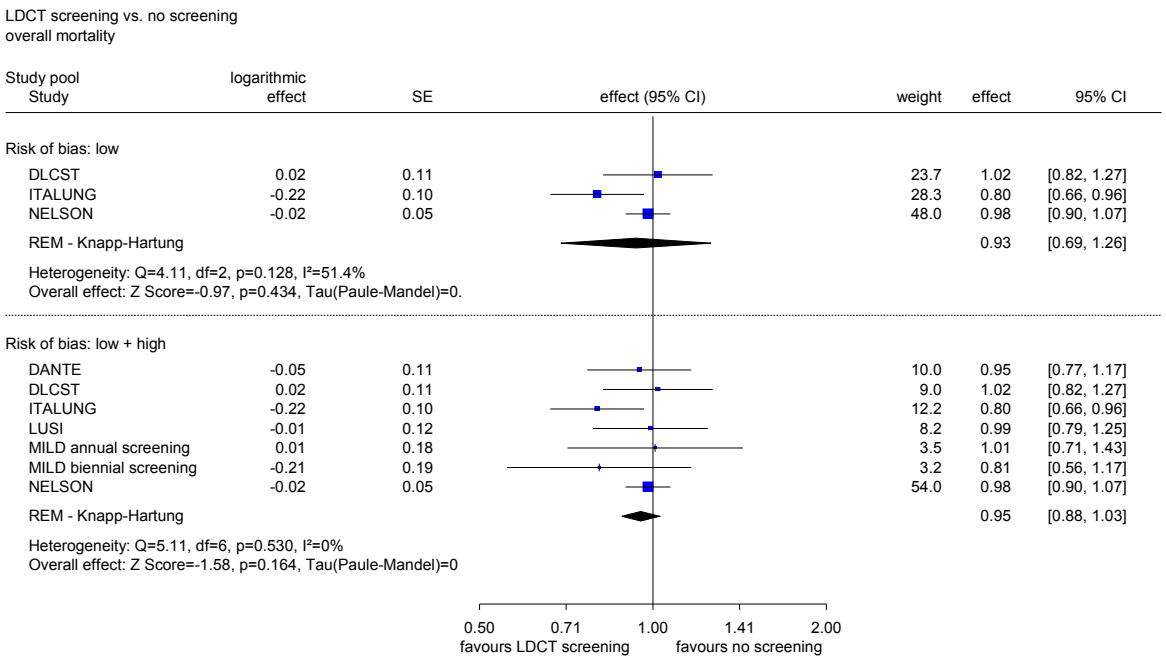


Figure 4.2: Forest plot for overall mortality, LDCT screening versus no screening, effect measure: incidence rate ratio

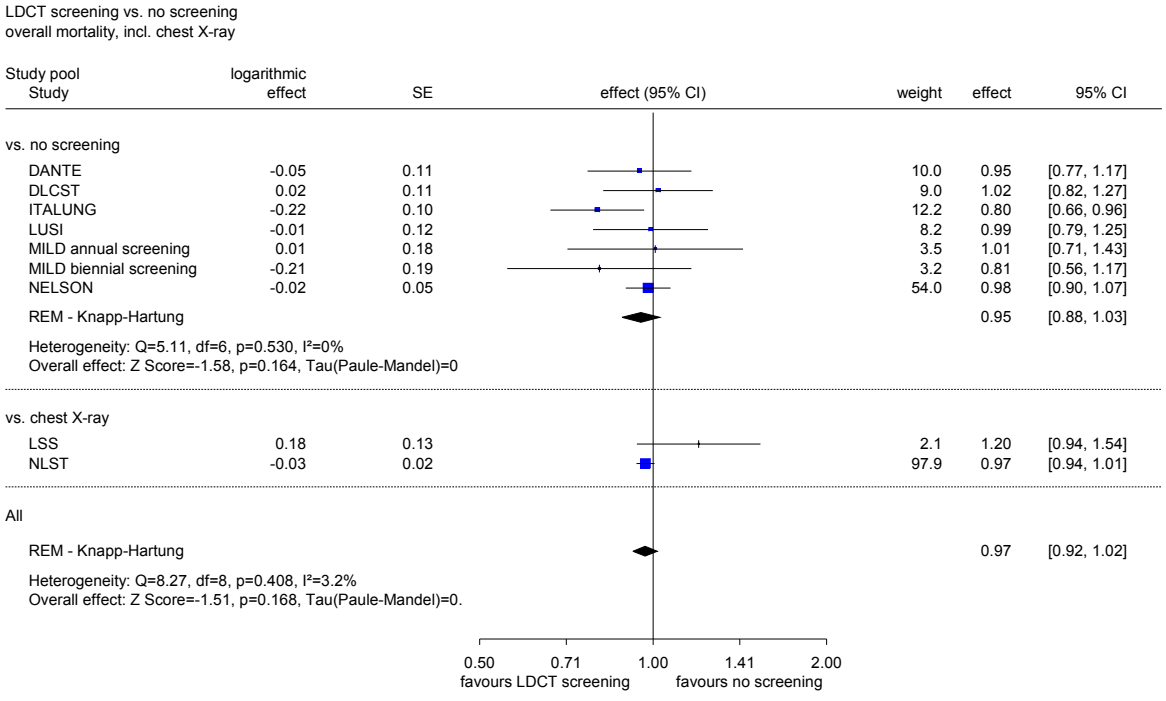


Figure 4.3: Forest plot for overall mortality, sensitivity analysis: addition of the studies that compared LDCT screening to chest X-ray screening, effect measure: incidence rate ratio

Conclusion on the quality of the evidence and on overall mortality

Screening for lung cancer with LDCT results in little or no difference in overall mortality compared with no screening. The conclusion is based on high-quality evidence. The quality of the evidence was rated as high, since the majority of the studies provided high-quality evidence.

Subgroup analyses

No subgroup analyses were performed for the subgroup characteristics of strength of exposure to tobacco (e.g., tobacco consumption, smoker status) or screening strategy (e.g., number of screening rounds) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristic. There were also no usable subgroup analyses conducted within individual study populations.

However, in the six studies included for comparison of LDCT screening to no screening (DANTE, DLCST, ITALUNG, MILD, LUSI and NELSON) and the two studies comparing LDCT screening to chest X-ray screening (LSS and NLST), the age of the devices used in the studies (including use of LDCT devices with < 16 slices vs exclusive use of LDCT devices with ≥ 16 slices) and the size of the screening centre as potential effect modifiers were investigated.

The size of the screening centre was approximated by relating the number of study participants recruited to the number of centres. The size of the participating centres was classified as small for an average number of < 3,000 participants per centre, or as large for ≥ 3,000 participants. If there was a switch from old to new devices during the course of the study, the classification was based on the devices that were mainly used in the study. The division of the studies into subgroups according to the age of the CT equipment and the size of the screening centre were identical. Studies using older CT equipment were conducted in small centres, while studies using newer CT equipment were conducted in large centres.

Furthermore, data available from four studies (DANTE, LUSI, NELSON and NLST) were used to investigate the sex of participants as a potential effect modifier.

In addition, within the three-arm MILD study, the length of the screening interval was investigated as an effect modifier, as screening was performed either annually or every 2 years in the two intervention groups.

The test for interaction did not show statistical significance in any of the subgroup analyses for the studies with no screening as the comparator. In a sensitivity analysis, consideration of the studies with chest X-ray screening as the comparator did not contradict these results.

For CT device age (p = 0.115), centre size (p = 0.115), sex of the participants (p = 0.05003) or the length of the screening interval (p = 0.389), no statistically significant interaction could be shown. A forest plot of the results is presented in Figure 4.4.

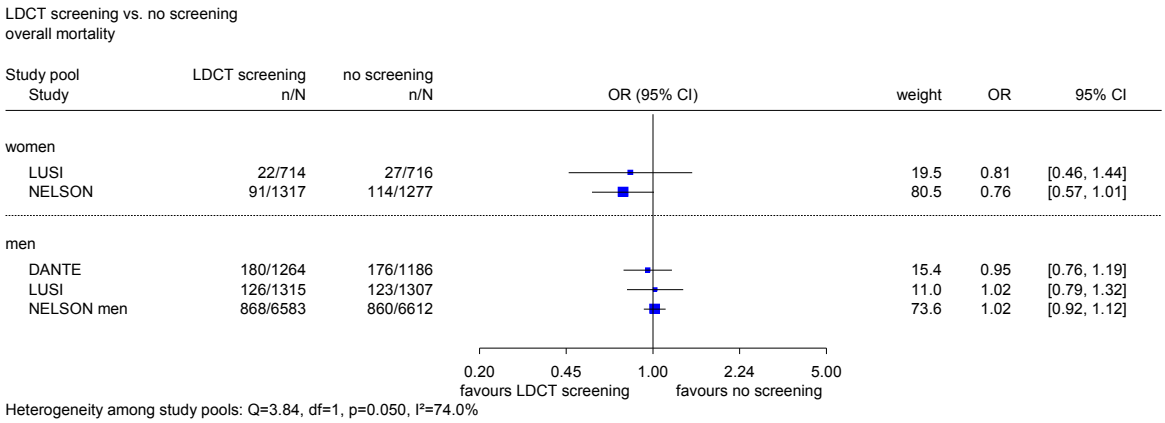


Figure 4.4: Forest plot for overall mortality, subgroup analysis by sex (meta-analysis to compare LDCT screening versus no screening), effect measure: odds ratio

Lung cancer mortality

For lung cancer mortality, data from three studies with low RoB (DLCST, ITALUNG, NELSON) and three studies with high RoB (DANTE, MILD, LUSI) were available for comparison against no screening. For all studies, the data for the longest observation period were used. This was between 8 and 11 years since randomisation.

Since the studies considered did not have sufficiently comparable study designs (e.g., with regard to screening intervals, selection criteria for the study participants and evaluation of the findings) to be able to base a meta-analysis on a fixed-effect model, meta-analyses with a random-effects model were used. The three studies with low RoB showed no statistically significant difference between the groups (IRR 0.80, 95% CI 0.60–1.06; p = 0.076). The combined analysis of studies with low and high RoB showed a statistically significant effect in favour of LDCT screening (IRR 0.81, 95% CI 0.72–0.91; p = 0.004).

For the comparison of LDCT screening to chest X-ray screening, data from two studies (LSS and NLST) with high RoB were available for lung cancer mortality. The data from the two studies for the longest observation period (5 and 12 years since randomisation) were considered in a sensitivity analysis, which does not contradict the results for the comparison of LDCT screening to no screening (IRR 0.89, 95% CI 0.82–0.96; p = 0.010).

The results are presented in Table 4.13, while Figure 4.5 and Figure 4.6 show forest plots.

Conclusion on the quality of the evidence and on lung cancer mortality

Screening for lung cancer with LDCT probably reduces lung cancer mortality compared with no screening. The conclusion is based on moderate-quality evidence. The quality of the evidence was downgraded by one level because the evaluation of the studies with low RoB alone showed no statistically significant difference between the groups.

Table 4.13: Results for lung cancer mortality

Study	Observation time since randomisation	Intervention					Comparator					Intervention vs comparator		
		N	Persons with event		PYs	Events per 1000 PYs [a]	*N*	Persons with event		PYs	Events per 1000 PY [a]	IRR	(95% CI)	*p* value
			n	%				*n*	%					
LDCT screening versus no screening														
DANTE	8.35 years (median)	1264	59	4.66	10,875	5.4 [b]	1186	55	4.64	10,104	5.4 [b]	0.99 [c]	(0.69–1.43)	n.r.
DLCST	≥ 9 years	2052	39	1.9 [b]	19,439	2.0	2052	38	1.9 [b]	19,547	1.9	1.03 [c]	(0.66–1.6)	0.888
ITALUNG	11.3 years (median)	1613	58	3.6 [b]	17,587	3.3 [b]	1593	74	4.6 [b]	17,051	4.3 [b]	0.76	(0.54–1.07)	0.12
LUSI	≥ 7 years; average 8.8 years	2029	29	1.4 [b]	n.r.	n.r.	2023	40	2.0 [b]	n.r.	n.r.	0.74 [d]	(0.46–1.19)	0.21
MILD														
Annual	10 years	1190	19 [e]	1.6 [b]	11,521	1.6 [b]	1723	40	2.3	16,210	2.5 [b]	n.r. [g]	n.r. [g]	n.r.
Biennial		1186	21 [f]	1.8 [b]	11,562	1.8 [b]						n.r. [g]	n.r. [g]	n.r.
NELSON	11 years	7900	205 [b]	2.6 [b]	81,967 [b]	2.50 [b]	7892	263 [b]	3.3	81,633 [b]	3.22 [b]	n.r. [g]	n.r. [g]	n.r.
LDCT screening versus chest X-ray screening														
LSS	5.2 years (median)	1660	32	1.9 [b]	8339	3.8	1658	26	1.6 [b]	8384	3.1	1.24	(0.74–2.08)	n.r.
NLST	12.3 years (median)	26,722	1147	4.3 [b]	n.r.	n.r.	26,730	1236	4.6 [b]	n.r.	n.r.	0.92	(0.85–1.00)	0.05

Abbreviations: CI=confidence interval; IRR=incidence rate ratio; LDCT=low-dose computed tomography; *n*=number of persons with event; *N*=number of individuals analysed; n.r.=not reported; PYs=person-years.

[a] To calculate the absolute effects, the IRR from the meta-analysis was applied to the median risk in the control group (baseline risk).

[b] Own calculation.

[c] Hazard ratio from the Cox proportional hazards model.

[d] Hazard ratio from the Cox proportional hazards model adjusted for age.

[e] For one person the cause of death was missing.

[f] For two people the cause of death was missing.

[g] This figure was not reported in the documents, but could be calculated for use in the meta-analysis.

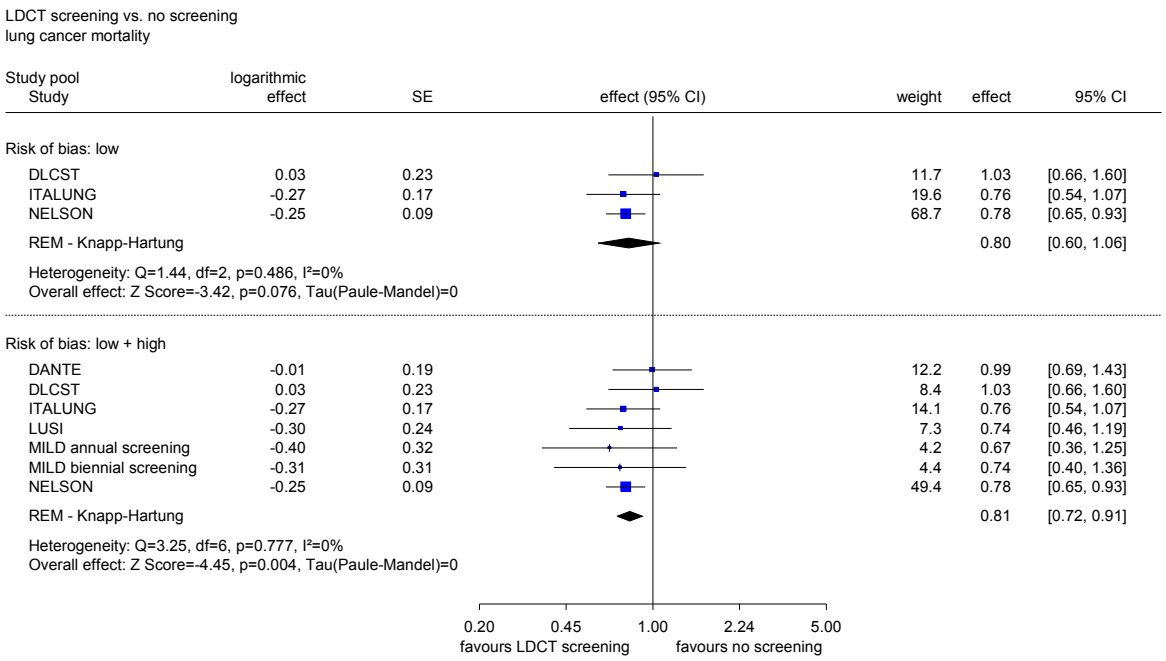


Figure 4.5: Forest plot for lung cancer mortality, LDCT screening versus no screening, effect measure: incidence rate ratio

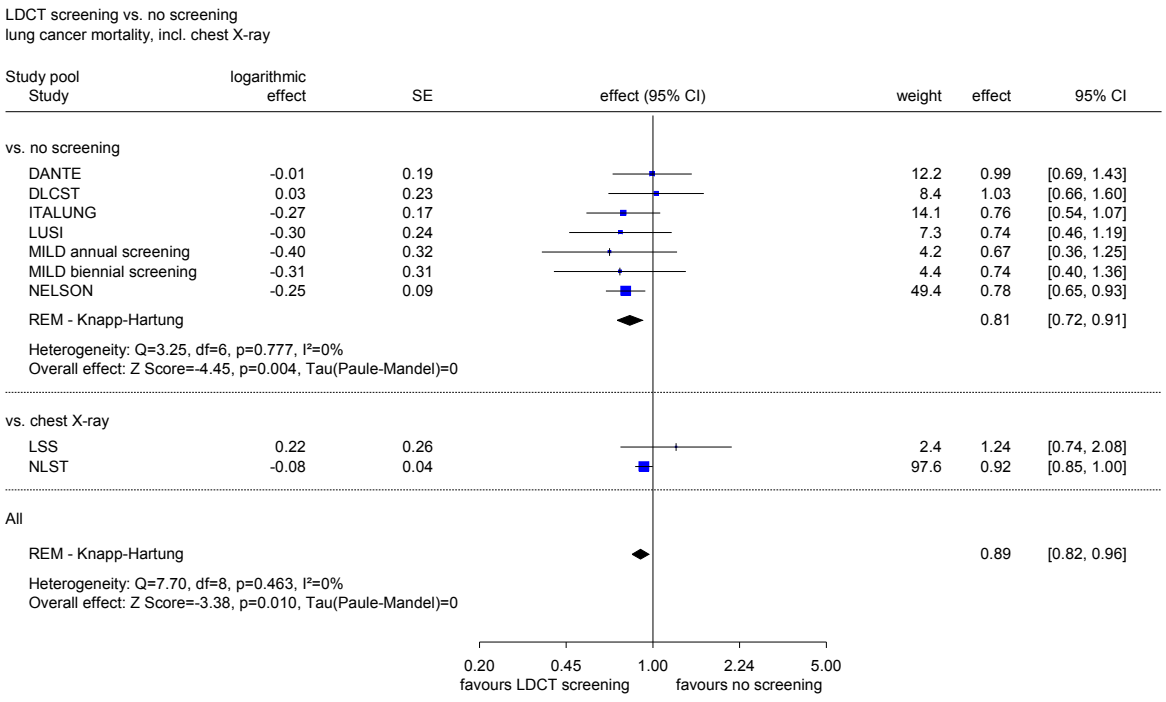


Figure 4.6: Forest plot for lung cancer mortality, sensitivity analysis: addition of the studies comparing LDCT screening to chest X-ray screening, effect measure: incidence rate ratio

Subgroup analyses

No subgroup analyses were performed for the subgroup characteristics of strength of exposure to tobacco (e.g., tobacco consumption, smoker status) or screening strategy (e.g., number of screening rounds) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristic. There were also no usable subgroup analyses conducted within individual study populations.

However, in the six studies comparing LDCT screening to no screening (DANTE, DLCST, ITALUNG, MILD, LUSI and NELSON) and the two studies comparing LDCT screening to chest X-ray screening, the age of the CT devices used in the studies and the size of the screening centre (small centres < 3,000 and large centres ≥ 3,000 participants recruited) were investigated as potential effect modifiers for lung cancer mortality.

Multislice CT devices with ≥ 16 slices and more were classified as new and all other CT devices with fewer slices as old. If there was a switch from old to new devices during the course of the study, classification was based on the devices that were mainly used in the study. The division of the studies into subgroups according to CT equipment age and screening centre size were identical. Studies using older CT equipment were conducted in small centres, while studies using newer CT equipment were conducted in large centres. The subgroup analysis for the studies for comparison against no screening showed no effect modification. Even when adding the studies for comparison against chest X-ray screening, no effect modification was found.

For lung cancer mortality it was also possible to investigate the following additional potential effect modifiers on the basis of subgroup analyses available or appropriately stratified evaluations of several studies: the presence of COPD at baseline (DLSCT), sex (DANTE, LUSI, NELSON and NLST), age of the participants (NELSON) and length of the screening interval (MILD: annual or biennial screening).

The test for interaction did not show statistical significance in any of the subgroup analyses. When possible, a sensitivity analysis including the studies comparing LDCT screening to chest X-ray screening was carried out. This did not contradict the results. There was no effect modification for lung cancer mortality with regard to CT device age, centre size, the presence of COPD at study initiation, sex or age of the participants or length of the screening interval.

A forest plot for subgroup analysis by sex is presented in Figure 4.7.

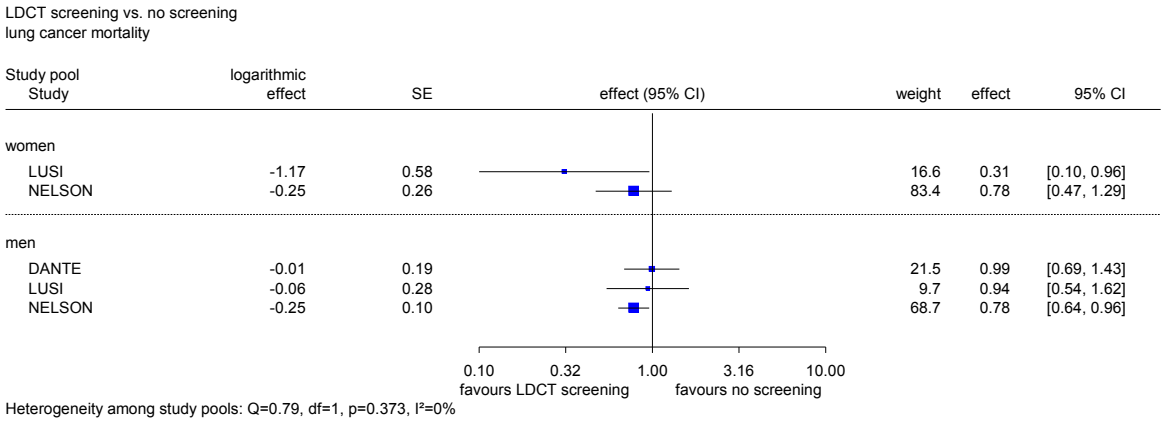


Figure 4.7: Forest plot for lung cancer mortality, subgroup analysis by sex (meta-analysis to compare LDCT screening versus no screening), effect measure: incidence rate ratio

Conclusion on the quality of the evidence and on the benefit statement regarding mortality

The quality of the evidence ranked from high to moderate across the two suboutcomes. For overall mortality, the quality of the evidence was rated as high, since the majority of the studies provided high-quality evidence. To that extent, screening for lung cancer with LDCT results in little or no difference in overall mortality compared with no screening. The results of the meta-analyses, however, point in the direction of a reduction in overall mortality. For lung cancer mortality, the quality of the evidence was downgraded by one level to moderate because the evaluation of the studies with low RoB alone showed no statistically significant difference between the groups. Thus, screening for lung cancer with LDCT probably reduces lung cancer mortality compared with no screening.

The estimate for the absolute effect is 5 fewer deaths per 1,000 persons (95% CI –3 to 12) for overall mortality and 5 fewer deaths per 1,000 persons (95% CI 3–8) for lung cancer mortality within approximately 10 years. Thus, the absolute effects and their corresponding CIs are of a similar order of magnitude. However, it should be taken into account that the CI for overall mortality includes no effect point, which means LCDT may be associated to 3 more deaths to 12 fewer deaths when compared to no screening.

Taking this further consideration into account, the quality of the evidence for the critical outcome of mortality can be assessed as low in summary. This rating of low comprises results for reduced lung cancer mortality in contrast to nonsignificant results for overall mortality. In conclusion, screening for lung cancer with LDCT may reduce mortality compared with no screening.

4.1.7.2 Morbidity

Adverse events

Adverse events may occur not only in the intervention group but also in the comparison group without screening and are therefore distinct from the following outcomes reported in Section "Harms resulting from screening". A complete survey of this outcome involves a great deal of effort, since systematic recording of events is also required for the non-screened comparison group.

For adverse events, data from only one study (DANTE) with high RoB were available for comparison against no screening. DANTE reported data on the occurrence of adverse events after surgery and of adverse events of severity level ≥ 3 after surgery. The results were presented for the longest observation period since randomisation (maximum 8 years). The evaluation showed a statistically significant difference in the incidence of adverse events after surgery for suspicious findings to the disadvantage of LDCT screening (OR 3.48, 95% CI 1.41–8.62; p = 0.004). Further restriction to adverse events of severity ≥ 3 also showed a statistically significant difference between the two study groups to the disadvantage of LDCT screening (OR 4.25, 95% CI 0.92–19.69; p = 0.046).

Conclusion on the quality of the evidence and on benefit statement regarding adverse events

The quality of the evidence for the important outcome of adverse events was rated as low. In DANTE, the quality of the evidence was downgraded by two levels owing to the high RoB and serious imprecision as the results are based on one relatively small study, leading to a large CI. In conclusion, screening for lung cancer with LDCT may increase adverse events when compared with no screening.

The results are presented in Table 4.14.

Table 4.14: Results for adverse events

Study	Observation time	Intervention				Comparator				Intervention vs comparator		
		Participants	Surgery	Cases [a] with AE		Participants	Surgery	Cases [a] with AE				
		N	*n*	*n*	Per participant included %	*N*	*n*	*n*	Per participant included %	OR	(95% CI)	*p* value
LDCT screening versus no screening												
DANTE												
AE after surgery for suspicious findings	End of observation time, maximum observation time 8 years	1264	77	22	1.7 [b]	1186	31	6	0.5 [b]	3.48 [b]	(1.41–8.62) [c]	0.004 [d]
AE of severity ≥ 3 [e] after surgery for suspicious findings	End of observation time, maximum observation time 8 years	1264	77	9	0.7 [b]	1186	31	2	0.2 [b]	4.25 [b]	(0.92–19.69) [c]	0.046 [f]

Abbreviations: AE=adverse event; CI=confidence interval; LDCT=low-dose computed tomography; *n*=number of persons with event; *N*=number of persons analysed; OR=odds ratio.

[a] It was assumed that the number of reported cases with AEs corresponds to the number of persons with AEs.

[b] Own calculation.

[c] Own calculation (asymptotic).

[d] Own calculation (unconditional exact test, CSZ method according to [307]).

[e] Not specified further.

[f] Own calculation (unconditional exact test, CSZ method according to [307]). Discrepancy between *p* value (exact) and CI (asymptotic) due to different calculation methods.

4.1.7.3 Harms resulting from screening

Consequences of false-negative screening results

Data on consequences of false-negative screening results were not reported in the studies.

Consequences of false-positive screening results

For the consequences of false-positive screening results as an outcome, data were used for screening participants who had a positive screening result and for whom the suspicion of lung cancer was not confirmed in the subsequent invasive diagnostic investigation. In this context, invasive diagnostic procedures are understood to be procedures used to obtain histological or cytological confirmation. For the consequences of false-positive screening results, data for both purely diagnostic interventional clarifications and data for surgical therapeutic interventions were used if the treatment and diagnosis of lung tissue of unclear distinction could not be clearly separated. This is the case when both can be performed via a single procedure, such as VATS. The complications associated with these procedures in individuals for whom benign findings were subsequently observed were also considered under this outcome. The observation period chosen was the time at which the screening phase in the respective studies was completed.

For the consequences of false-positive screening results, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, MILD and LUSI) were available.

The need for invasive diagnostic workup was recorded in the studies only for the intervention groups. The DANTE study is an exception. Although all studies compare LDCT screening against no screening, in the DANTE study all study participants underwent chest X-ray screening and 3-day sputum cytology regardless of group allocation at baseline. It therefore remains unclear whether the group difference is due solely to LDCT screening.

The presentation of invasive diagnostic procedures was different in the studies: some studies included joint presentation of operations and biopsies, whereas other studies reported the procedures individually. For some studies, several operationalisations are available that show that this has a strong impact on the number of events. Therefore, no summary overall estimate is given for this endpoint, but rather a range (minimum–maximum) of effect estimates from the individual studies.

Between 0.1% and 1.5% of the participants invited to screening in the studies received an invasive diagnostic workup that was only made necessary by a false-positive result in the screening. Surgery on individuals with benign findings was performed in 0.1%–1.3% of the participants invited for screening. Overall, between 0.1% and 1.5% of the participants in the studies experienced a consequence of false-positive findings.

Complications in individuals undergoing surgery with final benign findings were reported for two studies (DLCST and NELSON). In the DLCST study, minor complications occurred in two out of seven patients undergoing surgery with benign findings, so 0.1% of all participants invited for screening suffered a minor complication after surgery for benign findings. In the NELSON study, complications were not reported for all patients undergoing surgery with benign findings, but only for those who underwent either thoracotomy or VATS. A total of three serious complications and 20 minor complications occurred among these individuals undergoing surgery with benign findings. Thus, 0.04% and 0.3% of all participants invited to the screening experienced serious or minor complications.

Conclusion on the quality of the evidence and on the benefit statement regarding the consequences of false-positive screening results

Screening for lung cancer with LDCT leads to harm due to consequences of false-positive screening results when compared with no screening. The conclusion is based on high-quality evidence. The quality of the evidence for this important outcome was rated as high, since the majority of the studies provided high-quality evidence.

The results are presented in Table 4.15.

Table 4.15: Results for consequences of false-positive screening results

Study	Observation time	*N*	Persons with events	
			n	%
Results for LDCT screening group				
DANTE [a]				
Surgery [b] with benign findings	During the entire screening phase	I: 1264 C: 1186	I: 17 C:5	I: 1.3 C: 0.4
DLCST				
Surgery [c] with benign findings	~1 year after the last screening	2052	7	0.3 [d]
Minor complications after surgery with benign findings	~1 year after the last screening	2052	2 [e]	0.1 [d]
ITALUNG				
Negative optical FBS	During the entire screening phase (4 screening rounds, T0–T3)	1613	16 [f]	1.0 [d]
Resection with benign lung pathology	During the entire screening phase (4 screening rounds, T0–T3)	1613	4	0.2 [d]
LUSI				
Biopsies for benign findings	Screening round 1	2029	30	1.5
	Screening round 2	2000	19	1.0 [d]
	Screening round 3	1978	12	0.6 [d]
	Screening round 4	1954	16	0.8 [d]
	Screening round 5	1925	13	0.7 [d]
MILD				
Invasive diagnostic procedure [g] for benign findings	7.3 years median	Annual screening: after 7 rounds		
		1190	1	0.1 [d]
		Biennial screening: after 4 rounds		
		1186	3	0.3 [d]
Lung resections with benign histology	10 years	Annual screening		
		1190	0	0
		Biennial screening		
		1186	3	0.3 [d]
NELSON				
Invasive diagnostic procedures [i] following one or more false-positive screening results	after 3 screening rounds [h]	7915	67	0.8 [d]

Study	Observation time	*N*	Persons with events	
			n	%
Serious [j] complications in patients undergoing surgery [k] with benign findings	April 2004 to December 2008 [h]	7915	3	0 [d,l]
Minor [m] complications in patients undergoing surgery [k] with benign findings		7915	20	0.3 [d]

Abbreviations: C=comparator; FBS=fibrobronchoscopy; I=intervention; LDCT=low-dose computed tomography; *N*=number of persons invited to the screening; VATS=video-assisted thoracoscopy.

[a] In both study arms, chest X-ray and 3-day sputum cytology were performed at baseline.
This study alone reported data for the intervention and control groups for this endpoint.

[b] Mediastinoscopies, VATS wedge resections, open wedge resections and VATS biopsies.

[c] VATS.

[d] Own calculation.

[e] One person with an air leak for more than 7 days and one person with atrial fibrillation.

[f] In six other cases, lung cancer was diagnosed in a later examination.

[g] Transthoracic fine-needle puncture, FBS and transbronchial fine-needle puncture.

[h] The screening phase was not yet complete at the time these values were collected, but was largely completed.

[i] 61 operations (mediastinoscopy, sternotomy, VATS, thoracotomy) and six transthoracic biopsies.

[j] Serious complications included: bleeding requiring reoperation, empyema, pneumonia, myocardial infarction, renal failure, postoperative stroke, critical arrhythmia and pulmonary embolism, respiratory arrest and postoperative heart failure with pulmonary oedema, chylothorax, haemothorax and gastrointestinal complications requiring surgical re-intervention, and laparotomy.

[k] Complications have only been reported for benign cases that have undergone VATS or thoracotomy.
Complications are not known for all cases undergoing surgery with benign findings.

[l] 0.04 rounded to 0.

[m] Non–life-threatening complications.

Overdiagnosis

All eight studies were RCTs for which observation of the participants in both groups usually continued for approximately 5 years after the screening phase. The studies recorded a high participation rate (adherence to screening) and low contamination. Overall, all studies were found to be suitable for calculating the risk of overdiagnosis of lung cancer. This issue is addressed in the conclusion on the quality of the evidence (see below).

For overdiagnosis, data from three studies with low RoB (DLCST, ITALUNG and NELSON) and three studies with high RoB (DANTE, LUSI and MILD) were available for comparison against no screening. For the comparison of LDCT screening to chest X-ray screening, data from two studies (LSS and NLST) with high RoB were available.

In this report, a summary overall estimate of overdiagnosis is not given. For the overdiagnosis related to individuals with a lung cancer diagnosis during the screening phase, the proportions between the studies varied so much that an overall estimate could not be interpreted meaningfully. Concrete reasons for the heterogeneity of the results, such as individual aspects of the screening strategy and characteristics of the study population, could not be identified. The heterogeneity was less clear for the proportion of overdiagnoses in relation to individuals invited to screening and it was generally possible to give an overall estimate for the studies for comparison against no screening. However, the associated CIs are as wide as the range of individual point estimators in the studies. Thus, the pooled estimator with CI has no additional information. In order to present the results transparently and uniformly, the proportion of overdiagnoses is given for both reference values as a range (minimum–maximum) of the point estimates of the individual studies.

Overdiagnosis related to individuals invited for screening

From all eight studies included, the overdiagnosis risk could be determined in relation to all participants invited to screening.

Among the six studies comparing LDCT screening to no screening, ITALUNG is the only one with fewer lung cancer cases diagnosed during overall follow-up in the intervention group than in the control group. Thus, no overdiagnosis could be detected in this study. No overdiagnosis was found in the biennial screening group in the MILD study either. In the DANTE and DLCST studies, the risk of overdiagnosis was highest at 2.2% and 2.1%, respectively. For the LUSI and NELSON studies and the annual screening group in the MILD study, the risk of overdiagnosis calculated for study participants is 0.9%, 0.6% and 1.4%, respectively. For the LSS and NLST studies comparing LDCT screening to chest X-ray screening, an overdiagnosis risk of 1.2% and 0.1%, respectively, was calculated.

Overdiagnosis in relation to individuals diagnosed with lung cancer during the screening phase

Data that could be used to calculate the overdiagnosis risk in the presence of a lung cancer diagnosis were available from five studies, including four with no screening as the comparator (DLCST, ITALUNG, LUSI and NELSON). The result from the DLCST study is particularly striking, as an overdiagnosis risk of 63.2% was calculated (using the total number of lung cancer diagnoses in the intervention group as the denominator). For the LUSI and NELSON studies, the overdiagnosis risk is 28.6% and 16.2%, respectively. For the ITALUNG study, no overdiagnosis could be detected. An overdiagnosis risk of 2.8% was calculated for the NLST study for comparison against chest X-ray screening.

Subgroup analyses

As meta-analyses were not performed for overdiagnosis, no interaction tests were calculated. Therefore, results for the subgroups are presented in tabular form and assessed qualitatively.

For the DANTE and NELSON studies, only data for men were available. For the LUSI study, data were available separately for women and men. These data do not suggest that there is an effect modification by sex. The NLST study for comparison against chest X-ray screening also reported separate data by sex that speak against such an effect modification.

For the MILD study, data were available for annual and biennial screening. For the screening intervals, the numerical differences in the proportion of overdiagnosis between the two screening groups are probably random. This is suggested by the fact that the 95% CI for the two estimators overlap and contain the point estimates of the other group. Therefore, this result also speaks against an effect modification by the screening interval on overdiagnosis.

Conclusion on the quality of the evidence and on the benefit statement regarding overdiagnosis

The risks of overdiagnosis can be derived with high-quality evidence from adequate RCTs if at least the following criteria are met [308]:

1. The intervention group is offered a screening strategy (early detection measure and, if necessary, treatment) over a certain fixed period of time (screening phase, period 1).
2. This screening strategy is not offered in the parallel control group (period 1).
3. Both groups are followed up after period 1 without further early detection measures for a sufficient duration (period 2).

All the studies meet the first criterion. For the studies comparing LDCT screening to chest X-ray screening, it was assumed that chest X-ray screening is comparable to no screening. Consequently, all the studies also meet the second criterion. However, a low participation rate (adherence to screening) in the intervention group and a high level of contamination in the control group may distort the results to the extent that the risk of overdiagnosis is underestimated [309]. Of the studies, four reported contamination of between 1% and 7%. It remains open how valid this information is. For the other four studies, no information on contamination is available. The participation rates (adherence to screening) vary between 96% and 81% (Table 4.8).

In order to adequately estimate the risk of overdiagnosis, sufficient follow-up after the screening phase is necessary. The minimum time for period 2 should correspond to the lead time, but should be significantly longer if possible, otherwise the risk of overdiagnosis is overestimated. The lead time is the length of time by which a diagnosis is brought forward by screening. The lead time cannot be observed and can only be estimated [309]. On the basis of modelling, Patz et al. [120] estimated the preclinical phase or lead time for NSCLC as an average of 3.6 years. The authors excluded the often slow-growing bronchioloalveolar carcinoma, which is an adenocarcinoma (and has been replaced by the term lepidic adenocarcinoma [310]). This cancer requires a much longer period of further observation, as its preclinical phase was estimated as 32.1 years [120]. In contrast to NSCLCs, SCLCs, which account for approximately 15% of all lung cancers, are rapidly progressive [311].

The data from the DLCST study refer to a 5-year observation period after completion of the screening phase. In the DANTE, MILD and NELSON studies, data were reported for a slightly shorter follow-up period than in the DLCST study. For the NLST and ITALUNG studies, the follow-up period after completion of the screening phase was significantly longer. At an average of 3.8 years, the follow-up period for the LUSI study was the shortest. For the LSS study, no post-screening follow-up data were available. Overall, with the exception of the LSS study, the duration of period 2 is considered sufficient for all other studies, so that criterion 3 is also considered fulfilled.

At the same time, the heterogeneity addressed above was also taken into account when rating the quality of the evidence for the overdiagnosis outcome.

Diagnosis of lung cancer requires histological or cytological diagnostic confirmation. It can be assumed that almost all lung cancer diagnoses were also treated. Every diagnostic procedure and treatment/therapy carries the risk of side effects and complications.

Taking all these considerations into account, the quality of the evidence for the important outcome of overdiagnosis can be assessed as high in summary. In conclusion, screening for lung cancer with LDCT leads to harm compared to no screening in the sense of overdiagnosis, that is, from the resulting invasive clarification diagnostics and treatment, including the associated complications and side effects.

The results are presented in Table 4.16 and Table 4.17.

Table 4.16: Results for overdiagnosis

Study	Observation time since randomisation	Intervention					Comparator				Risk of overdiagnosis, % [a,b] (95% CI) [a,b]	
		N_s	Persons with event		PYs	Events per 1000 PYs	N_c	Persons with event	PYs	Events per 1000 PYs	In relation to persons invited to screening ($S_2/N_s - C_2/N_c$)	In relation to persons diagnosed with lung cancer during the screening phase ($S_2 - C_2)/S_1$
			S_1	S_2				C_2				
LDCT screening versus no screening												
DANTE	8.35 years (median)	1264	n.r.	104	n.r.	n.r.	1186	72	n.r.	n.r.	2.2 (0.1–4.2)	n.r.
DLCST	≥ 9 years	2052	68	96	19,439	4.9 [a]	2052	53	19,547	2.7 [a]	2.1 (1.0–3.2)	63.2 (29.0–137.8)
ITALUNG	11.3 years (median)	1613	42	91	16,870	5.4 [a]	1593	100	17,306	5.8 [a]	0 [c] (0–1.1)	0 [c]
LUSI	≥ 7 years; average 8.8 years	2029	63	85	n.r.	n.r.	2023	67	n.r.	n.r.	0.9 (0–2.0)	28.6 (6.0–135.9)
MILD												
Annual	10 years	1190	n.r.	58	11,285 [a]	5.1 [a]	1723	60	16,102	3.7 [a]	1.4 (0–3.1)	n.r.
Biennial		1186	n.r.	40	11,429 [a]	3.5 [a]					0 [c] (0–1.5)	n.r.
NELSON (only males)	10 years	6583	247	344	n.r.	5.58	6612	304	n.r.	4.9	0.6 (0–1.4)	16.2 (4.2–61.8)
LDCT screening versus chest X-ray screening												
LSS	1 year	1660	n.r.	40	n.r.	n.r.	1658	20	n.r.	n.r.	1.2 (0.3–2.1)	n.r.
NLST	11.3 years (median)	26 722	720	1701	n.r.	6.38	26,730	1681	n.r.	6.3	0.1 (0–0.5)	2.8 (0.0–742.1)

Abbreviations: C_2=number of participants diagnosed with lung cancer in the control group at the end of the observation time; CI=confidence interval; LDCT=low-dose computed tomography; n.r.=not reported; N_C=number of persons in the control group; N_s=number of persons in the screening group; PYs=person-years; S_1=number of participants diagnosed with lung cancer in the screening group at the end of the screening phase; S_2=number of participants diagnosed with lung cancer in the screening group at the end of the observation time.

[a] Own calculation.

[b] Negative estimators were set to 0.

[c] Fewer lung cancer cases were diagnosed in the intervention group than in the control group. Thus, no overdiagnoses can be detected.

Table 4.17: Results for overdiagnosis separated by sex

Study	Observation time since randomisation	Intervention					Comparator				Risk of overdiagnosis	
		N_s	Persons with events		PYs	Events per 1000 PYs	N_c	Persons with event	PYs	Events per 1000 PYs	In relation to persons invited to screening ($S_2/N_s - C_2/N_c$)	In relation to persons diagnosed with lung cancer during the screening phase ($S_2 - C_2)/S_1$
			S_1	S_2				C_2			% [a,b] (95% CI) [a,b]	% [a] (95% CI) [a]
LDCT screening versus no screening												
LUSI												
Women	≥ 7 years; average 8.8 years	714	20	26	n.r.	n.r.	716	21	n.r.	n.r.	0.7 (0–2.6)	25.0 (1.2–540.9)
Men		1315	43	59	n.r.	n.r.	1307	46	n.r.	n.r.	1.0 ([0–2.5)	30.2 (5.0–184.2)
LDCT screening versus chest X-ray screening												
NLST												
Women	6.5 years (median)	10,953	n.r.	434	n.r.	63.8 [a]	10,969	395	n.r.	58.0 [a]	0.4 (0–0.9)	n.r.
Men		15,769	n.r.	655	n.r.	67.8 [a]	15,761	574	n.r.	59.4 [a]	0.5 (0.1–0.9)	n.r.

Abbreviations: C_2=number of participants diagnosed with lung cancer in the control group at the end of the observation time; CI=confidence interval; LDCT=low-dose computed tomography; n.r.=not reported; N_C=number of persons in the control group; N_s=number of persons in the screening group; S_1=number of participants diagnosed with lung cancer in the screening group at the end of the screening phase; S_2=number of participants diagnosed with lung cancer in the screening group at the end of the observation time.

[a] Own calculation.

[b] Negative estimators were set to 0.

4.1.7.4 Health-related quality of life

Data on HRQoL were not reported in the studies or were not usable for the benefit assessment.

4.1.8 Subgroup analyses

For the overall mortality outcome, the age of the CT equipment (8 studies), the size of the screening centre (8 studies), the sex of the participants (4 studies) and the length of screening interval (1 study) were examined as potential effect modifiers. For the lung cancer mortality outcome, the age of the CT equipment (8 studies), the size of the screening centre (8 studies), the presence of COPD at baseline (1 study), the sex (4 studies) and age of the participants (1 study) and the length of screening interval (1 study) were investigated as potential effect modifiers.

The size of the screening centre was approximated by relating the number of study participants recruited to the number of centres. The size of the participating centres was classified as small for an average number of < 3,000 participants per centre, or as large for ≥ 3,000 participants. The division of the studies into subgroups according to the age of the CT equipment and the size of the screening centre was ultimately identical. Studies using older CT equipment were conducted in small centres, while studies using newer CT equipment were conducted in large centres.

There was no statistically significant interaction for any of the subgroup characteristics mentioned. As the interaction *p* value for overall mortality was close to the significance threshold for the subgroup analysis by sex if only the studies with no screening as the comparator were considered, all results for this subgroup analysis are presented in the sections on overall mortality and lung cancer mortality.

For the overdiagnosis outcome, two studies exclusively reported results for men, while two other studies provided data separated by sex. In addition, the MILD study provided separate data for annual and biennial screening intervals. As meta-analyses were not performed for overdiagnosis, no interaction tests were calculated. Therefore, the results for the subgroups are presented in tabular form and assessed qualitatively. These results did not indicate an interaction.

No subgroup analyses were performed for the outcomes of adverse events and consequences of false-positive screening results, as no (usable) data were available. For false-positive screening results, the MILD study provided separate data for annual and biennial screening intervals. Of the three lung resections for benign histology, all interventions were performed in the biennial screening group. As the total number of these interventions was very low, this result is not very reliable and is not interpreted as an interaction.

No subgroup analyses were performed for the subgroup characteristics of strength of exposure to tobacco (e.g., tobacco consumption, smoker status) and screening strategy (e.g., number of screening rounds) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristic. There were also no usable subgroup analyses conducted within individual studies.

4.1.9 Summary

4.1.9.1 Balancing of benefits and harms

Every screening causes harm through false screening results and overdiagnosis. Screening is only justified if the harm is more than outweighed by the benefit. When weighing up the benefits and harms, it must also be taken into account that the results are weighted differently for the various outcomes.

Benefit

The studies have shown that LDCT screening probably reduces the risk of lung cancer death in (formerly) heavy smokers. LDCT screening prevents approximately 5 out of 1,000 people (95% CI 3–8) from dying of lung cancer within approximately 10 years. On the basis of the study results, however, it cannot be statistically proven that overall mortality is also improved by screening. It is conceivable that owing to competing causes of death, in particular other tobacco-related diseases such as other cancers and cardiovascular diseases, some of the screening participants saved from lung cancer death may die at a comparable time and thus the life span of these individuals may not be significantly extended.

The recently published NELSON study in particular highlighted this problem [54]. Despite a statistically significant reduction in lung cancer mortality (IRR 0.76, 95% CI 0.61–0.94), no detectable change in overall mortality was found in the main analysis (IRR 1.01, 95% CI 0.92–1.11). Instead, it was found that other causes of death tended to occur more frequently. Critics have thus argued that LDCT screening might only lead to “an exchange of death from lung cancer for death from another cause” [200], without conveying an overall benefit in mortality [201]. However, the figures quoted by the authors for the NELSON study refer to men alone, whereas in the meta-analysis for this report, a numerical reduction in overall mortality among women was quite visible (Figure 4.4). In this report, the NELSON study was included with data for both men and women (16% of the study population).

In addition, the results for overall mortality taken together do not contradict the results for lung cancer mortality. Thus, the two estimators for the respective meta-analyses point in the same direction. Moreover, the absolute effect estimate and its corresponding confidence interval for overall mortality are similar to the effect for lung cancer mortality. The estimate for the absolute effect is 5 per 1000 persons (95% CI –3 to 12) for overall mortality and 5 per 1000 persons (95% CI 3–8) for lung cancer mortality within approximately 10 years. It is therefore considered likely that the effect of LDCT screening on lung cancer mortality is also reflected in overall survival. In conclusion, screening for lung cancer with LDCT may reduce mortality compared with no screening.

Harm

Results for adverse events after surgery indicate harm in itself. However, very few data were available on adverse events (all forms of treatment) for the intervention and comparison groups, so the actual harm based on these data is unclear (see Section 5.7). However, it can be assumed that the effect of screening on the rate of adverse events is essentially represented by the overdiagnosis outcome. Harms resulting from radiation exposure are specifically described in Section 5.9.

No data were available on the consequences of false-negative screening results. In the case of false-negative screening results, individuals falsely believe that they have no lung cancer. The most significant consequence would be to ignore symptoms, which could delay diagnosis and subse-

quent treatment. However, should this result in an increase in mortality, this would be reflected in the lung cancer mortality outcome. Overall, the influence of the lack of specific data on consequences of false-negative screening results on the balancing of benefit and harm is estimated to be small. In the case of false-positive screening results, individuals suffer harm through the reporting of a worrying finding, the subsequent diagnostic workup and the complications associated with this. According to the results of this assessment, 1–15 out of every 1,000 participants invited for lung cancer screening will receive an invasive diagnostic workup or a resection with subsequent benign findings. The most common complication of lung biopsy is pneumothorax [202]. The risk of developing pneumothorax varies depending on the biopsy procedure and the location of the pulmonary nodule. Some of these individuals will require thoracic drainage.

It is conceivable that removal of a benign pulmonary nodule can also provide information about other diagnoses and prevent future complications (e.g., retention pneumonia). For example, the NELSON study documented incidental findings in the screening group [72]. A systematic investigation of incidental findings on LDCT screening was not performed for the present assessment, as information on such events and their consequences is only available for the screening groups. It therefore remains unclear whether these findings benefit or harm individuals. Although the NLST study considered random findings in both groups, chest X-ray screening is not an adequate comparator to investigate the effect compared to no screening. For example, Loomans-Kropp et al. [168] investigated whether random findings can lead to an increase in the incidence and overdiagnosis of thyroid carcinoma. In the authors' view, the data could indicate this. After a median observation period of 6.6 years and 6.5 years in the intervention and control groups, respectively, 35 thyroid carcinomas were diagnosed in the LDCT screening group (n = 26,457) and 25 in the chest X-ray screening group (n = 26,238). In total, seven of the 60 people with thyroid cancer died, six of them in the LDCT screening group, with malignant neoplasia of the thyroid gland being the cause of death in only three people. Other causes of death were other diagnoses of cancer or heart disease.

The risk of overdiagnosis related to those with a lung cancer diagnosis during the screening phase varied greatly between studies, ranging from 0% (no overdiagnosis in the ITALUNG study) to 63% (in the DLCST study). The studies showed that an estimated 0–22 out of every 1000 people invited for lung cancer screening were diagnosed with lung cancer that would not have caused symptoms for the rest of their lives.

No usable data were available for the HRQoL outcome. It can be assumed that the reporting of a suspicious finding for screening participants impairs their HRQoL. Since this effect is likely to be only short-term in the case of false-positive results, only the screening participants with true-positive results can be expected to be significantly impaired. The effect of screening on HRQoL is therefore likely to be partly reflected by the overdiagnosis outcome.

4.1.9.2 Other risk factors

No RCT data were found on LDCT screening in individuals with other risk factors, such as exposure to radon, asbestos or fine particles, COPD or idiopathic pulmonary fibrosis or a family history of lung cancer. However, one of the RCTs, UKLS [3-12], was not restricted to smokers and included patients with a higher risk of lung cancer according to the Liverpool Lung Project risk prediction model, but no results that could be used for the benefit assessment were reported. For two reasons, it is not possible to transfer (or extrapolate) the results for screening in (former) smokers to individuals with other risk factors. First, it is quite possible that LDCT is less accurate in examining lungs that are affected by specific risk factors, such as asbestos exposure. Second, tumour type

or growth could differ between different risk factors, thus affecting the effectiveness of screening, diagnostic or therapeutic interventions for lung cancer. In addition, smoking as a risk factor is much easier to elicit and to quantify than other risk factors. In summary, no reliable evidence is available to support LDCT screening in individuals with other risk factors.

4.1.9.3 Conclusion

High-quality evidence shows that screening for lung cancer with LDCT results in little or no difference in overall mortality when compared with no screening. For lung cancer mortality, moderate-quality evidence shows that screening for lung cancer with LDCT probably reduces lung cancer mortality when compared with no screening. Since the respective absolute effects and their corresponding CIs are of a similar order of magnitude, the assumption that screening also has a positive effect on overall mortality seems justified. Taking together the considerations for the two sub-outcomes for mortality, we can conclude that screening for lung cancer with LDCT may have a mortality benefit.

However, screening for lung cancer with LDCT may increase adverse events and lead to harm due to the consequences of false-positive screening results. In addition, it leads to harm in terms of overdiagnosis. Consequences of false-negative screening results were not reported in the studies. Their influence on the balancing of benefit and harm is estimated to be small. Only data from one study were available for the adverse events outcome and no usable data were available for the HRQoL outcome. However, the effect of screening on the rate of adverse events and on HRQoL is likely to be partly covered by the effect on overdiagnosis.

LDCT screening probably saves approximately 5 out of 1,000 people (95% CI 3–8) from dying of lung cancer within approximately 10 years and may potentially extend the life of some of these screening participants when compared to no screening. The benefit in terms of mortality is mainly opposed by the harm resulting from false-positive screening results and overdiagnosis. Owing to false-positive screening results, invasive procedures occur in at least 1 in 1,000 persons, but at most in 15 in 1,000 persons, that would not have been performed without the screening. These procedures can cause complications such as the occurrence of pneumothorax. Overdiagnosis is considered as harm because of the unnecessary subsequent diagnostic tests and therapy, including the resulting complications. The risk of overdiagnosis in the individual studies is between 0 and 22 per 1,000 persons invited for screening. The risk of overdiagnosis in the presence of a lung cancer diagnosis is between 0% and 63% in the individual studies. This underlines how important it is for a positive benefit-to-harm ratio to keep the risk of overdiagnosis low with optimal screening strategies.

4.2 Research question 2

4.2.1 Information retrieval

Figure 4.8 shows the results for information retrieval from the main and additional information sources according to the predefined inclusion criteria. References for the documents that were excluded after checking the full text are presented in Appendix 4 with the reasons for exclusion.

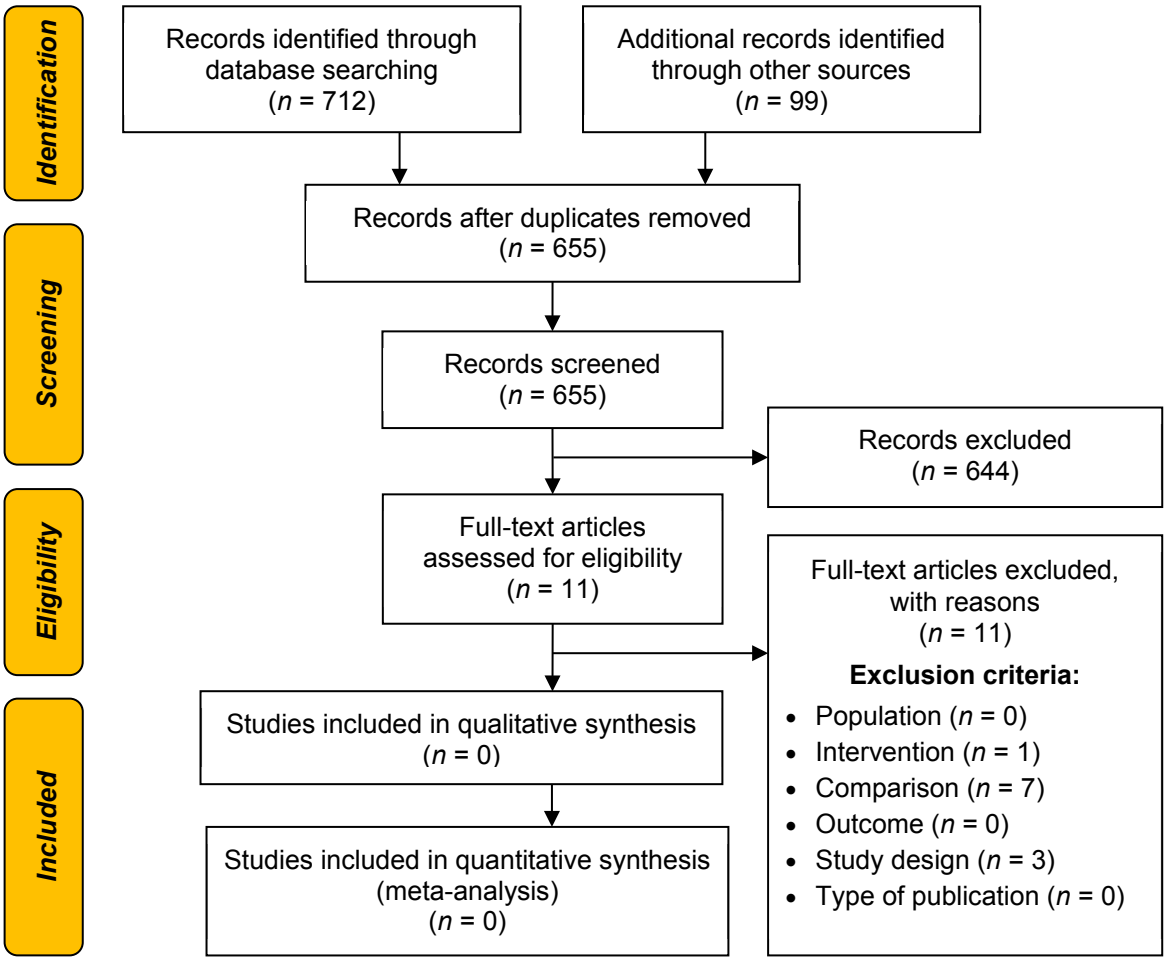


Figure 4.8: Flow chart of information retrieval for clinical effectiveness and safety in research question 2

Information retrieval identified no RCTs (0 documents) as relevant for the research question about the benefit and harm of screening for lung cancer using biomarkers in addition to LDCT compared to screening using LDCT alone in individuals at elevated risk of lung cancer (research question 2). In addition, no ongoing, planned, withdrawn or completed RCTs for this comparison were identified. The last search in bibliographic databases was performed on 2nd July 2020. The search in study registries was performed on 7th July 2020.

4.2.2 Summary

In the absence of eligible RCTs, no conclusion is possible whether the use of biomarkers in addition to LDCT within the process of screening for lung cancer in risk groups would result in an additional benefit or less harm compared to lung cancer screening using LDCT alone.

4.3 Research question 3

4.3.1 Information retrieval

For research question 3 no separate literature search was carried out. RCTs included for research questions 1 and 2 were used to perform subgroup analyses by different screening modalities if relevant information was available.

Information retrieval for research question 1 identified nine randomised trials (184 documents), of which eight RCTs (175 documents) were potentially relevant for research question 3. UKLS [3-12] was a feasibility study with no usable results for clinical effectiveness assessment reported and therefore it was not relevant for research question 3. The literature search for research question 2 resulted in no relevant RCTs and therefore no additional potentially relevant studies for research question 3 could be identified. For further detail see information retrieval Sections 4.1.1. and 4.2.1.

4.3.2 Studies included in the assessment and RoB assessment

For details on the study characteristics and RoB assessment, see Sections 4.1.3 and 4.1.5.

4.3.3 Results on clinical effectiveness and safety

For research question 1, subgroup analyses were carried out with regard to participant and organisational characteristics. The conclusions from these analyses regarding clinical effectiveness and safety are presented above (Section 4.1.7).

Beyond these analyses, no further subgroup analyses could be performed for different screening strategies (e.g., number of screening rounds or organisational differences) because the studies could not be assigned to appropriate categories or there were no significant differences between the studies with regard to the characteristics.

However, regarding the screening interval, one of the RCTs, MILD, was a three-arm study in which participants in the intervention groups were screened either annually or every 2 years (biennially). For these two screening groups, results after 10 years of follow-up are available for overall mortality and lung cancer mortality [47].

According to the 10-year data from MILD, biennial as compared to annual LDCT screening results in similar overall mortality (HR 0.80, 95% CI 0.57–1.12; p = 0.191) and similar lung cancer mortality (HR 1.10, 95% CI 0.59–2.05; p= 0.760).

However, the quality of the evidence on biennial versus annual LDCT screening was rated as very low because these two screening intervals have so far only been directly compared in a single study (i.e., lack of independent replication). In addition, the study has high RoB and lacks the necessary statistical precision. The assessment of the outcome-specific quality of the evidence is presented in Table A18 in Appendix 6.

4.3.4 Summary

In terms of organisational variations in screening, the studies comparing lung cancer screening using LDCT to no screening were either largely comparable (inclusion criteria with regard to smoking status) or there was no statistically significant interaction (screening interval, screening centre size,

age of the CT equipment, sex or age of the participants) or they could not be assigned to appropriate categories (such as screening invitation processes or investigation strategy). From the single study that directly compared biennial versus annual LDCT screening, only results of very low quality were available.

Therefore, the available evidence is not sufficient to answer the research question of whether one specific strategy in lung cancer screening is favourable compared to other screening strategies.

4.4 Research question 4

4.4.1 Information retrieval

Figure 4.9 shows the results for information retrieval from the main and additional information sources according to the predefined inclusion criteria. References for the documents that were excluded after checking the full texts are presented in Appendix 4 with the reasons for exclusion.

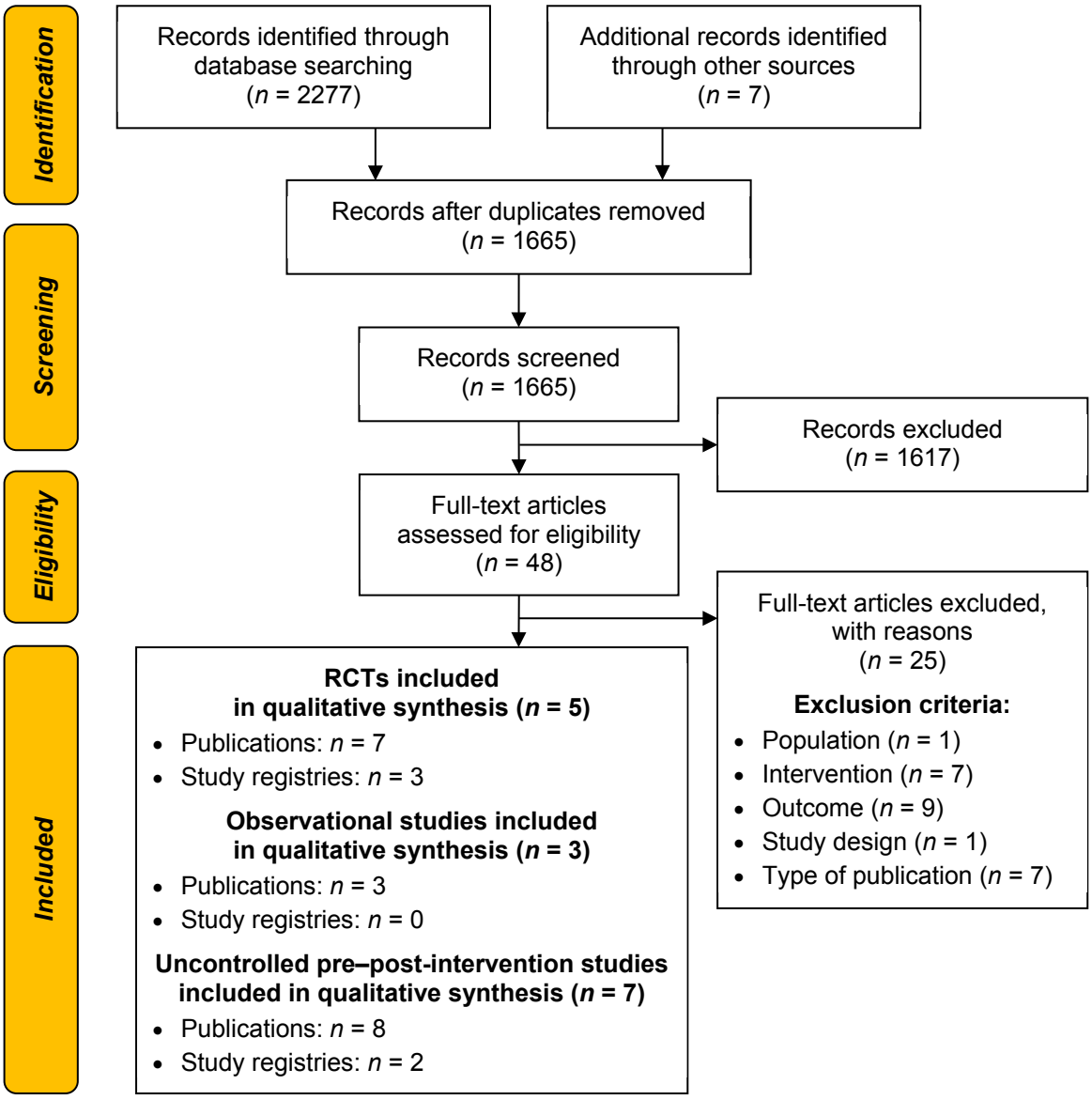


Figure 4.9: Flow chart of information retrieval for clinical effectiveness (research question 4)

Information retrieval identified 15 studies (23 articles) as relevant for the research question about the effectiveness of different strategies to inform individuals in the target group about lung cancer screening. In terms of design, the studies included could be categorised as follows: five randomised trials (10 documents) [177-186], three controlled observational studies (3 documents) [187-189] and seven uncon-trolled pre–post-intervention (PPI) studies (10 documents) [190-199]. The last search was performed on 24th July 2020.

4.4.2 Studies included in the assessment

The studies listed in Table 4.18 were included in the assessment.

Table 4.18: Study pool: list of relevant studies used for the assessment

Study	Documents available	Study registry entries	Result report from study registries
Lung cancer screening information/invitation interventions			
Quaife 2020	Yes [177, 178]	Yes [185, 186]	No
Sharma 2018	Yes [181]	No	–
Yoshida 2012	Yes [189]	No	–
Shared decision making in lung cancer screening			
Hoffman 2018	Yes [190, 191]	Yes [198]	No
Lau 2015	Yes [192]	No	–
Lowenstein 2020	Yes [187]	No	–
Mazzone 2017	Yes [193]	No	–
Reuland 2018	Yes [194]	Yes [199]	No
Ruparel 2019	Yes [179]	Yes [185, 186]	No
Sakoda 2019	Yes [195]	No	–
Sferra 2020	Yes [180]	No	–
Studts 2020	Yes [196]	No	–
Tanner 2019	Yes [188]	No	–
Volk 2014	Yes [197]	No	–
Volk 2020	Yes [182, 183]	Yes	Yes [184]

4.4.3 Description of the evidence used

Table 4.19, Table 4.20 and Table 4.21 describe the studies used for the assessment.

Two RCTs and one nonrandomised comparative study compared different information or invitation materials/strategies for lung cancer screening The remaining 12 studies (three RCTs, two observational studies and seven uncontrolled PPI studies) assessed the effect of different shared decision-making strategies or tools for individuals eligible for lung cancer screening.

4.4.3.1 Lung cancer screening information/invitation interventions

There are two RCTs on the topic of different invitation strategies for lung cancer screening. The first RCT (2012 participants) evaluated the effect of a targeted, stepped and low-burden invitation strategy compared to standard invitations used in the National Health Service (NHS) cancer screening programmes in the UK regarding screening attendance and informed decision-making outcomes [177, 178]. In the second RCT, 1,000 participants received a brochure and were contacted by telephone for in-depth messaging regarding lung cancer, or they just received the brochure on lung cancer screening without further contact. This trial was conducted in the USA [181]. One observational study [189] evaluated whether the distribution of an information leaflet on lung cancer screening compared to no intervention affects the screening rate among different age groups in an urban area in Japan.

4.4.3.2 Information strategies/tools for informed decisions in lung cancer screening

The remaining 12 studies (three RCTs, two observational studies and seven uncontrolled PPI studies) included 2069 participants and evaluated the effects of different information strategies on informed decisions to participate in lung cancer screening. All studies were conducted in the USA. The use of different types of decision aid (e.g., video-based, web-based) was investigated in RCTs by Volk 2020 [182, 183] and Sferra 2020 [180], while one observational study [187] used standard information material for lung cancer screening and counselling using option grids as comparators. Decision aids were also investigated in five single-arm studies (Hoffman 2018 [190, 191], Lau 2015 [192], Mazzone 2017 [193], Reuland 2018 [194] and Volk 2014 [197]). Two other studies examined educational materials [196] or educational classes [195] for screening participants. One RCT investigated the benefit of an information film in addition to a booklet in comparison to an information booklet alone [179]. The remaining observational study compared in-person shared decision-making counselling to telephone counselling [188].

Table 4.19: Characteristics of the studies included

Study	Study location and period	Study type	Intervention (*N*)	Comparator(s) (*N*)	Patient population	Primary and patient-relevant secondary endpoints [a]	Funding
LCS information/invitation interventions							
Quaife 2020	UK, 2014–2019	RCT	Targeted screening invitation strategy (*N* = 1006)	Standard invitation material for UK screening programmes (*N* = 1006)	Current smokers during 2010 or in subsequent years, aged 60–75 years	**Primary:** • Attendance for the Lung Health Check appointment **Secondary:** • Demographics of invited persons • Smoking data • Lung cancer risk • Psychological burden of screening • Screening eligibility • Uptake of CT scans and willingness to be screened • Informed decision-making outcomes (decisional conflict, decisional satisfaction, knowledge of LCS)	• University College, London • University College London Hospitals • Homerton University Hospital NHS Foundation Trust
Sharma 2018	USA, n.r.	RCT	In-depth telephone counselling + brochure (*N* = 500)	Brochure alone (*N* = 500)	Current smokers, aged 55–79 years	**Primary:** n.r. **Secondary:** n.r **Other outcomes:** • Speaking to a physician about LCS • Speaking to an insurance company about LCS	• Cancer Prevention and Research Institute of Texas • M.D. Anderson Cancer Center
Yoshida 2012	Japan, n.r.	Observational	Information leaflet on LCS (*N* = 214)	No leaflet (*N* = 174)	Men and women aged 40–59 years eligible for LCS	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • LCS rates	n.r.

Study	Study location and period	Study type	Intervention (*N*)	Comparator(s) (*N*)	Patient population	Primary and patient-relevant secondary endpoints [a]	Funding
Information strategies/tools for informed decision in LCS							
Hoffman 2018	USA, 2016	Single-arm PPI	Video-based decision aid (*N* = 31)	–	Smokers or former smokers (within 15 years of quitting), aged 55–80 years, who were eligible for LCS	**Primary:** • Informed decisions regarding LCS **Secondary:** • None	• M.D. Anderson Cancer Center • Patient-Centered Outcomes Research Institute
Lau 2015	USA, 2014	Single-arm PPI	Web-based patient decision aid (*N* = 60)	–	Smokers or former smokers, aged 45–80 years	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Decisional conflict • Knowledge regarding LCS • Screening acceptability	• University of Michigan Comprehensive Cancer Center
Lowenstein 2020	USA, 2016–2017	Observational	Interactive decision aid + decision coaching (*N* = 30)	No decision aid or coaching (*N* = 51)	Adults who participated in LCS (control) or who presented for LCS (intervention)	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Informed decisions regarding LCS • Knowledge regarding LCS • Participant satisfaction with visit	• M.D. Anderson Cancer Center • Duncan Family Institute for Cancer Prevention and Risk Assessment • National Cancer Institute
Mazzone 2017	USA, 2015–2016	Single-arm PPI	SDM counselling visit, which includes an online decision aid (*N* = 155)	–	Adults eligible for LCS	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Knowledge regarding LCS	n.r.
Reuland 2018	USA, 2015–2016	Single-arm PPI	Patient decision aid (*N* = 62)	–	Smokers or former smokers aged 55–80 years	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Knowledge regarding LCS • Screening preferences • Screening participation • Decision aid acceptability	• UNC Lineberger Comprehensive Cancer Center

Study	Study location and period	Study type	Intervention (*N*)	Comparator(s) (*N*)	Patient population	Primary and patient-relevant secondary endpoints [a]	Funding
Ruparel 2019	UK, 2016–2017	Nested RCT within the Lung Screen Uptake Trial (Quaife 2020)	LCS information film + booklet (*N* = 126)	LCS information booklet alone (*N* = 120)	Smokers or former smokers (within 5 years of quitting), aged 60–75 years, identified for a lung health check	**Primary:** • Knowledge regarding LCS (postintervention 10-point objective knowledge score) **Secondary:** • Knowledge regarding LCS (5-point subjective investigator-designed knowledge score) • Decisional conflict scale (DCS) • LDCT completion • Feedback on the information materials	• University College, London • University College London Hospitals • Homerton University Hospital NHS Foundation Trust
Sakoda 2019	USA, 2017–2018	Single-arm PPI	Patient education class for SDM (*N* = 269)	–	Smokers or former smokers, aged 55–80 years eligible for LCS	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Knowledge regarding LCS • Informed decisions regarding LCS	• National Cancer Institute
Sferra 2020	USA, 2015–2017	RCT	Directed SDM discussion utilising option grids (*N* = 128)	Online decision aid (*N* = 109)	Smokers or former smokers (within 15 years of quitting), aged 55–80 years, who were eligible for LCS with LDCT	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Informed decisions regarding LCS • Decisional conflict • Knowledge regarding LCS	• Temple University Fox Chase Cancer Center/ HC Regional Comprehensive Cancer Health Disparity Partnership • National Cancer Institute
Studts 2020	USA, n.r.	Single-arm PPI	Values clarification/ preference elicitation exercise and brief educational intervention (*N* = 210)	–	Smokers or former smokers, aged 45 years or older	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Decisional conflict	• National Institutes of Health • Behavioral and Community-Based Research Shared Resource Facility of the University of Kentucky Markey Cancer Center

Study	Study location and period	Study type	Intervention (*N*)	Comparator(s) (*N*)	Patient population	Primary and patient-relevant secondary endpoints [a]	Funding
Tanner 2019	USA, 2015–2016	Prospective observational study	In-person SDM visit (*N* = 80)	Telephone SDM visit (*N* = 70)	Adults eligible for LCS based on their age and tobacco pack-year history	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Screening participation rate • Decisional conflict • Decisional satisfaction	• Veterans Affairs Health Services • American Cancer Society
Volk 2014	USA, 2011–2012	Single-arm PPI	Video-based decision aid (*N* = 52)	–	Current or former smokers aged 45–75 years from a cancer centre tobacco treatment programme	**Primary:** n.r. **Secondary:** n.r. **Other outcomes:** • Knowledge regarding LCS • Decisional conflict • Decision aid acceptability	n.r.
Volk 2020	USA, 2015–2017	RCT	Video-based decision aid (*N* = 259)	Standard educational material (*N* = 257)	Smokers or former smokers (within 15 years of quitting), aged 55–77 years recruited from state-based tobacco cessation helplines	**Primary:** • Informed decisions regarding LCS • Decisional conflict **Secondary:** • Knowledge regarding LCS	• M.D. Anderson Cancer Center • Patient-Centered Outcomes Research Institute

Abbreviations: CT=computed tomography; LCS=lung cancer screening; LDCT=low-dose computed tomography; *N*=number of patients randomised (included); n.r.=not reported; PPI=pre–post-intervention; RCT=randomised controlled trial; SDM=shared decision-making.

[a] Primary endpoints contain information without consideration of its relevance for this assessment. Secondary endpoints contain exclusively information on the relevant available outcomes for this assessment.

Table 4.20: Inclusion and exclusion criteria

Study	Inclusion criteria	Exclusion criteria
Lung cancer screening information/invitation interventions		
Quaife 2020	• Men and women aged 60–75 years • Recorded by their GP practice as smokers since April 2010 (within 7 years of invitation)	• Active lung cancer diagnosis or metastases • On the palliative care register • Had undergone recent CT of the thorax (<12 months) • Lacked capacity • Insufficient English • Comorbidity contraindicating screening or treatment
Sharma 2018	• Men and women aged 55–79 years • Current smokers • Former smokers (quit smoking within the past 15 years) • Participants residing in New York state, but outside of Erie and Niagara counties • Smoking history of at least 30 pack-years • Agreed to be recontacted for a 4-month follow-up survey • Able to communicate in English	n.r.
Yoshida 2012	• Men and women aged 40–59 years	n.r.
Information strategies/tools for informed decisions in lung cancer screening		
Hoffman 2018	• Men and women aged 55–80 years • Current smoker or quit smoking within the past 15 years • Able to communicate in English	• History of lung cancer
Lau 2015	• Men and women aged 45–80 years • Current or former smoker	• History of lung cancer • Chest CT scan with in previous year
Lowenstein 2020	• Adults who already participated in lung cancer screening or presented in clinic for lung cancer screening	n.r.
Mazzone 2017	• Eligible for lung cancer screening based on their age and smoking history	n.r.
Reuland 2018	• Men and women aged 55–80 years • Current smoker or quit smoking within the past 15 years	• History of lung cancer • Treatment for other cancer with chemotherapy or radiation within 18 months
Ruparel 2019	• Individuals aged 60–75 years • Recorded as a current smoker in 2010 or subsequent years	• Active diagnosis of lung cancer or metastases • CT of the thorax within the past year • Inability to consent to the study • Palliative care register • GP alert to comorbidity that contraindicates screening or treatment for lung cancer
Sakoda 2019	• Men and women aged 55–80 years • Current or former smoker	n.r.

Study	Inclusion criteria	Exclusion criteria
Sferra 2020	• Men and women aged 55–80 years • Actively smoking or quit smoking within the past 15 years • Smoking history of at least 30 pack-years • Reliable communication by mail and telephone • Reading level at least 6th grade according to Rapid Estimate of Adult Literacy in Medicine criteria • Able to communicate in English • Not cognitively impaired.	• Symptoms suggestive of lung cancer, such as haemoptysis or unexplained weight loss • Previous lung cancer • Previous cancer of any origin with active treatment within the past 5 years • Any comorbidity or condition precluding them from lung cancer treatment
Studts 2020	• Men and women 45 years or older • Smoking history ≥ 20 pack-year • Able to communicate in English	• History of lung cancer
Tanner 2019	• Eligible for lung cancer screening based on their age and tobacco pack-year history according to the US Preventive Service Task Force 2014 recommendations	n.r.
Volk 2014	• Men and women aged 45–75 years • Current or former smoker from a tobacco treatment programme • Able to communicate in English	• History of lung cancer
Volk 2020	• Men and women aged 55–77 years • Current smoker or quit smoking within the past 15 years. • Smoking history ≥ 30 pack-year • Able to communicate in English	• History of lung cancer

Abbreviations: CT=computed tomography; GP=general practitioner; n.r.=not reported.

Table 4.21: Characterisation of the interventions

Study reference	Intervention	Comparator	Additional intervention in all groups
LCS information/invitation interventions			
Quaife 2020	**Targeted, stepped and low-burden invitation strategy:** participants received an "M.O.T. For Your Lungs" leaflet, designed to target psychological barriers to attendance (fear, fatalism, and stigma), to be low-burden (sufficient for deciding to attend and consider the screening offer), and stepped (full information given at the appointment using the control group's booklet or available before via a website, phone, or post). An M.O.T. is an annual roadworthy test for vehicles and was a lay concept perceived to be analogous to a medical check-up and preferred by patient and public involvement groups.	Participants received an **information booklet** mimicking the fact booklets of UK NHS cancer screening programmes.	All participants received the same postal invitation letters from their primary care practice: preinvitation letter, invitation letter with scheduled appointment, and reminder reinvitation letter with a second scheduled appointment (sent to nonresponders >4 wk after missed appointment). The invitation letters were identical with two exceptions: 1) Letters for the intervention group referred to "ever smokers" whereas letters for the control group referred to "current and former smokers". 2) Letters for the intervention group included a bullet-point summary of the Lung Health Check, including an LDCT scan offer, on the reverse side.
Sharma 2018	Participants received the same **brochure** as in the control group along with **coach-delivered in-depth messaging** regarding LCS over the **telephone**. This additional messaging included awareness education about LCS, and expanded information on the perceived benefits, perceived barriers/cost, along with advice to speak with their doctor (cue to action).	Participants received a **brochure** on LCS that provided information on the benefits associated with screening, information about insurance coverage, some of the perceived risks from screening, and advice to talk with their doctor via a tear-off feature in the brochure (cue to action). The control group also received a brief message to check for the brochure in the mail.	–
Yoshida 2012	**A leaflet** titled "Do you know lung cancer screening" from the National Cancer Center on LCS. The leaflet consisted of 5 parts: questions and answers on lung cancer, a flowchart of LCS, tobacco and lung cancer, sites of occurrence of lung cancer, and LCS. The leaflet pointed out the necessity of LCS, importance of early detection and early treatment, and high mortality rate of lung cancer with data.	**No leaflet**	Questionnaire of 10 multiple-choice questions on their cancer screening record, knowledge and interest in cancer, occupation, and smoking and alcohol drinking habit.

Study reference	Intervention	Comparator	Additional intervention in all groups
Information strategies/tools for informed decision in LCS			
Hoffman 2018	**Video-based patient decision aid** about LCS (Lung Cancer Screening: Is it right for me?) of 9.5 minutes; content based on US Preventive Services Task Force 2014 recommendation for LCS and the CMS eligibility criteria for LCS. Includes information about: eligibility for LCS and a calculation of tobacco pack-year smoking history, lung cancer epidemiology and importance of quitting smoking, a video of a patient in a CT scanner, an icon arrays graphically depicting the magnitude of mortality reduction, false-positive results and harms from invasive diagnostic procedures, and radiation exposure depicted within the context of other sources of radiation (e.g., a screening mammogram).	–	–
Lau 2015	**Online decision aid** (www.shouldiscreen.com) that includes a web-based calculator consisting of 12 questions to calculate the risks of lung cancer. The results indicate how much a person stands to benefit from getting screened and help the person better determine whether their potential benefit from screening outweighs the harms. The participants navigated through the website on their own.	–	–
Lowenstein 2020	**Interactive decision aid** based on the content of a video-based decision aid (Lung Cancer Screening: Is it right for me?) and a second video-based decision aid on LCS. The adapted decision aid included descriptions of the LCS process and of potential benefits and harms of LCS. Participants' values were assessed using a series of interactive questions about benefits and harms related to LCS. Finally, the application provided a list of tailored discussion topics on the basis of the responses. The decision coaching module was based on the Ottawa Decision Support Framework and addressed CMS-required elements for SDM. A series of 6 interactive pages guided clinicians through the decision coaching procedures.	**Usual LCS procedure** in USA.	–
Mazzone 2017	SDM counselling visit: 6-minute **narrative video slideshow** describing the benefits and harms of LCS, and use of a decision aid (www.shouldiscreen.com) to individualise the discussion of benefits and risks. Participants had an opportunity to ask questions throughout the visit.	–	–
Reuland 2018	**Self-developed video-based decision aid** based on CMS standards and requirements (length 6 minutes). Written text was read aloud, and technical terms and concepts were explained using narration, graphics	–	–

Study reference	Intervention	Comparator	Additional intervention in all groups
Reuland 2018 *(continuation)*	and animations. Content included the rationale for screening, eligibility criteria, description of the LDCT procedure and a dynamic icon array (pictogram) sequentially depicting estimates for the benefits and harms of screening among 1000 individuals screened annually for 3 years.		
Ruparel 2019	LCS **information film** (5.5 minutes long) in addition to the **information booklet** used in the control group; 10 minutes to watch the film and/or read the booklet in the presence of a healthcare professional. It addresses lung cancer, the benefits and harms of LCS (including indeterminate pulmonary nodules and false positives, overdiagnosis and radiation damage), the LDCT procedure, and possible results after the scan.	**Information booklet** (10 pages) on lung health check, designed to be clear and comprehensible for individuals with a reading age of 11–13 years: It addresses lung cancer, the benefits and harms of LCS (including indeterminate pulmonary nodules and false positives, overdiagnosis, and radiation damage), the LDCT procedure, and possible results after the scan; 10 minutes to read the booklet in the presence of a healthcare professional.	Participants in both groups were subsequently informed of an elevated lung cancer risk (if applicable) compared with the general population and thus eligibility for LDCT. If the participant was happy to proceed, written consent to undergo LDCT was taken by the healthcare professional.
Sakoda 2019	**Patient education class** on LCS before face-to-face SDM visit with primary care physician. The class provides the opportunity for patients to decide whether LCS is right for them. Key aspects, including the eligibility criteria and potential benefits and harms, are presented. A risk assessment is illustrated for a hypothetical patient during class and then later personalised and discussed at the SDM visit if a patient chooses to continue with screening. The importance of smoking abstinence is stressed to encourage current smokers to quit. Patient education materials and a decision worksheet handout, all developed by our Regional Health Education department, are provided to support the learning process. The class was taught by a clinical specialist (80% pulmonologists)	–	–
Sferra 2020	Directed SDM discussion utilising **Option Grids** (www.optiongrid.org), a brief information sheet to guide a physician–patient encounter in which patients and providers can select/compare LCS options and made a decision.	**Online decision aid** (www.shouldiscreen.com) that includes a web-based calculator consisting of 12 questions to calculate the individual risk of lung cancer. The results indicate how much a person stands to benefit from getting screened and help the person better determine whether their potential benefit from screening outweighs the harms. The physician navigated the participants through the website.	LCS programme that incorporates an SDM visit, LDCT scan and discussion of results in a single-day visit. Participants of both groups had an opportunity for further discussion with a physician before deciding if they would pursue screening.

Study reference	Intervention	Comparator	Additional intervention in all groups
Studts 2020	Full-profile **conjoint value analysis instrument** with 22 cards/vignettes and a **brief educational narrative** on LCS. The conjoint exercise consisted of 5 attributes: expected mortality reduction (benefit), false positive rate (harm), cost, provider recommendation, and access. After each scenario, a 9-point Likert-type ratings scale anchored by ‘‘would definitely not get screened’’ and ‘‘would definitely get screened’’ was used to assess importance scores. All participants received the same scenarios, although the order of scenario presentation and of attributes varied. In addition to the conjoint valuation survey, a brief educational narrative was provided that described the LCS decision, introduced the conjoint procedure and defined a false-positive screening result. The brief educational narrative included 410 words written at the 7.5 grade level according to the Flesch-Kinkaid grade level formula.	–	–
Tanner 2019	Recruitment using waiting room advertisements with return cards and/or telephone contact. **In-person SDM visits** were conducted by a pulmonologist or a nurse practitioner at random as part of usual care. The visit took an average of 15 minutes. Participants received a paper decision aid covering the harms and benefits of LCS. The visit started with explanatory counselling about the benefits and potential harms of LCS using the decision aid. The participants received a personalised risk assessment for developing lung cancer over the next 6 years using the PLCO modified 2012 calculator.	Recruitment using postcard mailers and telephone contact. **Telephone SDM visits** were conducted by a nurse practitioner as part of usual care in the LCS programme. The visit took an average of 15 minutes. Participants received a paper decision aid covering the harms and benefits of LCS in the mail 1 week before the telephone SDM visit. The visit started with explanatory counselling about the benefits and potential harms of LCS using the decision aid. Participants received a personalised risk assessment for developing lung cancer over the next 6 years using the PLCO modified 2012 calculator.	–
Volk 2014	**Video-based patient decision aid** on LCS (Lung Cancer Screening: Is it right for me?) of 6 minutes; content written at the 8th-grade reading level. Features include an on-screen narrator, information about lung cancer and its risk factors, footage of a patient undergoing a scan, animations communicating the magnitude of harms and benefits of LDCT screening, and an implicit values clarification component that depicts trade-offs between potential harms and benefits. Uses animated pictographs to depict the likelihood of benefit from LDCT screening and the false-positive rate associated with testing.	–	–

Study reference	Intervention	Comparator	Additional intervention in all groups
Volk 2020	**Video-based patient decision aid** on LCS (Lung Cancer Screening: Is it right for me?) of 9.5 minutes; content based on US Preventive Services Task Force 2014 recommendation for LCS and the CMS eligibility criteria for LCS. It included information about: 1) eligibility for LCS and a calculation of tobacco pack-year smoking history, 2) Lung cancer epidemiology and risk factors 3) Video of a patient in a CT scanner 4) Icon arrays to graphically depict the magnitude of mortality reductions, false-positive results and harms from invasive diagnostic procedures 5) Radiation exposure depicted within the context of other sources of radiation (e.g., a screening mammogram) Smoking cessation was emphasised throughout the decision aid.	**Standard educational material** for LCS (2-page brochure) including information on: 1) Eligibility for screening 2) Harms and benefits of screening 3) What to expect when undergoing an LDCT scan 4) Costs of screening 5) How to interpret LDCT results 6) Importance of smoking cessation 7) Where to find more information about lung cancer and screening Benefits and harms were described, but no probabilities of outcomes were included. Patient values related to the positive and negative features of LCS were not addressed.	–

Abbreviations: CMS=Centers for Medicare & Medicaid Services; CT=computed tomography; LCS=lung cancer screening; LDCT=low-dose CT; NHS=National Health Service; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SDM=shared decision-making.

4.4.3.3 Lung cancer screening information/invitation interventions

The two RCTs included current or former smokers who had quit smoking within the previous 15 years. In the Sharma 2018 study, the participants had to have a smoking history of at least 30-pack-years, while in the second RCT (Quaife 2020) no pack-years were defined. The ratio between men and women was balanced in these trials. The mean age of the participants was 62 and 66 years, respectively. One Japanese study (Yoshida 2012) focussed on younger persons potentially eligible for lung cancer screening (40–49 years) because the study aim was to improve cancer screening rates at an earlier phase of life. The percentage of women in this study was approximately 59%.

4.4.3.4 Information strategies/tools for informed decisions in lung cancer screening

All of the studies included man and women eligible for lung cancer screening, defined as current or former smokers aged ≥ 45 years or ≥ 55 years. In four studies, former smokers were included only if they had stopped smoking within the last 15 years (Hoffman 2018, Reuland 2018, Sferra 2020 and Volk 2020). A smoking history of at least 20 or 30 pack-years was an inclusion criterion in three studies (Sferra 2020, Volk 2020 and Studts 2020). The percentage of women in the studies ranged from 40% to 65%. The mean age of the participants in the studies ranged from 59 years to 65 years.

Table 4.22 shows the characteristics of the participants in the studies included.

Table 4.22: Baseline characteristics of the study population

Study and characteristics	Intervention	Comparator
Lung cancer screening information/invitation interventions		
Quaife 2020	***N* = 1006** [a]	***N* = 1006** [a]
Age [years], mean (SD)	66.1 (4.3)	65.9 (4.3)
Sex [F], %	44.7	47.8
Ethnicity, % *Asian* *Black* *Mixed* *White* *Other* *Not stated*	 2.3 9.4 1.4 79.6 3.1 4.2	 1.9 9.7 2.0 79.8 2.8 3.8
Smoking status, % *Current smoker* *Quit smoking* *Never smoked tobacco* *Refused/not stated* *Missing* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, median* *Years smoked, median*	 76.2 23.0 0.8 0 0 n.r. n.r. n.r.	 72.8 26.4 0.5 0.2 0.1 n.r. n.r. n.r.
Study discontinuation, *n* (%)	0	0
Sharma 2018	***N* = 500** [a]	***N* = 500** [a]
Age [years], mean (SD)	62.0 (6.3)	61.0 (5.6)
Sex [F], %	54.2	53.2
Ethnicity, % *White* *African American* *Other/not reported*	 67.6 12.0 20.4	 68.8 12.2 19.0

Study and characteristics	Intervention	Comparator
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median (SD)* *Number of pack-years, median (SD)* *Years smoked, median (SD)*	 n.r. n.r. 20.0 (8.4) 45 (20.1) 40 (9.0)	 n.r. n.r. 20.0 (9.4) 45 (21.4) 40 (8.4)
Study discontinuation, *n* (%)	172 (55.6)	284 (56.8)
Yoshida 2012	***N* = 214** [a]	***N* = 174** [a]
Age, % *40–44 years* *45–49 years* *50–54 years* *55–59 years* *Unknown*	 15.4 22.9 31.3 28.0 2.3	 18.3 28.7 26.4 24.1 2.3
Sex [F], %	56.5	62.0
Ethnicity, %	n.r.	n.r.
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, median* *Years smoked, median*	 17 n.r. n.r. n.r. n.r.	 16 n.r. n.r. n.r. n.r.
Alcohol drinking, %	44	42
Study discontinuation, *n* (%)	0	0
Information strategies/tools for informed decision in lung cancer screening		
Hoffman 2018	***N* = 31** [a]	**–**
Age [years], mean (SD) [b]	61.5 (4.67)	–
Sex [F], % [b]	50.0	–
Ethnicity, % [b] *White* *Non-white*	 63.3 36.7	–
Smoking status, % [b] *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (range)* *Years smoked, median*	 67 33 n.r. 30.4 (4.6–90) n.r.	–
Study discontinuation, *n* (%)	1 (3.2)	–
Lau 2015	***N* = 60** [a]	**–**
Age [years], mean (SD)	60.6 (7.3)	–
Sex [F], %	50.0	–
Ethnicity, % *White* *African American*	 88 12	–
Smoking status, % *Current smoker* *Quit smoking >15 years ago* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (SD)* *Years smoked, median*	 27 50 n.r. 24.08 (23.85) n.r.	–
Study discontinuation, *n* (%)	0	–

Study and characteristics	Intervention	Comparator
Lowenstein 2020	***N* = 30** [a]	***N* = 51** [a]
Age [years], mean (SD)	n.r.	n.r.
Sex [F], %	n.r.	n.r.
Ethnicity, %	n.r.	n.r.
Smoking status, %	n.r.	n.r.
Study discontinuation, *n* (%)	0	0
Mazzone 2017	***N* = 155** [a]	**–**
Age [years], mean (range)	64.4 (55–77)	–
Sex [F], %	33.9	–
Ethnicity, %	n.r.	–
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (range)* *Years smoked, median*	 45.2 n.r. n.r. 53.0 (30–112) n.r.	–
Study discontinuation, *n* (%)	42 (27)	–
Reuland 2018	***N* = 62** [a]	**–**
Age [years], mean (SD) [c]	63 (n.r.)	–
Sex [F], % [c]	48	–
Ethnicity, % [c] *White* *African American* *Other*	 58 30 12	–
Smoking status, % [c] *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (SD)* *Years smoked, median*	 46 n.r. n.r. 52 (n.r.) n.r.	–
Study discontinuation, *n* (%)	12 (19.3)	–
Ruparel 2019	***N* = 126** [a]	***N* = 120** [a]
Age, % [d] *60–63 years* *64–67 years* *68–71 years* *72–76 years*	 33.33 27.50 27.50 11.67	 40.37 29.36 18.35 11.93
Sex [F], % [d]	54.17	49.54
Ethnicity, % [d] *White* *Black/ African/Caribbean* *Asian* *Other*	 81.67 10.83 2.50 5.00	 84.40 7.34 3.67 4.59
Smoking status, % [d] *Current smoker* *Quit smoking* *Average cigarette smoking (cig/day), median (IQR)* *Number of pack-years, median(IQR)* *Years smoked, median (IQR)*	 n.r. n.r. 16 (10–20) 38 (21–50) 47 (43–52)	 n.r. n.r. 15 (10–20) 35 (21–51) 46 (42–51)
Study discontinuation, *n* (%)	6 (4.8)	11 (9.2)

Study and characteristics	Intervention	Comparator
Sakoda 2019	***N* = 269** [a]	**–**
Age [years], median (IQR)	64.0 (60–69)	–
Sex [f], %	40.2	–
Ethnicity, % *White* *African American* *Hispanic* *Asian* *Other*	 82.9 2.3 6.2 7.8 0.8	–
Smoking status, % *Current smoker* *Quit smoking* *Not smoking* *Average cigarette smoking (cig/day), median (IQR)* *Number of pack-years, mean* *Years smoked, %* *<30* *30–39* *40–49* *≥50*	 50.9 n.r. 49.1 40.0 (37–50) n.r. 3.0 26.4 45.0 25.6	–
Study discontinuation, *n* (%)	0	–
Sferra 2020	***N* = 128** [a]	***N* = 109** [a]
Age [years], mean (SD)	64 (n.r.)	64 (n.r.)
Sex [F], %	55.5	46.8
Ethnicity, % *African American* *Caucasian* *Hispanic* *Asian/Pacific Islander* *Unknown*	 55.5 35.9 6.3 1.6 0.8	 68.8 21.1 8.3 0.9 0.9
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, median* *Years smoked, median*	 n.r. n.r. n.r. 42 n.r.	 n.r. n.r. n.r. 44 n.r.
Study discontinuation, *n* (%)	n.r. [e]	n.r. [e]
Studts 2020	***N* = 210** [a]	**–**
Age [years], mean (SD)	61.69 (8.46)	–
Sex [F], %	52	–
Ethnicity, % *White* *African American* *Hispanic*	 46 24 28	–
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (SD)* *Years smoked, median*	 n.r. n.r. n.r. 39.95 (20.10) n.r.	–
Study discontinuation, *n* (%)	1 (0.5)	
Tanner 2019	***N* = 80** [a]	***N* = 70** [a]
Age [years], mean (SD) [f]	64.1 (6.0)	65.2 (6.2)
Sex [F], % [f]	52.2	5.9

Study and characteristics	Intervention	Comparator
Ethnicity, % [f] *African American* *Caucasian* *Hispanic* *American Indian* *Other* Smoking status, % [f]	 28.5 64.2 5.1 0 1.5 n.r.	 27.9 63.2 5.9 2.9 0 n.r.
Family history of lung cancer (%) [f]	23.2	26.5
Individual lung cancer risk, mean (SD) [f]	5.2 (4.2)	5.2 (3.9)
Study discontinuation, *n* (%)	11 (13.8)	2 (2.9)
Volk 2014	***N* = 52** [a]	**–**
Age [years], mean (range)	58.5 (45–75)	–
Sex [F], %	65.4	–
Ethnicity, % *White* *African American* *Hispanic*	 74.8 19.2 6	–
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cigarettes/day), median* *Number of pack-years, mean (SD)* *Years smoked, mean (SD)*	 44.2 55.8 n.r. 30.0 (n.r.) 34.8 (n.r.)	–
Study discontinuation, *n* (%)	0	–
Volk 2020	***N* = 259** [a]	***N* = 257** [a]
Age, % *≥ 65 years* *< 65 years*	 26.6 73.4	 30.0 70.0
Sex [F], %	60.6	63.4
Ethnicity, % *White* *Black/African* *Native Hawaiian or other Pacific Islander* *Asian* *Hispanic or Latino* *Other*	 71.4 23.9 0 0 2.7 0.8	 68.9 29.6 0.4 0 0.4 0
Smoking status, % *Current smoker* *Quit smoking* *Average cigarette smoking (cig/day), median (IQR)* *Number of pack-years, median (IQR)* *Years smoked, median (IQR)*	 n.r. n.r. 20.0 (20.0–30.0) 47.0 (40.0–63.0) 42.0 (40.0–49.0)	 n.r. n.r. 20.0 (20.0–30.0) 49.0 (40.0–63.8) 44.0 (40.0–50.0)
Study discontinuation, *n* (%)	41 (15.8)	32 (12.5)

Abbreviations: F=female; IQR=interquartile range; *n*=number of patients in the category; *N*=number of patients randomised/included; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Number of randomised patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

[b] *N* = 30.

[c] *N* = 50.

[d] Intervention: *N* = 120; comparator: *N* = 109.

[e] No separate information for the study groups; 209 of 237 participants in both groups (88.2%) completed the CollaboRATE questionnaire, 179 of 237 participants in both groups (75.5%) completed the Decision Regret questionnaire, and 87 of 237 participants in both groups (36.7%) completed the follow-up knowledge questionnaire.

[f] Intervention: *N* = 69; comparator: *N* = 68.

4.4.4 Outcomes included

Table 4.23 shows for which of the outcomes to be included in the assessment data were available in the studies included. All but four studies reported data on participants' change in knowledge about lung cancer screening. Participant empowerment was evaluated in nine studies, all focusing on the decisional conflict of the participants, while five studies also investigated whether the participants were prepared to make a decision about lung cancer screening (informed decision-making). Participants' satisfaction with the information was evaluated in three studies, and the participation rate was defined as an outcome in eight of the studies.

Table 4.23: Matrix of outcomes in the included studies to be assessed

Study (design)	Outcomes				
	Increased knowledge	Informed decision-making	Participant empowerment	Participant satisfaction	Screening participation rate
Lung cancer screening information/invitation interventions					
Quaife 2020 (RCT)	Y	N	Y	Y	Y
Sharma 2018 (RCT)	N	N	N	N	Y
Yoshida 2012 (non-RCT)	N	N	N	N	Y
Information strategies/tools for informed decision in lung cancer screening					
Hoffman 2018 (single arm)	Y	Y	Y	N	Y
Lau 2015 (single arm)	Y	N	Y	N	N
Lowenstein 2020 (non-RCT)	Y	Y	N	Y	N
Mazzone 2017 (single arm)	Y	N	N	N	N
Reuland 2018 (single arm)	Y	N	N	N	Y
Ruparel 2019 (RCT)	Y	N	Y	N	Y
Sakoda 2019 (single arm)	Y	Y	N	N	N
Sferra 2020 (RCT)	Y	Y	Y	N	N
Studts 2020 (single arm)	N	N	Y	N	N
Tanner 2019 (non-RCT)	N	N	Y	Y	Y
Volk 2014 (single arm)	Y	N	Y	N	N
Volk 2020 (RCT)	Y	Y	Y	N	Y

Abbreviations: N=no; RCT=randomised controlled trial; Y=yes.

4.4.5 RoB assessment

Table 4.24, Table 4.25 and Table 4.26 describe RoB at the study level and for the relevant outcomes. The RoB at the study level was rated as low for two RCTs (Quaife 2020 and Volk 2020) and as high for three RCTs (Sharma 2018, Ruparel 2019 and Sferra 2020). In these trials, it was unclear whether the randomisation sequence was adequately generated and/or whether the allocation concealment was adequate. In the Sharma 2018 study it was also unclear whether reporting was independent of the results (e.g., lack of information on the planned endpoints). The RoB for increased knowledge, participant empowerment, informed decision-making, participant satisfaction

and the screening participation rate was rated low in the Quaife 2020 and Volk 2020 RCTs. For the other three RCTs in which the RoB at the study level was already classified as high, there is therefore high RoB at the outcome level.

The RoB for the observational studies and single-arm PPI studies was rated low for four studies (Hoffman 2018, Lau 2015, Studts 2020 and Volk 2014) at the outcome level for all of the outcomes reported (increased knowledge, informed decision-making, participant empowerment and the screening participation rate). The RoB for the remaining six studies (Lowenstein 2020, Mazzone 2017, Reuland 2018, Sakoda 2019, Tanner 2019 and Yoshida 2012) was rated high at the outcome level for all of the outcomes reported. The main reasons for the high RoB were missing data, selective outcome reporting or bias in the selection of the study participants. Owing to the nature of the interventions, the participants and those delivering the treatment were not blinded in all the RCTs and the other studies.

Table 4.24: Risk of bias in randomised studies at the study level

Study	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias at study level
			Patient	Treating person			
Lung cancer screening information/invitation interventions							
Quaife 2020	Y	Y	N [b]	Y	Y	Y	L
Sharma 2018	U [a]	U [a]	N [b]	U [a]	U [a]	Y	H
Information strategies/tools for informed decisions in lung cancer screening							
Ruparel 2019	Y	U [a]	N [b]	N [b]	Y	Y	H
Sferra 2020	Y	U [a]	N [b]	N [b]	Y	Y	H
Volk 2020	Y	Y	N [b]	N [b]	Y	Y	L

Abbreviations: H=high risk; L=low risk; N=no; U=unclear; Y=yes.

[a] No information available.

[b] Owing to the nature of the intervention, blinding was not possible.

Table 4.25: Risk of bias in randomised studies for relevant outcomes

Study	Endpoint					
	Risk of bias at the study level	Blinding: outcome assessors	ITT principle adequately realised	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias at the outcome level
Lung cancer screening information/invitation interventions						
Increased knowledge						
Quaife 2020	L	U [a]	Y	Y	Y	L
Participant empowerment						
Quaife 2020	L	U [a]	Y	Y	Y	L
Participant satisfaction						
Quaife 2020	L	U [a]	Y	Y	Y	L
Screening participation rate						
Quaife 2020	L	U [a]	Y	Y	Y	L
Sharma 2018	H	U [b]	U [b]	U [b]	N [c]	H
Information strategies/tools for informed decisions in lung cancer screening						
Increased knowledge						
Ruparel 2019	L	U [b]	U [b]	Y	Y	H
Sferra 2020	L	U [b]	N [c]	Y	N [d]	H
Volk 2020	L	Y	Y	Y	Y	L
Informed decision-making						
Sferra 2020	L	U [b]	U [b]	Y	N [d]	H
Volk 2020	L	Y	Y	Y	Y	L
Participant empowerment						
Ruparel 2019	L	U [b]	U [b]	Y	Y	H
Sferra 2020	L	U [b]	N [c]	Y	N [d]	H
Volk 2020	L	Y	Y	Y	Y	L
Screening participation rate						
Ruparel 2019	L	U [b]	U [b]	Y	Y	H
Volk 2020	L	Y	Y	Y	Y	L

Abbreviations: H=high risk; L=low risk; N=no; U=unclear; Y=yes.

[a] The researcher carrying out the analyses will be blinded to group allocation. Unblinding will occur after the primary data analysis is complete and has been checked and verified by a second researcher. Blinding of secondary analysis is unclear.

[b] No information available.

[c] Participants may respond to certain questions in a manner that they believe researchers would want (social desirability bias).

[d] No information on number of participants analysed in each study group; only 36.8% of the participants in both study groups completed the questionnaire.

Table 4.26: Risk of bias in nonrandomised/observational studies for relevant outcomes (ROBINS-I)

Study	Endpoint							
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Lung cancer screening information/invitation interventions								
Screening participation rate								
Yoshida 2012	NI	L	L	L	M	S [a]	M	S
Information strategies/tools for informed decision in lung cancer screening								
Increased knowledge								
Hoffman 2018	NI	L	L	L	L	S [a]	L	L
Lau 2015	NI	L	L	L	L	S [a]	L	L
Lowenstein 2020	NI	C [b]	L	L	L	S [a]	L	H
Mazzone 2017	NI	M	L	L	M	S [a]	L	H
Reuland 2018	NI	L	L	L	M	S [a]	L	H
Sakoda 2019	NI	L	L	L	M [c]	S [a]	L	H
Volk 2014	NI	L	L	L	L	S [a]	L	L
Informed decision-making								
Hoffman 2018	NI	L	L	L	L	S [a]	L	L
Lowenstein 2020	NI	C [b]	L	L	L	S [a]	L	H
Sakoda 2019	NI	L	L	L	M [c]	S [a]	S [e]	H
Participant empowerment								
Tanner 2019	NI	S [d]	L	L	M	S [a]	L	H
Hoffman 2018	NI	L	L	L	L	S [a]	L	L
Lau 2015	NI	L	L	L	L	S [a]	L	L
Studts 2020	NI	L	L	L	L	S [a]	L	L
Volk 2014	NI	L	L	L	L	S [a]	L	L
Participant satisfaction								
Tanner 2019	NI	S [d]	L	L	M	S [a]	L	H
Lowenstein 2020	NI	C [b]	L	L	L	S [a]	L	H
Screening participation rate								
Tanner 2019	NI	S [d]	L	L	M	S [a]	L	H
Hoffman 2018	NI	L	L	L	L	S [a]	L	L
Reuland 2018	NI	L	L	L	M	S [a]	L	H

Abbreviations: C=critical risk; H=high risk; L=low risk; M=moderate risk; NI=no information; S=serious risk.

[a] Owing to the nature of the intervention, the participants and personnel were not blinded.

[a] No information about characteristics of study participants; no information about matching of participants in intervention and control group

[c] Only 72.9% of the participants completed the 1-month follow-up questionnaire.

[d] Different recruitment strategies between the two study groups.

[e] Incomplete reporting of the results.

4.4.5.1 Quality of the evidence

The assessment of the outcome-specific quality of the evidence is presented in Tables A19 to A26 in Appendix 8.

4.4.6 External validity

The majority of the studies on invitation strategies or information materials for lung cancer screening were all conducted in the USA or Europe and included participants eligible for lung cancer screening according to current criteria. Only one study was conducted in Asia (Japan) (Yoshida 2012). In addition, the materials used in the interventions contain information on the benefits and harms of lung cancer screening according to the current guidelines. It can therefore be assumed that these or similar materials can also be used in clinical practice. Therefore, no downgrading due to indirectness was required in the GRADE assessment of invitation strategies or information materials for lung cancer screening. A summary characterising the applicability of studies can be found in Table 4.27.

Table 4.27: Summary table characterising the applicability of the body of studies

Domain	Description of the applicability of the evidence
Population	Regarding upper and lower age limits and lung cancer risk factors, the majority of the studies on information strategies or shared decision-making included individuals meeting the lung cancer screening criteria from current international guidelines. In addition, the populations in the studies consisted equally of men and women and included different ethnicities. There were no restrictions in the studies regarding the educational level or socioeconomic status of the study participants. All study populations were heterogeneous in this respect and included people with low to high household incomes and education levels ranging from less than high school to academic graduation. Therefore, the results allow for high applicability to European populations.
Intervention	As far as known, the contents of all information materials or decision support tools used in lung cancer screening are based on the evidence currently available from guidelines and studies. In addition, written texts used layman's language or films or graphics were used. Furthermore, the vast majority of the studies originate from the European or Anglo-American area, so that cultural aspects can be neglected with regard to the information material. Hence, the results of the studies seem to be transferable to the European context.
Comparators	In the majority of the studies, no comparator was used. In comparative studies, the comparator was non-use of specific information material, or use of information materials routinely used for cancer screening in the USA or the UK. Hence, the results from the studies seem to be transferable to the European context.
Outcomes	Changes in knowledge and decision conflict were the key outcomes in most of the studies. Therefore, no issue regarding applicability was identified.
Setting	All but one of the studies investigating information strategies or shared decision-making were conducted in the USA or Europe. These countries have relatively well-organised and well-financed health care systems. Therefore, the present results are considered to be transferable to all European countries.

4.4.7 Results on clinical effectiveness and safety

HTA CORE MODEL DOMAIN: EFF & SAF[8]

[8] This section addresses the following elements in the EFF and SAF domains of the HTA core model: D0017, D0020, H0202, H0203.

4.4.7.1 Increased knowledge

For increased knowledge about lung cancer screening as an outcome, data from 11 studies were available.

In one RCT (Qualife 2020) comparing a targeted invitation strategy for lung cancer screening to the use of standard information material, no statistically significant difference in the objective knowledge score at study end was observed between the two study groups.

Two studies – including one RCT (Volk 2020) – comparing the use of decision aids in the information process for lung cancer screening compared to standard information materials for cancer screening reported significantly higher knowledge scores and a significantly higher percentage of correct answers on knowledge questionnaires in the decision aid groups. In addition, in five single-arm PPI studies, the knowledge of the participants significantly increased after use of the decision aid. One RCT (Sferra 2020) comparing different decision-making strategies (shared decision-making counselling using an option grid versus a web-based decision aid) showed no significant differences in lung cancer screening knowledge between the groups after the intervention.

Beside the use of decision aids, integration of a standardised education class in the lung cancer-screening programme, which was evaluated in one single-arm study, also significantly enhanced knowledge about the benefits and harms of lung cancer screening among participants eligible for screening.

One further RCT (Ruparel 2019), comparing an information film in addition to an information booklet on lung cancer screening to the use of the information booklet alone, reported significantly increased objective and subjective knowledge scores after the intervention for participants who received the film and the booklet.

Table 4.28, Table 4.29 and Table 4.30 summarise the results for the studies included.

Conclusion on the quality of the evidence on knowledge about lung cancer screening

A targeted invitation strategy for lung cancer screening may result in little or no differences regarding knowledge about lung cancer screening compared to the use of standard information materials. The conclusion is based on low-quality evidence. The quality of the evidence was downgraded by 2 levels because of imprecision, as the results are based on one small RCT.

The use of decision aids in the lung cancer screening process probably increases the knowledge of the participants about lung cancer screening when compared to standard information materials. The conclusion is based on moderate-quality evidence. The quality of the evidence was downgraded by 1 level because of imprecision, as the results are based on two studies with a low number of participants. There may be little to no difference in participants´ knowledge between the two different types of decision aids. This conclusion is based on low-quality evidence. The quality of the evidence was downgraded by 2 levels because of high RoB and imprecision, as the results are based on one relatively small RCT.

The use of information films in the screening process may increase knowledge about lung cancer screening among participants. We are uncertain whether incorporation of education classes improves participant knowledge about lung cancer screening. These conclusions are based on evidence of low to very low quality due to high RoB and imprecision, as the results are based on single studies with low numbers of participants.

Table 4.28: Screening information/invitation interventions: results for knowledge regarding screening

Study (design)	Instrument used	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end, mean (SD)	*N*	Values at study start	Values at study end, mean (SD)	MD (95% CI); *p* value
Targeted invitation vs standard invitation material								
Quaife 2020 (RCT)	Objective knowledge score (maximum 9 points) [a]	388	n.r.	5.7 (2.3)	415	n.r.	5.5 (2.3)	Not significant

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Higher score represents better results.

Table 4.29: Information strategies/tools for informed decisions in lung cancer screening: results for knowledge regarding screening (RCTs/controlled studies)

Study (design)	Operationalisation	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end	*N*	Values at study start	Values at study end	MD (95% CI); *p* value
Decision aid vs no decision aid								
Lowenstein 2020 (non-RCT)	5-item knowledge questionnaire	30	n.r.	74.7% (19.6) [a]	51	n.r.	51.0% (20.5) [a]	$p < 0.01$
Volk 2020 (RCT)	9 items from LCS-12 knowledge measure	235 224 218	n.r.	57.5% (54.7–60.3) [b,c] 44.4% (41.9–47.0) [b,d] 49.9% (47.5–52.3) [b,e]	233 228 225	n.r.	40.1% (37.942.3) [b,c] 35.9% (33.7–38.1) [b,d] 40.0% (37.6–42.4) [b,e]	17.4% (13.9–21.0) [b,c] 8.5% (5.1–11.9) [b,d] 9.9% (6.5–13.3) [b,e] $p < 0.001$
Option grid vs web-based decision aid								
Sferra 2020 (RCT)	Knowledge retention questionnaire (14 questions)	n.r. [f]	n.r.	64.7% (n.r.) [a]	n.r. [f]	n.r.	62.4% (n.r.) [a]	n.r.; $p = 0.43$

Study (design)	Operationalisation	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end	*N*	Values at study start	Values at study end	MD (95% CI); *p* value
Information film + booklet vs booklet alone								
Ruparel 2019 (RCT)	10-point objective knowledge score [g]	120	5 [h]	8 [h] Δ = 2.16 (1.8) [i]; *p* < 0.001	109	5 [h]	7 [h] Δ = 1.84 (1.9) [i]; *p* < 0.001	0.62 (0.17–1.08); *p* = 0.007
	5-point subjective knowledge score [g]	120	4 [h]	5 [h] Δ = 0.92 (1.0) [i]; *p* < 0.001	109	4 [h]	5 [h] Δ = 0.55 (1.1) [i]; *p* < 0.001	0.32 (0.05–0.58); *p* = 0.02

Abbreviations: C=confidence interval; MD=mean difference; *N*=number of participants analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Percentage correct response: mean (SD).

[b] Percentage correct response: mean (95% CI).

[c] 1-week follow-up.

[d] 3-month follow-up.

[e] 6-month follow-up.

[f] No information on the number of participants analysed in each study group (87 participants in both study groups completed the questionnaire; 36.8%).

[g] Higher score represents better results.

[h] Median.

[i] Mean (SD).

Table 4.30: Information strategies/tools for informed decisions in lung cancer screening: results for knowledge regarding screening (uncontrolled PPI studies)

Study	Operationalisation	Intervention				Pre vs post intervention
		N	Values at study start, mean (SD)	Values at treatment end, mean (SD)		MD (95% CI); *p* value
Decision aid						
Hoffman 2018	LCS-12 knowledge measure (0–10) [a]	30	5.67 (n.r.)	9.6 (n.r.)		3.9 (2.9–5.0); $p < 0.001$
		30	47.3% [b]	80.3% [b]		n.r.
Lau 2015	Knowledge questionnaire (maximum 14 points) [a]	60	7.52 (1.89)	10.93 (2.19)		$p < 0.001$
Mazzone 2017	Knowledge questionnaire *Knowledge – Age range* *Knowledge – Smoking* *Knowledge – Benefit* *Knowledge – Harm*	155/122/113 [c]	 8.8% [b] 13.6% [b] 4.8% [b] 35.0% [b]	*Post intervention* 59.2% [b] 40.8% [b] 8.0% [b] 87.0% [b]	*1-mo follow-up* 21.4% [b] 35.5% [b] 3.2% [b] 70.0% [b]	n.r.
Reuland 2018	Knowledge questionnaire (0–9 points) [a]	50	2.6	5.5		2.8 (1.3–3.6); $p < 0.001$
Volk 2014	11-item LSC knowledge questionnaire	52	25.5% (20.7) [b]	74.8% (20.2) [b]		n.r.
Education class						
Sakoda 2019	Knowledge questionnaire [a] *Overall* *Knowledge – Smoking* *Knowledge – Benefit* *Knowledge – Harm*	269	n.r.	n.r.		 1.08 (2.26) [d]; $p < 0.0001$ 0.17 (0.42) [d]; $p < 0.0001$ 0.31 (1.33) [d]; $p = 0.0001$ 0.59 (1.31) [d]; $p < 0.0001$

Abbreviations: CI=confidence interval; LCS=lung cancer screening; MD=mean difference; N=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Higher score represents better results.

[b] Percentage of participants with correct answers.

[c] Number of participants analysed: pre-intervention/post-intervention/1-month follow-up.

[d] Standard deviation

4.4.7.2 Informed decision-making

For informed decision-making as an outcome, data from five studies investigating the effect of different information materials for individuals eligible for lung cancer screening were available. Two studies used the CollaboRATE shared decision-making score to evaluate whether the participants experienced perfect shared decision-making [312]. Two other studies used the Prepared for Decision Making scale and one study the Decision Making Capacity scale to evaluate whether the participants had all the information needed to make a screening decision.

One RCT (Volk 2020) and one observational study (Lowenstein 2020), both comparing the use of decision aids in the information process for lung cancer screening to standard information materials for cancer screening, reported significantly better shared-decision making scores for the decision aid group. In the Lowenstein 2020 study, the mean CollaboRATE score (max. 15 points) after implementation of a decision aid was 13.4 ± 1.9 points, compared to 11.7 ± 3.5 points before implementation (p = 0.01). In the Volk 2020 study, the mean score on the Prepared for Decision Making Scale was 79.4 (77.1–81.7) in the decision aid group, compared to 69.4 (66.4–72.4) in the standard materials group (mean difference 10.0, 95% CI 6.3–13.8; $p < 0.001$). A score ≥ 75 points indicates that participants are well prepared to make decisions. Using this cut point, 67.4% of the decision aid group were well prepared to make a screening decision, compared to 48.2% in the standard materials group.

One RCT (Sferra 2020) comparing different decision-making strategies (shared decision-making counselling using an option grid versus a web-based decision aid) showed no significant differences in CollaboRATE shared-decision making scores between the two interventions (97.4 vs 98.6 points).

In two single-arm studies, informed decision-making was only reported after the intervention. In both studies, approximately 80% of the participants felt clear about the risks and benefits of lung cancer screening.

Table 4.31 and Table 4.32 summarise the results for the studies included.

Conclusion on the quality of the evidence on informed decision-making

The use of decision aids in the lung cancer screening process probably strengthens informed decision-making among participants when compared to standard information materials. The conclusion is based on moderate-quality evidence. The quality of the evidence was downgraded by 1 level because of imprecision, as the results are based on two studies with a low number of participants. There may be little to no difference in informed decision-making between the two different types of decision aids. This conclusion is based on low-quality evidence. The quality of the evidence was downgraded by 2 levels because of high RoB and imprecision, as the results are based on one relatively small RCT.

We are uncertain whether the incorporation of education classes in the screening process strengthens informed decision-making among participants. This conclusion is based on evidence of very low quality due to very high RoB and imprecision, as the results are based on one study with a low number of participants.

Table 4.31: Information strategies/tools for informed decisions in lung cancer screening: results for informed decision-making (RCTs/controlled studies)

Study (study)	Instrument used (scale range)	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end, mean (SD)	*N*	Values at study start	Values at study end, mean (SD)	MD (95% CI); *p* value
Decision aid versus no decision aid								
Lowenstein 2020 (non-RCT)	CollaboRATE SDM score (3–15) [a]	30	n.r.	13.4 (1.9)	51	n.r.	11.7 (3.5)	$p = 0.01$
Volk 2020 (RCT)	Preparation for Decision Making Scale (0–100) [a]	227	n.r.	79.4 (77.1–81.7) [b]	224	n.r.	69.4 (66.4–72.4) [b]	10.0 (6.3–13.8); $p < 0.001$
Option grid vs web-based decision aid								
Sferra 2020 (RCT)	CollaboRATE SDM score (0–100) [a]	n.r. [c]	n.r.	97.4	n.r. [a]	n.r.	98.6	$p = 0.60$

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation; SDM=shared decision-making.

[a] Higher score represents better results.

[b] Mean score (95% CI).

[c] No information on the number of participants analysed in each study group (87 participants in both study groups completed the questionnaire; 36.8%).

Table 4.32: Information strategies/tools for informed decisions in lung cancer screening: results for informed decision-making (uncontrolled PPI studies)

Study	Instrument used (scale range)	Intervention			Pre vs post intervention
		N	Values at study start	Values at study end, mean (SD)	MD (95% CI); *p* value
Decision aid					
Hoffman 2018	Preparation for Decision Making Scale (0–100) [a]	30	n.r.	81.7 (21.3)	n.r.
Education class					
Sakoda 2019	Decision-Making Capacity (0–100) [a]	269	n.r.	78 [b]	n.r.

Abbreviations: CI=confidence interval; MD=mean difference; N=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Higher score represents better results.

[b] Percentage of participants having all the information needed.

4.4.7.3 Participant empowerment

For the participant empowerment outcome, data from one RCT (Quaife 2020) investigating the effect of different invitation strategies for lung cancer screening and eight studies investigation different information materials for individuals eligible for lung cancer screening were available. All studies used different versions of decisional conflict scales to evaluate the uncertainty of participants in choosing lung cancer screening.

In one RCT (Qualife 2020), comparing a targeted invitation strategy for lung cancer screening to the use of standard information material, no significant difference in Decisional Conflict Scale scores at the end of the study was reported between the two study groups.

One RCT (Volk 2020) comparing the use of decision aids in the information process for lung cancer screening to standard cancer screening information materials reported significantly lower scores for the Decisional Conflict Scale, indicating less decisional regret in the decision aid group than in the standard material group (informed subscale: 27.1 [95% CI 23.8–30.4] vs 42.1 [95% CI 38.1–46.0]; values clarity subscale: 17.6 [95% CI 14.2–21.0] vs 31.7 [95% CI 27–4-35.9]). For the informed subscale, 50.0% (117 of 234) of the participants in the decision aid group compared with 28.3% (66 of 233) of the participants in the standard education material group had low decisional conflict (OR 2.56, 95% CI 1.72–3.79; $p < 0.001$.) For the value clarity subscale, the corresponding proportions were 68.0% (159 of 234) and 47.4% (110 of 232) (OR 2.37, 95% CI 1.6–3.51; $p < 0.001$). In addition all single-arm studies investigating the use of decision aids reported low scores on the Decisional Conflict Scale after the intervention. One RCT (Sferra 2020) comparing different decision-making strategies (shared decision-making counselling using an option grid versus a web-based decision aid) showed significantly less regret regarding their decision to pursue screening among participants in group using option grids in direct shared-decision-making counselling compared to those using a web-based decision aid.

Besides decision aids, the use of educational material together with a value analysis instrument, evaluated in one single-arm study, also significantly lowered decisional regret about screening among participants eligible for screening.

One further RCT (Ruparel 2019), comparing an information film plus an information booklet on lung cancer screening to use of the information booklet alone, reported significantly higher decision certainty for the group receiving the film + booklet than in the booklet alone group. One observational study comparing in-person and telephone shared decision-making counselling reported low decisional conflicts in both study groups, with no between-group difference.

Table 4.33, Table 4.34 and Table 4.35 summarise the results for the studies.

Conclusion on the quality of the evidence on participant empowerment

A targeted invitation strategy for lung cancer screening may result in little to no differences regarding participant empowerment compared to the use of standard information materials. The conclusion is based on low quality of evidence. The quality of the evidence was downgraded by 2 levels because of imprecision, as the results are based on one small RCT.

The use of decision aids in the lung cancer screening process probably leads to greater participant empowerment when compared to standard information material. The conclusion is based on moderate-quality evidence. The quality of the evidence was downgraded by 1 level owing to imprecision, as the results are based on one RCT with a low number of participants. The use of an option grid compared to a web-based decision aid may improve participant empowerment regard-

ing decisions on participation in lung cancer screening. This conclusion is based on low-quality evidence. The quality of the evidence was downgraded by 2 levels because of high RoB and imprecision, as the results are based on a single RCT. In addition, the use of information films within the screening process may increase participant empowerment. This conclusion is based on low-quality evidence due to high RoB and imprecision, as the results are based on one RCT with a low number of participants. We are uncertain whether the delivery mode (telephone or in-person) for the shared decision-making counselling influences the magnitude of the improvement in participant empowerment. This conclusion is based on evidence of very low quality. The quality of the evidence was downgraded by 3 levels because of high RoB and imprecision, as the results are based on a single study with a low number of participants.

Table 4.33: Screening information/invitation interventions: results for participant empowerment (RCTs)

Study ' (design)	Instrument used (scale range)	Intervention			Comparator			Intervention vs. comparator
		N	Values at study start	Values at study end (% positive answers)	*N*	Values at study start	Values at study end (% positive answers)	MD (95% CI); *p* value
Targeted invitation vs standard invitation material								
Quaife 2020 (RCT)	Low-literacy Decisional Conflict Scale (0–100)	388	n.r.	≥ 83.2	415	n.r.	≥ 76.2	Not significant

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

Table 4.34: Information strategies/tools for informed decisions in lung cancer screening: results for participant empowerment (RCTs/controlled studies)

Study (design)	Instrument used (scale range)	Intervention			Comparator			Intervention vs comparator
		N	Values at study start, mean (SD)	Values at study end, mean (SD)	*N*	Values at study start, mean (SD)	Values at study end, mean (SD)	MD (95% CI); *p* value
Decision aid vs no decision aid								
Volk 2020 (RCT)	Decisional Conflict Scale (0–100) [b] *Informed subscale* *Values Clarity subscale*	 234 234	n.r.	 27.1 (23.8–30.4) [d] 17.6 (14.2–21.0) [d]	 233 232	n.r.	 42.1 (38.1–46.0) [d] 31.7 (27.4–35.9) [d]	 −14.9 (−20.1 to −9.7); $p < 0.001$ −14.1 (−19.5 to −8.7); $p < 0.001$
Option grid vs web-based decision aid								
Sferra 2020 (RCT)	Ottawa Decision Regret Scale (5–25) [b]	n.r. [c]	n.r.	6.0 (n.r.)	n.r. [c]	n.r.	10.2 (n.r.)	$p = 0.0198$
Information film + booklet vs booklet alone								
Ruparel 2019 (RCT)	Low-literacy Decisional Conflict Scale (maximum 9) [a]	120	n.r.	8.5 (1.25)	109	n.r.	8.24 (1.49)	$p = 0.007$ [e]
In-person SDM vs telephone SDM								
Tanner 2019 (non-RCT)	Ottawa Decision Support Framework (maximum 20) [b]	69	n.r.	11.3 (3.4)	68	n.r.	12.1 (3.4)	n.r.

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation; SDM=shared decision-making.

[a] Higher score represents better results.

[b] Lower score represents better results.

[c] No information on number of participants analysed in each study group (87 participants in both study groups completed the questionnaire; 36.8%).

[d] Mean score (95% CI).

[e] Multivariable analysis using multiple linear regression (which assumes that residuals, not the raw scores, are normally distributed) adjusted for baseline scores, age, educational level, ethnicity, Index of Multiple Deprivation score and smoking duration.

Table 4.35: Information strategies/tools for informed decisions in lung cancer screening: results for participant empowerment (uncontrolled PPI studies)

Study	Instrument used (scale range)	Intervention			Pre vs post intervention
		N	Values at study start, mean (SD)	Values at study end, mean (SD)	MD (95% CI); *p* value
Decision aid					
Hoffman 2018	Decisional Conflict Scale (0–100) [a] *Informed subscale* *Values Clarity subscale*	30	n.r.	 8.7 (1.6) 3.9 (10.4)	n.r.
Lau 2015	Decisional Conflict Scale (0–100) [a] *Overall* *Informed subscale* *Values Clarity subscale* *Uncertainty subscale* *Support subscale*	60	 46.33 (29.69) 62.22 (39.28) 48.33 (41.65) 55.0 (40.07) 23.33 (21.74)	 15.08 (25.78) 16.94 (30.91) 16.25 (34.08) 18.33 (34.71) 10.28 (21.50)	n.r.
Volk 2014	Decisional Conflict Scale (0–100) [a] *Values Clarity subscale*	52	n.r.	 7.84 (23.18)	n.r.
Education intervention					
Studts 2020	Low-literacy Decisional Conflict Scale (0–100) [a] *Overall* *Informed subscale* *Values Clarity subscale* *Uncertainty subscale* *Support subscale*	209	 47.61 (27.24) 52.21 (30.54) 49.04 (35.08) 53.23 (37.72) 35.45 (28.80)	 18.31 (22.15) 16.89 (24.49) 17.22 (28.31) 25.48 (33.79) 16.67 (23.23)	 29.30; $p < 0.0001$ 35.32; $p < 0.0001$ 31.82; $p < 0.0001$ 27.75; $p < 0.0001$ 18.78; $p < 0.0001$

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Higher score represents better results.

4.4.7.4 Participant satisfaction

For the participant satisfaction outcome, data from one RCT investigating the effect of different invitation strategies for lung cancer screening and two observational studies investigating different information materials for individuals eligible for lung cancer screening were available. Two studies evaluated the satisfaction of the participants with their decision regarding lung cancer screening, and one study evaluated participants' satisfaction with the shared decision-making visit.

In one RCT (Quaife 2020) comparing a targeted invitation strategy for lung cancer screening to the use of standard information material, nearly all participants in both study groups (98%–99%) were satisfied with their decision regarding screening participation, with no significant difference between the groups.

One observational study comparing in-person and telephone shared decision-making counselling reported no differences in participants´ satisfaction with the visit between the study groups.

Table 4.36 and Table 4.37 summarise the results for the studies included.

Conclusion on the quality of the evidence on participant satisfaction

A targeted invitation strategy for lung cancer screening may result in little to no differences regarding satisfaction of the participants with their decision regarding screening participation compared to the use of standard information material. The conclusion is based on low quality of evidence. The quality of the evidence was downgraded by 2 levels because of imprecision, as the results are based on one small RCT.

We are uncertain whether the use of decision aids in a lung cancer screening programme improves the satisfaction of the participants with their decision regarding screening participation when compared to standard information materials. The conclusion is based on evidence of very low quality. The quality of the evidence was downgraded by 3 levels owing to very high RoB and imprecision, as the results are based on one observational study with a very low number of participants. We are also uncertain whether the delivery mode for shared decision-making counselling (in-person or telephone) influences participant satisfaction. This conclusion is based on evidence of very low quality. The quality of the evidence was downgraded by 3 levels owing to very high RoB and imprecision, as the results are based on one observational study with a very low number of participants.

Overall, evidence regarding participant satisfaction is very weak for all the interventions investigated (information/invitation strategies, use of decision aids or delivery mode for shared decision making counselling).

Table 4.36: Screening information/invitation interventions: results for participant satisfaction (RCTs)

Study (design)	Instrument used (scale range)	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end (% positive answers)	*N*	Values at study start	Values at study end (% positive answers)	MD (95% CI) (*p* value)
Targeted invitation vs standard invitation material								
Quaife 2020 (RCT)	Decisional satisfaction (0–100) [a]	388	n.r.	≥ 98.7	415	n.r.	≥ 97.3	Not significant

Abbreviations: CI=confidence interval; MD=mean difference; N=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation.

[a] Higher score represents better results.

Table 4.37: Information strategies/tools for informed decisions in lung cancer screening: results for participant satisfaction (controlled studies)

Study (design)	Instrument used (scale range)	Intervention			Comparator			Intervention vs comparator
		N	Values at study start	Values at study end, mean (SD)	*N*	Values at study start	Values at study end, mean (SD)	MD (95% CI) (*p* value)
Decision aid vs no decision aid								
Lowenstein 2020 (non-RCT)	Satisfaction with visit score (1–5) [a]	30	–	4.8 (0.8)	51	–	4.7 (0.6)	*p* = 0.61
In-person SDM vs telephone SDM								
Tanner 2019 (non-RCT)	Decisional satisfaction score (maximum 30) [a]	69	–	26.7 (2.8)	68	–	24.6 (5.6)	n.r.

Abbreviations: CI=confidence interval; MD=mean difference; *N*=number of patients analysed; n.r.=not reported; RCT=randomised controlled trial; SD=standard deviation; SDM=shared decision-making.

[a] Higher score represents better results.

4.4.7.5 Screening participation rate

For the outcome screening participation rate, data from one observational study investigating the effect of an information leaflet for lung cancer screening, two RCTs investigating different invitation strategies for lung cancer screening and five studies investigation different information materials for people eligible for lung cancer screening were available.

In all the controlled studies (RCTs: Quaife 2020, Ruparel 2019, Sharma 2018 and Volk 2020; observational studies: Tanner 2019 and Yoshida 2012), no differences in the participation rates for lung cancer screening were reported between the study groups with different invitation or information strategies. A single-arm PPI study also showed no change in the intention to undergo screening after the use of decision aids compared to pre-intervention.

Table 4.38, Table 4.39 and Table 4.40 summarise the results for the studies included.

Conclusion on the quality of the evidence on the screening participation rate

A targeted invitation strategy for lung cancer screening may have little to no influence on the lung cancer screening participation rate when compared to the use of standard information materials. The conclusion is based on low-quality evidence. The quality of the evidence was downgraded by two levels because of imprecision as the results are based on one small RCT. We are uncertain whether distribution of an information leaflet on lung cancer screening influences the participation rate in lung cancer screening. The conclusion is based on evidence of very low quality. The quality of the evidence was rated as very low because of the indirectness of the study results (study conducted in Japan) and imprecision, as the results are based on one small observational study with high RoB. We are also uncertain as to whether a telephone consultation in addition to an information brochure as part of the screening invitation strategy increases the screening participation rate when compared to a brochure alone. The conclusion is based on evidence of very low quality. The quality of the evidence was downgraded by three levels because of high RoB and imprecision, as the results are based on one small RCT.

The use of decision aids in the lung cancer screening process probably has no influence on the participation rate. The conclusion is based on moderate-quality evidence. The quality of the evidence was downgraded by one level because of imprecision, as the results are based on one RCT with a low number of participants. We are uncertain whether the delivery mode for shared decision-making counselling (in-person or telephone) influences the participation rate. This conclusion is based on evidence of very low quality. The quality of the evidence was downgraded by three levels because of very high RoB and imprecision, as the results are based on one observational study with a very low number of participants.

The use of information films in addition to an information booklet in the screening process may result in little to no difference in the participation rate in lung cancer screening when compared to use of an information booklet alone. This conclusion is based on low-quality evidence due to high RoB and imprecision, as the results are based on an RCT with a low number of participants.

Table 4.38: Screening information/invitation interventions: results for the screening participation rate (RCTs/controlled studies)

Study (study design)	Operationalisation	Intervention		Comparator		Intervention vs comparator
		N	*n* (%)	*N*	*n* (%)	Odds ratio (95% CI)
Targeted invitation vs standard invitation material						
Quaife 2020 (RCT)	Uptake of LDCT scan	416 [a]	386 (92.8)	429 [a]	384 (89.7)	1.47 (0.91–2.40); *p* = 0.177 [b]
Telephone counselling + brochure vs brochure alone						
Sharma 2018 (RCT)	Decision to speak to physician about getting LDCT scan	213	n.r.	218	n.r.	1.10 (0.70–1.72); *p* = n.r.
Information leaflet vs no leaflet						
Yoshida 2012 (non-RCT)	Undergone lung cancer screening in 2011	240	Screened: 93 (38.8) Plan to be screened: 27 (11.3)	244	Screened: 92 (37.7) Plan to be screened: 28 (11.5)	n.r.

Abbreviations: CI=confidence interval; LDCT=low-dose computed tomography; *N*=number of patients analysed; *n*=number of patients with at least one event; n.r.=not reported; RCT=randomised controlled trial.

[a] Participants eligible for LDCT screening.

[b] Unadjusted odds ratio.

Table 4.39: Information strategies/tools for informed decision-making in lung cancer screening: results for the screening participation rate (RCTs/controlled studies)

Study (study design)	Operationalisation	Intervention		Comparator		Intervention vs comparator
		N	*n* (%)	*N*	*n* (%)	Odds ratio (95% CI)
Decision aid vs no decision aid						
Volk 2020 (RCT)	Lung cancer screening (6-month follow-up)	67	57 (85.1)	85	68 (80.0)	1.27 (0.52–3.11); *p* = 0.60
	Scheduled CT for lung cancer screening (6-month follow-up)	237	70 (29.5)	238	89 (37.4)	0.70 (0.47–1.03); *p* = 0.07
	Intent to be screened within 1 year (1-week assessment)	233	165 (70.8)	232	151 (65.1)	1.25 (0.83–1.89); *p* = 0.29
Information film + booklet vs booklet alone						
Ruparel 2019 (RCT)	LDCT completion rate	120	n.r. (76.7)	109	n.r. (78.9)	*p* = 0.66
In-person SDM vs telephone SDM						
Tanner 2019 (non-RCT)	LDCT participation rate	69	61 (88.4)	68	60 (88.2)	*p* = 0.98

Abbreviations: CI=confidence interval CT=computed tomography; LDCT=low-dose CT; *N*=number of patients analysed; *n*=number of patients with at least one event; n.r.=not reported; RCT=randomised controlled trial; SDM=shared decision-making.

Table 4.40: Information strategies/tools for informed decision-making in lung cancer screening: results for the screening participation rate (uncontrolled PPI studies)

Study reference	Operationalisation	Intervention				Pre vs post intervention
		Start of study		End of treatment		Odds ratio (95% CI)
		N	*n* (%)	*N*	*n* (%)	
Decision aid						
Hoffman 2018	Intent to be screened within 1 year (1-week assessment)	30	n.r.	30	19 (63.3)	n.r.
Reuland 2018	Intent to be screened	50	27 (54)	50	25 (50)	0.73 (0.54–0.98); *p* = 0.03

Abbreviations: CI=confidence interval; *N*=number of patients analysed; *n*=number of patients with at least one event; n.r.=not reported.

4.4.8 Subgroup analyses

No subgroup analyses were planned or performed for this research question.

4.4.9 Summary

Only a few RCTs or observational studies are available that evaluated the effectiveness of different information or invitation strategies to raise awareness for lung cancer screening programmes and to strengthen the decision made by men and women eligible for screening for or against screening participation. Between the different invitation strategies for lung cancer screening there was no clear difference in the increase in knowledge about lung cancer screening among the participants or in participant satisfaction. Overall, the current evidence is not sufficient to assess the effectiveness of a particular information strategy for lung cancer screening.

However, there are some RCTs and observational studies that investigated the effect of shared decision-making counselling and the use of decision aids as part of the lung cancer screening process. Compared to standard information materials, the use of decision aids resulted in an increase in knowledge among participants about lung cancer screening and higher decisional certainty regarding screening participation. The type of decision aid or mode of delivery for shared decision-making counselling seems to have no significant effect on the outcomes, but the current evidence is limited.

5 DISCUSSION

5.1 This report in comparison to other SRs and guidelines

The focused information retrieval process identified the SR by Snowsill et al. [2] from 2018 that was evaluated as up-to-date and of high quality. The results are only partly consistent with the findings of this report. Deviations can be attributed, among other things, to the inclusion of more recent publications with longer observation periods (e.g., NELSON) compared to the studies already known from Snowsill et al. and to methodological differences. For example, Snowsill et al. found it likely that chest X-ray screening is the standard of care for early detection of lung cancer. Consequently, the results of the NLST study were incorporated into the main analyses of that SR. In contrast to Snowsill et al., in the present report we did not consider screening via X-rays to be equivalent to the usual standard care. Accordingly, the studies with chest X-ray screening as a control intervention were not included in the main analysis, but rather in a sensitivity analysis.

No statistically significant effect could be shown by Snowsill 2018 et al. with regard to overall mortality and lung cancer mortality. Data were pooled from four studies that reported an observation period of at least 5 years (DANTE, DLCST, MILD and NLST). The results from subgroup analyses for studies exclusively comparing LDCT screening versus no screening also showed no statistically significant effects. For HRQoL and the psychosocial consequences of screening, the authors concluded on the basis of four studies (NELSON, NLST, DLCST and UKLS) that the results were not very meaningful because of a lack of statistical significance (NELSON and NLST) or questionable clinical relevance (DLCST and UKLS). Where there were statistically significant differences, these occurred in favour of lung cancer screening rather than no screening at all. For the present report, we did not consider the data for this outcome to be usable for various reasons (Section 4.1.9). With regard to overdiagnosis, Snowsill et al. point to limited data availability and cite the results from the NLST study, which reported an overdiagnosis rate of 18.5% (95% CI 5.4–30.6) among individuals with a lung cancer diagnosis after an observation period of 6.5 years. In the present report, data from five studies (DLCST, ITALUNG, LUSI, NELSON and NLST) on estimation of the overdiagnosis risk per positive finding for an observation period of at least 8.5 years show a strongly divergent proportion of 0%–63%, which can probably be attributed to study-specific differences, such as the use of different CT devices (Section 4.1.7). With respect to adverse events, Snowsill et al. reported data from two studies with results for both the intervention group and the control group (DANTE and NLST). According to the authors of the SR, the higher proportion of significant complications in the intervention group was remarkable. In the present report, on the basis of the DANTE study, an effect to the disadvantage of screening was also shown for adverse events. The data on adverse events from the NLST study have not been taken into account for the present report as it is doubted that chest X-ray screening is an adequate comparator to investigate the effect of LDCT screening compared to no screening for the occurrence of adverse events. Snowsill et al. concluded that LDCT screening has a positive effect — with considerable uncertainties — regarding the reduction in mortality. They also considered harm due to overdiagnosis.

In 2014, the USPSTF issued a recommendation for national lung cancer screening using LDCT [313]. The previous recommendation was based on level B evidence, that is, the USPSTF concluded with moderate certainty that annual LDCT screening provides a substantial benefit to active or former smokers (minimum 30 pack-years, maximum 15 years of smoking cessation) aged 55–80 years. Taking into account more recent study data, the assessment was updated and a draft statement of recommendations was published for comment in July 2020 [314]. To assess LDCT screening with respect to mortality, the authors identified results from a total of seven RCTs (NLST, DANTE, DLCST, ITALUNG, LSS, LUSI and NELSON) for the current report. The study quality of MILD was rated as poor by the authors, which is why this study was not included in the USPSTF

assessment. All other RCTs were identical to those in the present EUnetHTA report. In contrast to the present report, no meta-analyses were conducted on the grounds that there was considerable clinical and methodological heterogeneity. The fact that the studies included differ in design was taken into account in the present assessment by conducting meta-analyses on the basis of a random-effects model. Studies that compared LDCT with chest X-ray screening were only used for sensitivity analyses. The USPSTF authors base their conclusions primarily on mortality data from the two largest studies, NLST and NELSON. They concluded that LDCT screening of high-risk individual "can reduce lung cancer mortality and may reduce all-cause mortality". The USPSTF report and the present benefit assessment agree that there were no usable data on HRQoL. However, the authors reported results on the psychosocial consequences of screening in a separate chapter. For this evaluation, not only RCTs but also cohort studies and study results without data for the control group were used. Prospective cohort studies or case–control studies were also considered suitable for assessing the harm caused by screening due to radiation exposure, overdiagnosis or false-positive findings. Estimations of radiation-induced cancer are based on results from modelling studies. Information on overdiagnosis was taken from the studies, so no uniform calculation method was used. The authors report a range for overdiagnosis from 0% to 67% in relation to individuals diagnosed with lung cancer during the screening phase. For the consequences of false-positive screening results, the USPSTF assessment reported the proportion of screened participants who underwent a needle biopsy for false-positive findings (0.09%–0.56%), the proportion of complications resulting from this (0.03%–0.07%) and the proportion of surgical procedures for false positives (0.5 to 1.3%). (In the case of surgical resections the proportion is 0.1%–0.5%). These results are within the range of values in the present assessment. The USPSTF estimated the potential benefits of a screening programme on the basis of a modelling study in which the best benefit-to-harm ratio was weighed using varying inclusion criteria [315]. Annual risk-factor–based screening strategies with a minimum criterion of 20 pack-years from the age of 50 or 55 years until the age of 80 years were shown to be most effective and resulted in more lung cancer deaths prevented and more life years gained with limited additional harm compared to the strategy recommended in 2013. The USPSTF has adapted its screening recommendation accordingly [316].

The 2020 white paper by the ESR and ERS [263] describes the current evidence on LDCT screening, including the screening activities of individual European countries, based on a narrative, non-systematic literature review. The authors emphasise the importance of the participants, especially as partners in the decision-making process in screening. Furthermore, the authors discuss current standards regarding risk prediction models, smoking cessation programmes, diagnostic algorithms, LDCT examinations (maximum effective dose, computer-assisted and other supportive procedures), avoidance of overdiagnosis and harm, and how to deal with additional non-lung cancer–specific findings and biomarker tests. Finally, the authors outline an action plan for the introduction of organised LDCT screening at European, national and local levels, in which lung specialists and radiologists play key roles. Risk prevention models should serve not only to determine the duration and intensity of screening but also to efficiently identify screening participants. Organised treatment pathways for early diagnosis are recommended to reduce mortality. At European level, for example, a European Council recommendation or guideline on population-based screening programmes in all EU countries is being sought, including the definition of minimum standards by a core ERS and ESR team. At national level, in addition to the establishment of a national expert group involving patient representatives, standard operating procedures and quality assurance measurements including benefit/harm analyses are recommended. At local level, a multidisciplinary group of experts (including patient representatives) should also be set up and appointed, and local infrastructure and pathways should be defined. Quality assurance registers are to be set up at all levels and pooled at European level.

5.2 Publication bias

For this assessment, the results from eight studies involving more than 90,000 participants could be used. However, the results from three other studies were missing. For two studies (Depiscan 2007 [285] and Garg 2002 [286]), publication was incomplete. In these cases, only baseline results could be identified. Both studies are characterised by a low number of cases at 400 [286] and 1,000 [285] participants. Another study without published results is a completed so-called pilot study with 2000 participants to investigate the feasibility, compliance and costs of a large RCT [304]. However, the information available does not indicate a publication bias.

5.3 Consistency of the mortality effect of screening

The overall benefit of LDCT screening critically hinges on proof of a mortality benefit. Because only a small proportion of deaths in a screening trial are caused by the cancer for which screening is carried out, the statistical power of a screening trial for detection of a difference in all-cause mortality is very low [317, 318]. Cancer-specific mortality, by contrast, allows easier detection of a screening effect but may also introduce bias through uncertainties in determining the exact cause of death [317, 319]. The controversy between researchers who prefer all-cause mortality as the primary decisional criterion and those who also accept cancer-specific mortality is unresolved [320-322]. In the present report, therefore, a balanced approach based on both endpoints was chosen. The fact that the effect on overall mortality was not significant is well reflected in the summary conmclusion for the mortality outcome. Still, it is justified to assume that a mortality benefit exists, because overall mortality also showed a (nonsignificant) reduction of similar magnitude to the effect on cancer-specific mortality. In summary, the certainty of a mortality benefit is neither moderate nor very low, but low.

When examining the mortality effects in the primary studies, these considerations are even more important, because some studies failed to show this similarity in mortality endpoints. In the NELSON study [54], a cause-of-death statistic was reported for the male participants. There were 6 percentage points fewer lung cancer deaths in the screening group than in the control group (160 [18.4%] versus 210 [24.4%]). In addition, more people died in the screening group than in the control group (868 [13.2%] versus 860 [13.0%]), with cancer mortality (excluding lung cancer) in the screening group 3 percentage points higher than in the comparison group (318 [36.6%] versus 289 [33.6%]). It is not clear from the publication [54] how these data fit together. To explain these results, further analyses and information are required, such as a time-to-event analysis. It can currently only be speculated whether the higher proportion of fatal cancers in the intervention group is the result of a systematic error (e.g., misclassification of unknown causes) or, for example, competing risks.

On the contrary, ITALUNG data raise the question of whether LDCT screening might improve mortality beyond the direct effect on lung cancer mortality. In ITALUNG, after a median follow-up period of 11.3 years, a statistically significant difference was found in favour of screening with regard to overall mortality, but not lung cancer mortality. In addition, cardiovascular diseases were a significantly less frequent cause of death in the screened group. The authors speculated that passing on information about the presence of coronary artery calcification to the family doctor in charge could be a “teachable moment” for those affected to become aware of their own risk and to lead a healthier lifestyle. However, the authors suggested that allocation to the screening group may have also led to a healthier lifestyle, which could also explain the reduction in cardiovascular mortality in the screening group [39].

5.4 Non-usable data on HRQoL

Data on HRQoL were reported in four studies comparing LDCT screening to no screening. These data were not used for various reasons.

Although the NELSON study reported extensive data on HRQoL, their incompleteness critically undermines their validity. Data were mainly only reported for the intervention group; when data were also collected in the control group, the completeness of follow-up grossly differed between the groups. As between-group differences of > 15% in follow-up lead to substantial RoB [323], these results were not acceptable for the present report.

The data on psychosocial consequences of lung cancer screening reported in the DLCST study are not usable for the benefit assessment as the questionnaire used in the study was designed to assess psychosocial consequences of false-positive findings. In the present publication, however, it was only examined how participants assess their assignment to the intervention or comparison group. These data were not collected with an appropriately validated instrument and do not answer the question posed in this report.

In the UKLS study, as in DLCST, the influence of assignment to the intervention or control group was examined on the one hand, and the influence of the screening result in the intervention group on psychosocial stress on the other hand. Neither of these is relevant for the benefit assessment.

The data on HRQoL from the NLST study were not considered for this report because it is doubtful that X-ray chest screening is an adequate comparator to investigate the corresponding effect of LDCT screening compared to no screening.

5.5 Non-consideration of diagnostic workup, treatment and stage-shifting as outcomes

The type and number of interventions that follow as a direct result of screening were not considered as an outcome. The differing frequency and intensity of diagnostic and therapeutic interventions in the two study groups cannot be interpreted in terms of benefit and harm to the participants. The aim of lung cancer screening is an earlier diagnosis. The associated earlier treatment leads to a change in treatment due to the stage shift. The group differences or unequal treatment are therefore a direct consequence of an intentional earlier diagnosis of lung cancer. As the corresponding data are mostly missing for the control group, numerous assumptions regarding the frequency and intensity of the intervention in the control group would be necessary, so the possibility of interpreting these data is questionable. Furthermore, it is difficult to differentiate between purely diagnostic and purely therapeutic procedures in the study results. It is believed that detection of lung cancer at an earlier stage improves the survival rate. This assumption is supported by corresponding results for mortality. The stage shift in itself is therefore not a patient-relevant outcome. The benefit of the different interventions (i.e., the screening) must ultimately be reflected in the mortality outcome. Harm can be depicted in the form of overdiagnosis (due to subsequent diagnostics and therapy and the resulting complications) and adverse events resulting from diagnostic workup and therapy in a comparison of the groups. The consequences of false-positive findings are an exception. Here, invasive follow-up interventions for the clarification of ultimately benign findings were considered as an outcome, since they are dispensable, potentially complication-prone interventions that are likely to occur only to a small extent in the group without screening. Other studies have concluded that 14%–34% of all invasive procedures result in benign findings and therefore these procedures would not have been necessary without screening [306].

5.6 Definition of false-positive screening results

For the assessment of harm, the consequences of false-positive screening results were considered. Only findings that were suspicious in the screening CT and for which the suspicion of lung cancer was not confirmed by subsequent invasive diagnostic investigation (e.g., biopsy) were considered. This is the clarification of a positive finding with the aim of histological or cytological confirmation of the diagnosis within the scope of (1) bronchoscopic or endobronchial biopsies, (2) transthoracic biopsies (e.g., ultrasound- or CT-guided punctures) or (3) surgical procedures (thoracoscopy, thoracotomy, mediastinoscopy or VATS). Thus, the findings for screening participants who, after an initial abnormal CT finding, were examined solely via imaging diagnostics such as another CT scan after a few months do not fall under this definition.

5.7 Adverse events as a result of treatment

For the assessment, usable data on adverse events were only available for one of the six studies using no screening as the comparator, namely the DANTE study. The aim of screening is to detect lung cancer as early as possible so that it is still operable. Owing to the higher rate of surgeries in the intervention group, the risk of suffering an adverse event as a result of surgery also increases. The corresponding results from the DANTE study are therefore plausible. However, the study did not carry out a complete survey of all adverse events, and only reported the adverse events that occurred after surgery for a suspicious finding. Thus, adverse events resulting from other forms of treatment such as chemotherapy are not covered. Moreover, the occurrence of adverse events in the screening group and in the control group is not directly comparable. Thus, it is likely that if the time of diagnosis is brought forward in the screening group, adverse events will occur significantly earlier than in the control group as a result of earlier treatment. Owing to the different forms of treatment for different stages of cancer, it can also be expected that the adverse events in the intervention and control group differed in their severity. However, the studies do not provide sufficient data to be able to make a statement in this regard. The data presented therefore provide only a very small section of the dynamics of time, type and severity of adverse events that can occur when comparing screened and non-screened groups. Moreover, such results are only available from one of six studies. Owing to the data availability, the results on adverse events are therefore of little significance when weighing up the benefits and harms of screening.

5.8 Range for estimating overdiagnosis

The risk of overdiagnosis for individuals who were diagnosed with lung cancer during the screening phase showed a wide range (from 0% to 63%) among trials. While no overdiagnosis was found in the ITALUNG study, DLCST showed the highest values. The inclusion and exclusion criteria for both studies as well as the study designs are largely consistent. Both studies were started in 2004, but the ITALUNG study also used older CT equipment (single-slice scanners), while the DLCST study only used multislice CT devices(16-slice scanners). In the LUSI and NELSON studies, in which the risk of overdiagnosis was 29% and 16%, respectively, newer CT equipment was also used. In the NLST study (with chest X-ray screening as the comparator) the risk of overdiagnosis was relatively low at 2.8%. In this study, as in ITALUNG, mainly older CT equipment was used.

The screening strategies in the ITALUNG and DLCST studies are comparable with regard to the cut-off for the diameter of a pulmonary nodule so that it is classified as a positive finding when it first occurs (≥ 5 mm in diameter). In contrast to the ITALUNG study, in the DLCST study a com-

puter-based volume calculation is carried out, so that in a follow-up CT the increase in volume for a pulmonary nodule can be determined and an evaluation of the malignancy can be made based on the change in volume. In the LUSI and NELSON studies, such a computer-based evaluation was also used to classify a pulmonary nodule. One possible explanation would be that the use of modern CT equipment and computer-based determination of the growth rate of a pulmonary nodule can lead to more true-positive findings and thus to more overdiagnosis.

The risk of overdiagnosis in relation to all participants invited to the screening showed a range of 0 to 2.2% between trials. These figures do not show any interrelationship between the risk of overdiagnosis and screening strategies.

5.9 Harm from radiation exposure

As exposure to the ionising radiation of CT scanning increases the risk of developing other cancers, it is important to estimate the cumulative radiation exposure associated with LDCT screening for lung cancer. According to Rampinelli et al. [324], the median cumulative radiation exposure from annual LDCT screening over 10 years is approximately 9 mSv for men and 13 mSv for women. By combining these exposure data with standard risk models, the lifetime attributable risk of major cancers can be estimated to be in the range from 0.3 to 0.8 major cancers per 1,000 participants [324]. Compared to men, women have a clearly higher risk, first because CT scanning requires approximately 40% higher radiation dosages in females than in males [325] and second because women are more radiosensitive than men. Although the radiation risks associated with CT screening are non-negligible and highly variable, there is general consensus that these risks are acceptable [324] because more cancer deaths are avoided than caused by CT screening in a high-risk population.

5.10 Consideration of studies on LDCT screening versus chest X-ray screening for the overdiagnosis outcome

Under the assumption that chest X-ray screening is transferable to a control group without screening for detection of lung cancer, the LSS and NLST studies were also considered suitable for estimating overdiagnosis due to LDCT screening. Patz et al. [120] were able to show on the basis of a model that the proportion of overdiagnoses in LDCT screening was higher in comparison to no screening than in comparison to chest X-ray screening. Thus, in the LSS and NLST studies the proportion of overdiagnoses for LDCT screening could be underestimated, but the values for the proportion of overdiagnoses in relation to individuals invited to screening, at 1.2% and 0.1% for the LSS and NLST studies, respectively, are in the range of values for studies with no screening as the comparator (0%–2.2%).

5.11 Participants with risk factors for lung cancer other than tobacco smoking

In addition to tobacco smoking, which is considered the main risk factor for lung cancer and is responsible for 80%–90% of lung cancers, further factors increase the risk of lung cancer. According to current guidelines, these include a personal history of cancer or lung disease, family history of lung cancer, radon exposure and occupational exposure to carcinogens [210, 236, 247].

Current guidelines recommend regular screening for lung cancer primarily for active smokers or ex-smokers with high tobacco consumption. Screening is recommended for smokers and ex-smokers with lower tobacco consumption if an additional risk factor for lung cancer is also present. For non-smokers with one of the additional risk factors, there is currently no recommendation for lung cancer screening [210, 236, 247].

For this rapid assessment, only RCTs that investigated screening for lung cancer in current or former smokers could be identified. In one of the RCTs included (DLCST), results for lung cancer mortality for the subgroup of smokers with COPD at baseline were also examined. The subgroup analysis showed no effect modification by the presence of COPD as an additional risk factor for lung cancer. In another RCT (NLST), the proportion of individuals with asbestos work experience was 4.6% in the LDCT arm and 4.8% in the chest X-ray arm, but no separate results were available for these subgroups. Data on other risk factors in addition to tobacco smoke or from studies screening for lung cancer in individuals with one or more risk factors other than tobacco smoking were not available.

In addition, a recent SR of lung cancer screening by LDCT (Snowsill 2018 [2]) only has results for individuals with current or previous tobacco smoking as a risk factor. One of the studies included in this SR examined individuals with COPD as an additional risk factor (Garg 2002 [286]), but that was a feasibility study and no results for patient-relevant outcomes were reported. Another recent SR on lung cancer screening (Huang 2019 [326]) included a Chinese RCT with 6657 participants that investigated screening every 2 years in a mixed population with at least one risk factor for lung cancer [327]. The study presented results after only 2 years of follow-up (first screening round), which is probably too short to show any relevant effect. Nevertheless, no statistically significant difference in lung cancer-specific mortality was found between the study group with screening and the group without screening. Other reportable endpoints were not investigated in this RCT. The proportion of current or former smokers was approximately 28% and only 7.1% of the study participants met the NLST criteria for lung cancer screening. The most common risk factor in this study was long-term exposure to cooking-oil fumes (~60%), which is of high importance in Asia but of secondary importance in Europe. As long-term exposure to cooking-oil fumes is not listed as a risk factor for lung cancer in the current European or US guidelines and therefore does not meet the inclusion criteria for this rapid report for the relevant population, this RCT was not further considered. A review (Maisonneuve 2019 [328]) that examined LDCT screening in individuals exposed to asbestos at work and included 16 observational studies also concluded that LDCT screening might be effective for early detection of lung cancer in asbestos-exposed smokers, but screening of asbestos-exposed individuals with no additional risk factors for cancer is not viable because of the low detection rate.

There is currently no direct evidence from RCTs of lung cancer screening in individuals with risk factors for lung cancer other than tobacco smoking. The transferability of the results for screening for lung cancer in current or former smokers to individuals with other risk factors for lung cancer is unclear. The risk of developing lung cancer is estimated to be 11 times higher for smokers than for nonsmokers. The risk is assumed to be approximately two times higher for individuals with COPD, two to three times higher for those with a family history of lung cancer and approximately 1.5 times higher for individuals exposed to carcinogenic substances such as asbestos, chromium, diesel oil fumes and coal dust or soot. However no reliable statement can be made on the transferability of the results to other risk groups because of (possible) differences not only in lung cancer risk but also disease course, the diagnostic accuracy of screening or diagnostic tests, and treatment effectiveness.

5.12 Biomarkers for lung cancer screening

No studies that investigated a multimodal lung cancer screening strategy with LDCT and additional biomarkers compared to a screening strategy using LDCT alone could be identified. Furthermore, no corresponding ongoing studies could be found in the search of study registries. However, such RCTs are necessary to assess any possible additional benefit of the adjuvant use of biomarkers in the context of lung cancer screening.

A recent review (Seijo 2018 [271]) described two different applications of biomarkers in this context: (1) as an additional diagnostic tool to better assess the lung cancer risk of an individual before LDCT and thus to make a decision for or against LDCT; and (2) as an additional test after a positive LDCT finding to assess the malignancy and to take further appropriate measures. Overall, the use of biomarkers is expected to improve the accuracy of screening for lung cancer and to reduce false-positive results and associated unnecessary further diagnostic measures. According to the review, results for different biomarkers from several validation studies and from individual clinical studies have been published.

Multimodal screening using a biomarker panel was investigated in the ITALUNG study [29]. Blood samples from 517 study participants in the LDCT screening arm with screening-detected lung cancer and a random selection of subjects without a lung cancer diagnosis were subjected to biomarker measurement. In a post hoc analysis, multimodal screening with biomarker measurement and LDCT showed higher specificity of 90% compared to 74% with LDCT screening alone. One SR included three further studies on biomarkers for lung cancer screening (Chu 2018 [329]), two of which investigated the use of biomarkers alone. Only one study investigated the test properties of combined screening using biomarkers and LDCT compared to LDCT alone. Again, the combined screening showed an improvement in test accuracy. Overall, we conclude that biomarkers may be a promising complement to LDCT in lung cancer screening, but that the current evidence is insufficient to justify the use of biomarkers in clinical practice.

5.13 Lung cancer screening strategies

In terms of organisational variations in screening with and without invitation, approaches in the studies included could not be assigned to any clear categories. In some studies (e.g. NELSON, LUSI) a sample was identified through population registries and questionnaires on smoking history were then sent out. The recruitment in other studies (e.g., MILD and DLCST) was based on public announcements or campaigns to attract candidates to the screening programme. As a third option, potentially eligible individuals were identified and invited by general practitioners (e.g., ITALUNG). Different recruitment strategies were also combined in some trials. Therefore, no subgroup analyses was performed for the invitation/no invitation characteristic because the studies could not be assigned to appropriate categories. However, with regard to screening interval, the RCTs included were largely comparable as they mostly used annual screening. One study (MILD) had two intervention arms with 1- and 2-year screening, respectively, while in another RCT (NELSON) the screening interval was extended from 1 year to 2 years and then to 2.5 years during the screening rounds. With the publication of the MILD study results separated by screening interval (annual or biennial), data were available for a subgroup analysis for this characteristic. No statistically significant interaction could be shown. In addition, biennial as compared to annual LDCT screening resulted in similar overall mortality and similar lung cancer mortality. Taking into account the very low quality of the available evidence, the evidence is very uncertain about the effect of biennial compared to annual LDCT screening on mortality.

A regular discussion point is that a narrower screening interval would be appropriate for tumours with a rapid growth rate, as this could lead to more tumours being less advanced at the time of their discovery. This in turn could theoretically lead to better treatability of the cancer and lower lung cancer mortality. The speed of growth is often described using two measures: the doubling time, which is the time it takes for a tumour to double in volume (become twice as large); and the sojourn time, which is the period of time from when a tumour can be detected in principle until it becomes symptomatic. Compared to other types of cancer such as breast cancer (mean doubling time ~250 days [330]) the growth rate for lung cancer is high. The mean doubling time is approximately 190 days for NSCLC [331] and approximately 50 days for SCLC [332]. The mean sojourn time is given as approximately 180 days for NSCLC and 90 days for SCLC [333]. In this respect, there is reason to assume that a shorter screening interval (annually) could be more beneficial for lung cancer screening than a longer screening interval. However, an increase in the number of CT scans could be expected to lead to an increase in false-positive screening results and overdiagnosis. However, this is not apparent from the data available for the present assessment. Taken together, the overall evidence is insufficient to use a screening interval other than 1 year.

Considerations for the design of a screening programme

The introduction of lung cancer screening using LDCT would require the establishment of criteria that define a high-risk population. The six European studies show many similarities with regard to the study population. Active smokers and nonsmokers who stopped smoking < 10 years previously were considered. Most studies considered cigarette consumption of > 20 pack-years. The age of the study participants ranged from ~50 years to 75 years. In the German S-3 guidelines on lung cancer, taking into account the American NLST study, the high-risk population is somewhat narrower and screening is recommended for asymptomatic individuals aged between 55 and 74 years without additional risk factors who have consumed > 30 pack-years of tobacco and have been abstinent from smoking for < 15 years [210]. Various risk prediction models are currently being propagated for more accurate selection of high-risk individuals [[334, 335]. Other criteria besides age and smoking behaviour that could be used to select high-risk individuals include low body mass index, family history of lung cancer, other cancers, self-reported history of COPD, chest X-rays in the last 3 years, low educational level and African descent [335].

Since the information on smoking behaviour is based on self-reporting and is decisive for selection for screening, the question arises as to how reliable this approach is. The repeated survey of active and former smokers regarding their smoking behaviour showed that over short periods of time, self-disclosure is predominantly reliable if standard questions are used to record the smoking history [336].

The screening design in the studies mainly comprised an annual examination by LDCT. Participants were often offered counselling or a smoking cessation programme in parallel with the screening. Regarding the investigation strategy (definitions and consequences of screening results), the studies included showed considerable heterogeneity. This includes non-uniform classification of screening results into two or three categories (positive, negative and indeterminate) and different definitions for these categories. Depending on the category for the pulmonary nodule, the subsequent diagnostic workup and further examination intervals were determined. In addition, different types of equipment were used in the studies. In most of the studies, CT images were evaluated independently by two radiologists.

In some studies a computer-based volume calculation was carried out. By comparing the original and follow-up CT images, the increase in volume for a pulmonary nodule can be determined and the malignancy can be evaluated according to the change in volume. Seigneurin et al. [306] observed that computerised volumetry yielded low recall rates and similar lung cancer detection rates. This indicates that assessment of pulmonary nodules by volume allows more precise distinction between benign and malignant nodules than assessment by diameter alone, which might have a meaningful impact on overdiagnosis.

If LDCT screening is introduced, quality assurance measures must be put in place, including uniform protocols for evaluation of CT images and subsequent follow-up examinations, as well as diagnostic workup. The German Radiological Society and the German Society for Pneumology and Respiratory Medicine consider the Lung Imaging-Reporting and Data System (Lung-RADS) developed by the American College of Radiology to be suitable [337]. This system is used for classification of pulmonary nodules. The follow-up checks and further diagnostic procedures needed are also defined, depending on the findings [338]. In addition, the two societies advocate the use of uniform volumetry software [337]. Since the radiation dose can be significantly reduced with the newer generation of devices, use of a multislice CT device should be a prerequisite for screening. The quality of lung cancer screening should be continuously reviewed and improved. To this end, findings requiring monitoring (reappointment rates and the proportion of positive biopsies of all biopsies performed) must be recorded [263].

However, questions concerning implementation of screening are being examined in a recently launched European study [203]. This EU-funded project (4-IN THE LUNG RUN: INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening) is coordinated by the Erasmus University Medical Center in Rotterdam, The Netherlands. In addition to Germany, the UK, Spain, Italy and France are participating in the study. A total of 24,000 participants will be included in the RCT, with the aim of testing the safety of risk-based screening intervals. In addition, strategies for recruitment, smoking cessation, reduction of comorbidities (e.g., using a calcium score for cardiovascular disease) and biomarkers will be investigated. The planned study end date is December 2024.

5.14 Information strategies for lung cancer screening

Screening for lung cancer differs from other cancer screenings in that the target group cannot be clearly defined by age or sex, but includes people with different risk factors. One challenge is therefore to identify and invite suitable individuals for screening. Tobacco smoking is considered the main risk factor for lung cancer. The fact that smoking is a self-chosen behaviour can lead to lung cancer being regarded as a self-induced disease and can therefore cause stigmatisation. This in turn carries the risk that affected individuals will not seek preventive medical checkups or health services. Appropriate information and invitation strategies that help to minimise the stigma associated with the risk of cancer among smokers may improve access to screening programmes [263]. Another important aspect of screening programmes is to inform potential participants about the possible benefits and harms of the test. With regard to different information strategies for screening for lung cancer, the literature search revealed two major groups of studies. These were studies that dealt with information or invitation strategies for lung cancer screening for potential eligible individuals and studies that examined tools for shared decision-making before LDCT in the context of a lung cancer screening programme. The evidence for information or invitations strategies is generally very weak and therefore no reliable conclusion can be drawn on whether a specific strategy is more effective in increasing participant knowledge, empowerment or satisfaction. In an SR

[339] examining the influence of information brochures on the screening participation rate for different cancers (colorectal, prostate or lung cancer), only a few relevant studies could be identified. Furthermore, the studies showed inconsistent results. The use of information brochures significantly increased the screening participation rate in five of nine studies, but not in the other four studies.

Several studies on the use of tools such as decision aids that promote shared decision-making are available. The quality of the evidence is low to moderate. Overall, the studies showed that the use of different types of decision aids before participation in lung cancer screening can lead to an improvement in knowledge about the screening process itself and its benefits and harms, and to greater confidence in making a decision for or against participation in screening. Screening participation rates are not significantly influenced by the use of these tools. A recent SR of tools for shared decision-making in lung cancer screening also came to a similar conclusion [340].

A screening intervention is a medical procedure that is performed on a person who does not (knowingly) have a disease and usually has not applied for the intervention. For this reason, the ethics of conducting a screening test must be carefully weighed. Even if assessment of a screening programme generally shows a positive benefit-to-harm ratio, for individual cases the harm may outweigh the benefit. Therefore, comprehensive evidence-based information strategies and concepts for screening programmes are essential to ensure important ethical principles such as informed consent, decision-making and decisional capacity are met [341]. A collaborative approach between health care providers and screening participants allows decisions to be made jointly according to the preferences of the participant, incorporating the best available evidence and recommendations [263]. US guidelines also recommend comprehensive evidence-based counselling and a shared decision-making process for lung cancer screening programmes before LDCT screening [236, 247]. When screening is introduced in Europe, it is important to provide appropriate information material with a balanced presentation of the advantages and disadvantages of LDCT screening for the target group to facilitate informed decision-making (shared decision-making) before screening [263]. However, this also requires appropriate training of physicians, the provision of suitable evidence-based tools such as decision supports, and time and personnel resources.

6 CONCLUDING SUMMARY

High-quality evidence shows that screening for lung cancer with LDCT in (former) heavy smokers results in little or no difference in overall mortality when compared with no screening. For lung cancer mortality, moderate-quality evidence shows that screening for lung cancer with LDCT probably reduces mortality when compared with no screening. Since the absolute effects and the corresponding CIs are of a similar order of magnitude, the assumption that screening also has a positive effect on overall mortality seems justified. Taking together the considerations for the two suboutcomes for mortality, screening for lung cancer with LDCT may have a mortality benefit.

However, screening for lung cancer with LDCT may increase adverse events and lead to harm because of the consequences of false-positive screening results. In addition, it leads to harm in terms of overdiagnosis. Consequences of false-negative screening results were not reported in the studies considered. It is estimated that their influence on the balancing of benefit and harm is small. For the adverse events outcome, data from only one study were available. For the HRQoL outcome, no usable data were available. However, the effect of screening on the rate of adverse events and on HRQoL is likely to be partly covered by the overdiagnosis outcome.

LDCT screening probably saves approximately 5 individuals out of 1,000 (95% CI 3–8) from dying of lung cancer within ~10 years and may potentially extend the life of some of the screening participants compared to no screening. The benefit in terms of mortality is mainly opposed by the harm resulting from false-positive screening results and overdiagnosis. False-positive screening results lead to invasive procedures that would not have been performed without the screening in at least 1 individual in 1,000, but at most in 15 in 1,000. These procedures can cause complications such as pneumothorax. Overdiagnosis is considered as harm because of the unnecessary subsequent diagnostics and therapy, including resulting complications. The risk of overdiagnosis in the individual studies is between 0 and 22 per 1,000 individuals invited for screening. The risk of overdiagnosis in the presence of a lung cancer diagnosis is between 0% and 63% in the individual studies. This underlines how important it is for a positive benefit-to-harm ratio to keep the risk of overdiagnosis low with optimal screening strategies.

For risk groups other than (former) heavy smokers, no studies investigating lung cancer screening using LDCT compared to no screening could be identified. It is not possible to apply the potential benefit of screening for lung cancer by LDCT in (former) heavy smokers to individuals with other risk factors for lung cancer because of (possible) differences in lung cancer risk, disease course, diagnostic accuracy of screening or diagnostic tests and treatment effectiveness.

For the use of biomarkers as an adjunct to LDCT in lung cancer screening, no evidence from RCTs is currently available.

No conclusion can be drawn on how best to reach individuals eligible for screening, because the currently available studies used different recruitment strategies without obvious differences in effectiveness between strategies. With regard to screening interval, current evidence is insufficient to use a screening interval other than 1 year.

Current evidence is insufficient to conclude whether there is an appropriate information strategy to reach individuals potentially eligible for lung cancer screening. Moderate-quality evidence shows that the use of decision aids before LDCT in the context of a lung cancer screening programme probably increases knowledge about the benefits and harms of lung cancer screening and probably reduces decisional conflict for or against screening participation.

7 REFERENCES

[1] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Lungenkrebsscreening mittels Niedrigdosis-Computertomografie: Abschlussbericht; Auftrag S19-02*. 19.10.2020; Available from: https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentoese-verfahren/s-projekte/s19-02-lungenkrebsscreening-mittels-niedrigdosis-computertomografie.12379.html [cited 22.10.2020].

[2] Snowsill T, Yang H, Griffin E, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess*. 2018; 22 (69): 1-276

[3] Ali N, Lifford KJ, Carter B, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. *BMJ Open*. 2015; 5 (7): e008254

[4] Brain K, Carter B, Lifford KJ, et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. *Thorax*. 2017; 72 (10): 912-8

[5] Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax*. 2016; 71 (11): 996-1005

[6] Dunn CE, Edwards A, Carter B, et al. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. *Patient Education & Counseling*. 2017; 100 (8): 1572-9

[7] Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess*. 2016; 20 (40): 1-146

[8] Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax*. 2016; 71 (2): 161-70

[9] Marcus MW, Duffy SW, Devaraj A, et al. Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: the UKLS trial. *Thorax*. 2019; 74 (8): 761-7

[10] McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res (Phila)*. 2014; 7 (3): 362-71

[11] Nair A, Gartland N, Barton B, et al. Comparing the performance of trained radiographers against experienced radiologists in the UK Lung Cancer Screening (UKLS) trial. *Br J Radiol*. 2016; 89 (1066): 20160301

[12] Nair A, Screaton NJ, Holemans JA, et al. The impact of trained radiographers as concurrent readers on performance and reading time of experienced radiologists in the UK Lung Cancer Screening (UKLS) trial. *European Radiology*. 2018; 28 (1): 226-34

[13] Aggestrup LM, Hestbech MS, Siersma V, et al. Psychosocial consequences of allocation to lung cancer screening: a randomised controlled trial. *BMJ Open*. 2012; 2 (2): e000663

[14] Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. *Thorax*. 2014; 69 (6): 574-9

[15] Ashraf H, Tonnesen P, Holst Pedersen J, et al. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). *Thorax*. 2009; 64 (5): 388-92

[16] Bons LR, Sedghi Gamechi Z, Thijssen CGE, et al. Growth of the thoracic aorta in the smoking population: the Danish Lung Cancer Screening Trial. *International Journal of Cardiology*. 2020; 299: 276-81

[17] Heleno B, Siersma V, Brodersen J. Estimation of overdiagnosis of lung cancer in low-dose computed tomography screening: a secondary analysis of the Danish Lung Cancer Screening Trial. *JAMA Internal Medicine*. 2018; 178 (10): 1420-2

[18] Hoyer N, Wille MMW, Thomsen LH, et al. Interstitial lung abnormalities are associated with increased mortality in smokers. *Respiratory Medicine*. 2018; 136: 77-82

[19] Jensen MD, Siersma V, Rasmussen JF, et al. Direct and indirect healthcare costs of lung cancer CT screening in Denmark: a registry study. *BMJ Open*. 2020; 10 (1): e031768

[20] Malmqvist J, Siersma V, Thorsen H, et al. Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study. *BMJ Open*. 2020; 10 (2): e030871

[21] Pedersen JH, Ashraf H, Dirksen A, et al. The Danish Randomized Lung Cancer CT Screening Trial: overall design and results of the prevalence round. *J Thorac Oncol*. 2009; 4 (5): 608-14

[22] Petersen RH, Hansen HJ, Dirksen A, et al. Lung cancer screening and video-assisted thoracic surgery. *J Thorac Oncol*. 2012; 7 (6): 1026-31

[23] Rasmussen JF, Siersma V, Malmqvist J, et al. Psychosocial consequences of false positives in the Danish Lung Cancer CT Screening Trial: a nested matched cohort study. *BMJ Open*. 2020; 10 (6): e034682

[24] Rasmussen JF, Siersma V, Pedersen JH, et al. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). *Lung Cancer*. 2015; 87 (1): 65-72

[25] Roe OD, Markaki M, Tsamardinos I, et al. 'Reduced' HUNT model outperforms NLST and NELSON study criteria in predicting lung cancer in the Danish screening trial. *BMJ Open Respir Res*. 2019; 6 (1): e000512

[26] Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease: the randomised Danish Lung Cancer Screening Trial; status after five annual screening rounds with low-dose CT. *Thorax*. 2012; 67 (4): 296-301

[27] Sorensen L, Nielsen M, Petersen J, et al. Chronic obstructive pulmonary disease quantification using CT texture analysis and densitometry: results from the Danish Lung Cancer Screening Trial. *AJR: American Journal of Roentgenology*. 2020; 214 (6): 1269-79

[28] Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling. *Am J Respir Crit Care Med*. 2016; 193 (5): 542-51

[29] Carozzi FM, Bisanzi S, Carrozzi L, et al. Multimodal lung cancer screening using the ITALUNG biomarker panel and low dose computed tomography: results of the ITALUNG biomarker study. *International Journal of Cancer*. 2017; 141 (1): 94-101

[30] Lopes Pegna A, Picozzi G, Falaschi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. *J Thorac Oncol*. 2013; 8 (7): 866-75

[31] Lopes Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer*. 2009; 64 (1): 34-40

[32] Mascalchi M, Belli G, Zappa M, et al. Risk-benefit analysis of X-ray exposure associated with lung cancer screening in the Italung-CT trial. *AJR Am J Roentgenol*. 2006; 187 (2): 421-9

[33] Mascalchi M, Comin CE, Bertelli E, et al. Screen-detected multiple primary lung cancers in the ITALUNG trial. *Journal of Thoracic Disease*. 2018; 10 (2): 1058-66

[34] Mascalchi M, Mazzoni LN, Falchini M, et al. Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT. *Br J Radiol*. 2012; 85 (1016): 1134-9

[35] Mascalchi M, Picozzi G, Falchini M, et al. Initial LDCT appearance of incident lung cancers in the ITALUNG trial. *Eur J Radiol*. 2014; 83 (11): 2080-6

[36] Paci E, Puliti D, Carozzi FM, et al. Prognostic selection and long-term survival analysis to assess overdiagnosis risk in lung cancer screening randomized trials. *Journal of Medical Screening*. 2020: 969141320923030

[37] Paci E, Puliti D, Lopes Pegna A, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax*. 2017; 72 (9): 825-31

[38] Pistelli F, Aquilini F, Falaschi F, et al. Smoking cessation in the ITALUNG lung cancer screening: what does "teachable moment" mean? *Nicotine and Tobacco Research*. 2019; 23: 23

[39] Puliti D, Mascalchi M, Carozzi FM, et al. Decreased cardiovascular mortality in the ITALUNG lung cancer screening trial: Analysis of underlying factors. *Lung Cancer*. 2019; 138: 72-8

[40] Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomization. *J Thorac Oncol*. 2015; 10 (6): 890-6

[41] Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *J Cancer Res Clin Oncol*. 2012; 138 (9): 1475-86

[42] Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening: results from the randomized German LUSI trial. *International Journal of Cancer*. 2020; 146 (6): 1503-13

[43] Gonzalez Maldonado S, Delorme S, Husing A, et al. Evaluation of prediction models for identifying malignancy in pulmonary nodules detected via low-dose computed tomography. *JAMA Netw Open*. 2020; 3 (2): e1921221

[44] Sommer G, Tremper J, Koenigkam-Santos M, et al. Lung nodule detection in a high-risk population: comparison of magnetic resonance imaging and low-dose computed tomography. *Eur J Radiol*. 2014; 83 (3): 600-5

[45] Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012; 21 (3): 308-15

[46] Pastorino U, Silva M, Sestini S, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial. *Annals of Oncology*. 2019; 30 (7): 1162-9

[47] Pastorino U, Sverzellati N, Sestini S, et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. *European Journal of Cancer*. 2019; 118: 142-8

[48] Pozzi P, Munarini E, Bravi F, et al. A combined smoking cessation intervention within a lung cancer screening trial: a pilot observational study. *Tumori*. 2015; 101 (3): 306-11

[49] Silva M, Prokop M, Jacobs C, et al. Long-term active surveillance of screening detected subsolid nodules is a safe strategy to reduce overtreatment. *Journal of Thoracic Oncology*. 2018; 13 (10): 1454-63

[50] Sverzellati N, Cademartiri F, Bravi F, et al. Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. *Radiology*. 2012; 262 (2): 460-7

[51] Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J*. 2011; 38 (2): 392-400

[52] Sverzellati N, Silva M, Calareso G, et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. *Eur Radiol*. 2016; 26 (11): 3821-9

[53] Bunge EM, Van den Bergh KAM, Essink-Bot ML, et al. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer*. 2008; 62 (3): 385-90

[54] De Koning HJ, Van der Aalst CM, De Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020; 382 (6): 503-13

[55] Gietema HA, Schilham AM, Van Ginneken B, et al. Monitoring of smoking-induced emphysema with CT in a lung cancer screening setting: detection of real increase in extent of emphysema. *Radiology*. 2007; 244 (3): 890-7

[56] Gietema HA, Zanen P, Schilham A, et al. Distribution of emphysema in heavy smokers: impact on pulmonary function. *Respir Med*. 2010; 104 (1): 76-82

[57] Han D, Heuvelmans MA, Van der Aalst CM, et al. New fissure-attached nodules in lung cancer screening: a brief report from the NELSON Study. *Journal of Thoracic Oncology*. 2020; 15 (1): 125-9

[58] Han D, Heuvelmans MA, Vliegenthart R, et al. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening. *British Journal of Radiology*. 2018; 91 (1090): 20170405

[59] Heuvelmans MA, Oudkerk M, De Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol*. 2013; 23 (7): 1836-45

[60] Heuvelmans MA, Vliegenthart R, De Koning HJ, et al. Quantification of growth patterns of screen-detected lung cancers: the NELSON study. *Lung Cancer*. 2017; 108: 48-54

[61] Heuvelmans MA, Walter JE, Peters RB, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the NELSON study. *Lung Cancer*. 2017; 113: 45-50

[62] Heuvelmans MA, Walter JE, Vliegenthart R, et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. *Thorax*. 2018; 73 (8): 779-81

[63] Horeweg N, Scholten ET, De Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol*. 2014; 15 (12): 1342-50

[64] Horeweg N, Van der Aalst CM, Thunnissen E, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. *Am J Respir Crit Care Med*. 2013; 187 (8): 848-54

[65] Horeweg N, Van der Aalst CM, Vliegenthart R, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. *Eur Respir J*. 2013; 42 (6): 1659-67

[66] Horeweg N, Van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol*. 2014; 15 (12): 1332-41

[67] Hubers AJ, Heideman DAM, Duin S, et al. DNA hypermethylation analysis in sputum of asymptomatic subjects at risk for lung cancer participating in the NELSON trial: argument for maximum screening interval of 2 years. *Journal of Clinical Pathology*. 2017; 70 (3): 250-4

[68] Oudkerk M, Heuvelmans MA. Screening for lung cancer by imaging: the Nelson study. *JBR-BTR*. 2013; 96 (3): 163-6

[69] Ru Zhao Y, Xie X, De Koning HJ, et al. NELSON lung cancer screening study. *Cancer Imaging*. 2011; 11 (Spec No A): S79-S84

[70] Takx RA, Vliegenthart R, Mohamed Hoesein FA, et al. Pulmonary function and CT biomarkers as risk factors for cardiovascular events in male lung cancer screening participants: the NELSON study. *Eur Radiol*. 2015; 25 (1): 65-71

[71] Takx RAP, Isgum I, Willemink MJ, et al. Quantification of coronary artery calcium in nongated CT to predict cardiovascular events in male lung cancer screening participants: results of the NELSON study. *J Cardiovasc Comput Tomogr*. 2015; 9 (1): 50-7

[72] Van de Wiel JCM, Wang Y, Xu DM, et al. Neglectable benefit of searching for incidental findings in the Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT. *Eur Radiol*. 2007; 17 (6): 1474-82

[73] Van den Bergh KAM, Essink-Bot ML, Borsboom GJ, et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. *Eur Respir J*. 2011; 38 (1): 154-61

[74] Van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer*. 2010; 102 (1): 27-34

[75] Van den Bergh KAM, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer*. 2008; 113 (2): 396-404

[76] Van den Bergh KAM, Essink-Bot ML, Van Klaveren RJ, et al. Informed participation in a randomised controlled trial of computed tomography screening for lung cancer. *Eur Respir J*. 2009; 34 (3): 711-20

[77] Van der Aalst CM, De Koning HJ, Van den Bergh KAM, et al. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. *Lung Cancer*. 2012; 76 (2): 204-10

[78] Van der Aalst CM, Van den Bergh KAM, Willemsen MC, et al. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. *Thorax*. 2010; 65 (7): 600-5

[79] Van der Aalst CM, Van Klaveren RJ, Van den Bergh KAM, et al. The impact of a lung cancer computed tomography screening result on smoking abstinence. *Eur Respir J*. 2011; 37 (6): 1466-73

[80] Van Iersel CA, De Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer*. 2007; 120 (4): 868-74

[81] Van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med*. 2009; 361 (23): 2221-9

[82] Van't Westeinde SC, Horeweg N, De Leyn P, et al. Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial. *Eur J Cardiothorac Surg*. 2012; 42 (3): 420-9

[83] Walter JE, Heuvelmans MA, De Bock GH, et al. Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: the NELSON study. *Thorax*. 2018; 73 (8): 741-7

[84] Walter JE, Heuvelmans MA, De Bock GH, et al. Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: the NELSON study. *Lung Cancer*. 2018; 125: 103-8

[85] Walter JE, Heuvelmans MA, De Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. *Lancet Oncol*. 2016; 17 (7): 907-16

[86] Walter JE, Heuvelmans MA, Ten Haaf K, et al. Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study. *Thorax*. 2019; 74 (3): 247-53

[87] Walter JE, Heuvelmans MA, Yousaf-Khan U, et al. New subsolid pulmonary nodules in lung cancer screening: the NELSON Trial. *Journal of Thoracic Oncology*. 2018; 13 (9): 1410-4

[88] Xu DM, Gietema H, De Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer*. 2006; 54 (2): 177-84

[89] Yousaf-Khan AU, Van der Aalst CM, Aerts JGJV, et al. Uniform and blinded cause of death verification of the NELSON lung cancer screening participants. *Lung Cancer*. 2017; 111: 131-4

[90] Yousaf-Khan U, Horeweg N, Van der Aalst C, et al. Baseline characteristics and mortality outcomes of control group participants and eligible non-responders in the NELSON lung cancer screening study. *J Thorac Oncol*. 2015; 10 (5): 747-53

[91] Yousaf-Khan U, Van der Aalst C, De Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax*. 2017; 72 (1): 48-56

[92] Yousaf-Khan U, Van der Aalst C, de Jong PA, et al. Risk stratification based on screening history: the NELSON lung cancer screening study. *Thorax*. 2017; 72 (9): 819-24

[93] Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med*. 2009; 180 (5): 445-53

[94] Infante M, Cavuto S, Lutman FR, et al. Long-term follow-up rersults of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. *Am J Respir Crit Care Med*. 2015; 191 (10): 1166-75

[95] Infante M, Chiesa G, Solomon D, et al. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. *J Thorac Oncol*. 2011; 6 (2): 327-35

[96] Infante M, Lutman FR, Cavuto S, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer*. 2008; 59 (3): 355-63

[97] Lopci E, Castello A, Morenghi E, et al. Cost-effectiveness of second-line diagnostic investigations in patients included in the DANTE trial: a randomized controlled trial of lung cancer screening with low-dose computed tomography. *Nuclear Medicine Communications*. 2019; 40 (5): 508-16

[98] Croswell JM, Baker SG, Marcus PM, et al. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. *Ann Intern Med*. 2010; 152 (8):

[99] Doroudi M, Pinsky PF, Marcus PM. Lung cancer mortality in the Lung Screening Study feasibility trial. *JNCI Cancer Spectrum*. 2018; 2 (3): pky042

[100] Gohagan J, Marcus P, Fagerstrom R, et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the lung screening study of the National Cancer Institute. *Chest*. 2004; 126 (1): 114-21

[101] Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*. 2005; 47 (1): 9-15

[102] Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized National Lung Screening Trial. *J Natl Cancer Inst*. 2010; 102 (23): 1771-9

[103] Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med*. 2013; 369 (10): 920-31

[104] Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. *Radiology*. 2015; 276 (1): 82-90

[105] Chudgar NP, Bucciarelli PR, Jeffries EM, et al. Results of the National Lung Cancer Screening Trial: where are we now? *Thorac Surg Clin*. 2015; 25 (2): 145-53

[106] Clark MA, Gorelick JJ, Sicks JD, et al. The relations between false positive and negative screens and smoking cessation and relapse in the National Lung Screening Trial: implications for public health. *Nicotine Tob Res*. 2016; 18 (1): 17-24

[107] Dillard TA, Patel RR, Schroeder C. Uneven distribution of cancer histology in the National Lung Screening Trial. *Am J Med Sci*. 2015; 350 (3): 219-21

[108] Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer*. 2014; 120 (21): 3401-9

[109] Gierada DS, Pinsky P, Nath H, et al. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. *J Natl Cancer Inst*. 2014; 106 (11): dju284

[110] Horeweg N, Nackaerts K, Oudkerk M, et al. Low-dose computed tomography screening for lung cancer: results of the first screening round. *J Comp Eff Res*. 2013; 2 (5): 433-6

[111] Jin GY, Lynch D, Chawla A, et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology*. 2013; 268 (2): 563-71

[112] Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013; 369 (3): 245-54

[113] Kruger R, Flynn MJ, Judy PF, et al. Effective dose assessment for participants in the National Lung Screening Trial undergoing posteroanterior chest radiographic examinations. *AJR Am J Roentgenol*. 2013; 201 (1): 142-6

[114] Larke FJ, Kruger RL, Cagnon CH, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. *AJR Am J Roentgenol*. 2011; 197 (5): 1165-9

[115] Marcus PM, Doria-Rose VP, Gareen IF, et al. Did death certificates and a death review process agree on lung cancer cause of death in the National Lung Screening Trial? *Clin Trials*. 2016; 13 (4): 434-8

[116] National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365 (5): 395-409

[117] National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013; 368 (21): 1980-91

[118] Park ER, Gareen IF, Jain A, et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. *Cancer*. 2013; 119 (7): 1306-13

[119] Patz EF Jr, Greco E, Gatsonis C, et al. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. *Lancet Oncol*. 2016; 17 (5): 590-9

[120] Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014; 174 (2): 269-74

[121] Pinsky PF, Church TR, Izmirlian G, et al. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer*. 2013; 119 (22): 3976-83

[122] Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med*. 2015; 162 (7): 485-91

[123] Pinsky PF, Gierada DS, Hocking W, et al. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. *Ann Intern Med*. 2014; 161 (9): 627-33

[124] Pinsky PF, Gierada DS, Nath H, et al. ROC curves for low-dose CT in the National Lung Screening Trial. *J Med Screen*. 2013; 20 (3): 165-8

[125] Pinsky PF, Gierada DS, Nath PH, et al. National Lung Screening Trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013; 268 (3): 865-73

[126] Pinsky PF, Nath PH, Gierada DS, et al. Short- and long-term lung cancer risk associated with noncalcified nodules observed on low-dose CT. *Cancer Prev Res (Phila)*. 2014; 7 (12): 1179-85

[127] Tammemägi MC, Berg CD, Riley TL, et al. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst*. 2014; 106 (6): dju084

[128] Tanner NT, Gebregziabher M, Hughes Halbert C, et al. Racial differences in outcomes within the National Lung Screening Trial: implications for widespread implementation. *Am J Respir Crit Care Med*. 2015; 192 (2): 200-8

[129] Tanner NT, Kanodra NM, Gebregziabher M, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *Am J Respir Crit Care Med*. 2016; 193 (5): 534-41

[130] Yip R, Henschke CI, Yankelevitz DF, et al. CT screening for lung cancer: alternative definitions of positive test result based on the National Lung Screening Trial and International Early Lung Cancer Action Program databases. *Radiology*. 2014; 273 (2): 591-6

[131] Yip R, Yankelevitz DF, Hu M, et al. Lung cancer deaths in the National Lung Screening Trial attributed to nonsolid nodules. *Radiology*. 2016; 281 (2): 589-96

[132] Young RP, Duan F, Chiles C, et al. Airflow limitation and histology shift in the National Lung Screening Trial: the NLST-ACRIN cohort substudy. *Am J Respir Crit Care Med*. 2015; 192 (9): 1060-7

[133] Abdel-Rahman O. Impact of current versus former smoking status on the outcomes of non-metastatic non-small cell lung cancer treated with upfront surgery: findings from the National Lung Screening Trial. *Expert Review of Respiratory Medicine*. 2019; 13 (6): 585-91

[134] Balekian AA, Wisnivesky JP, Gould MK. Surgical disparities among patients with stage I lung cancer in the National Lung Screening Trial. *Chest*. 2019; 155 (1): 44-52

[135] Brown D, Zingone A, Yu Y, et al. Relationship between circulating inflammation proteins and lung cancer diagnosis in the National Lung Screening Trial. *Cancer Epidemiology, Biomarkers and Prevention*. 2019; 28 (1): 110-8

[136] Cherezov D, Hawkins SH, Goldgof DB, et al. Delta radiomic features improve prediction for lung cancer incidence: a nested case-control analysis of the National Lung Screening Trial. *Cancer Med*. 2018; 7 (12): 6340-56

[137] De-Torres JP, Wisnivesky JP, Bastarrika G, et al. The prevalence of obstructive lung disease in a lung cancer screening cohort: analysis of the National Lung Screening Trial; American College of Radiology Image Network Cohort. *Ann Am Thorac Soc*. 2019; 16 (5): 641-4

[138] Gallardo-Estrella L, Pompe E, De Jong PA, et al. Normalized emphysema scores on low dose CT: validation as an imaging biomarker for mortality. *PLoS ONE*. 2017; 12 (12): e0188902

[139] Gierada DS, Pinsky PF, Duan F, et al. Interval lung cancer after a negative CT screening examination: CT findings and outcomes in National Lung Screening Trial participants. *European Radiology*. 2017; 27 (8): 3249-56

[140] Gu F, Cheung LC, Freedman ND, et al. Potential impact of including time to first cigarette in risk models for selecting ever-smokers for lung cancer screening. *Journal of Thoracic Oncology*. 2017; 12 (11): 1646-53

[141] Hopkins RJ, Duan F, Chiles C, et al. Reduced expiratory flow rate among heavy smokers increases lung cancer risk: results from the National Lung Screening Trial; American College of Radiology Imaging Network Cohort. *Ann Am Thorac Soc*. 2017; 14 (3): 392-402

[142] Iaccarino JM, Silvestri GA, Wiener RS. Patient-level trajectories and outcomes after low-dose CT screening in the National Lung Screening Trial. *Chest*. 2019; 156 (5): 965-71

[143] Kamel MK, Lee B, Harrison S, et al. Do the surgical results in the National Lung Screening Trial reflect modern thoracic surgical practice? *Journal of Thoracic and Cardiovascular Surgery*. 2019; 157 (5):

[144] Kumar V, Cohen JT, Van Klaveren D, et al. Risk-targeted lung cancer screening: a cost-effectiveness analysis. *Annals of Internal Medicine*. 2018; 168 (3): 161-9

[145] Lee C, Flynn MJ, Judy PF, et al. Body size-specific organ and effective doses of chest CT screening examinations of the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 208 (5): 1082-8

[146] Li Q, Balagurunathan Y, Liu Y, et al. Comparison between radiological semantic features and Lung-RADS in predicting malignancy of screen-detected lung nodules in the National Lung Screening Trial. *Clinical Lung Cancer*. 2018; 19 (2):

[147] Liu Y, Wang H, Li Q, et al. Radiologic features of small pulmonary nodules and lung cancer risk in the National Lung Screening Trial: a nested case-control study. *Radiology*. 2018; 286 (1): 298-306

[148] Lu H, Mu W, Balagurunathan Y, et al. Multi-window CT based Radiomic signatures in differentiating indolent versus aggressive lung cancers in the National Lung Screening Trial: a retrospective study. *Cancer Imaging*. 2019; 19 (1): 45

[149] National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019; 14 (10): 1732-42

[150] Nguyen XV, Davies L, Eastwood JD, et al. Extrapulmonary findings and malignancies in participants screened with chest CT in the National Lung Screening Trial. *Journal of the American College of Radiology*. 2017; 14 (3): 324-30

[151] Pinsky PF, Bellinger CR, Miller DP Jr. False-positive screens and lung cancer risk in the National Lung Screening Trial: implications for shared decision-making. *Journal of Medical Screening*. 2018; 25 (2): 110-2

[152] Pinsky PF, Gierada DS, Nath PH, et al. Lung cancer risk associated with new solid nodules in the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 209 (5): 1009-14

[153] Pompe E, De Jong PA, Lynch DA, et al. Computed tomographic findings in subjects who died from respiratory disease in the National Lung Screening Trial. *European Respiratory Journal*. 2017; 49: 1601814

[154] Robbins HA, Katki HA, Cheung LC, et al. Insights for management of ground-glass opacities from the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019; 14 (9): 1662-5

[155] Rojewski AM, Tanner NT, Dai L, et al. Tobacco dependence predicts higher lung cancer and mortality rates and lower rates of smoking cessation in the National Lung Screening Trial. *Chest*. 2018; 154 (1): 110-8

[156] Sonavane SK, Pinsky P, Watts J Jr, et al. The relationship of cancer characteristics and patient outcome with time to lung cancer diagnosis after an abnormal screening CT. *European Radiology*. 2017; 27 (12): 5113-8

[157] Thomas A, Pattanayak P, Szabo E, et al. Characteristics and outcomes of small cell lung cancer detected by CT screening. *Chest*. 2018; 154 (6): 1284-90

[158] Wong JYY, Bassig BA, Seow WJ, et al. Lung cancer risk in welders and foundry workers with a history of heavy smoking in the USA: the National Lung Screening Trial. *Occupational and Environmental Medicine*. 2017; 74 (6): 440-8

[159] Yip R, Henschke CI, Xu DM, et al. Lung cancers manifesting as part-solid nodules in the National Lung Screening Trial. *AJR: American Journal of Roentgenology*. 2017; 208 (5): 1011-21

[160] Zhu J, Nelson K, Toth J, et al. Nicotine dependence as an independent risk factor for atherosclerosis in the National Lung Screening Trial. *BMC Public Health*. 2019; 19 (1): 103

[161] National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology*. 2011; 258 (1): 243-53

[162] Bahl M. Incidental thyroid nodules in the National Lung Screening Trial: estimation of prevalence, malignancy rate, and strategy for workup. *Academic Radiology*. 2018; 25 (9): 1152-5

[163] De-Torres JP, Wisnivesky JP, Bastarrika G, et al. Exploring the impact of lung cancer screening on lung cancer mortality of smokers with obstructive lung disease: analysis of the NLST-ACRIN Cohort. *Archivos de Bronconeumologia*. 2020; In press: https://doi.org/10.1016/j.arbres.2020.03.023

[164] Gareen IF, Black WC, Tosteson TD, et al. Medical care costs were similar across the low-dose computed tomography and chest x-ray arms of the National Lung Screening Trial despite different rates of significant incidental findings. *Medical Care*. 2018; 56 (5): 403-9

[165] Hammer MM, Palazzo LL, Kong CY, et al. Cancer risk in subsolid nodules in the National Lung Screening Trial. *Radiology*. 2019; 293 (2): 441-8

[166] Kaminsky DA, Daphtary N, Estepar RSJ, et al. Ventilation heterogeneity and its association with nodule formation among participants in the National Lung Screening Trial: a preliminary investigation. *Academic Radiology*. 2020; 27 (5): 630-5

[167] Kaufman AR, Dwyer LA, Land SR, et al. Smoking-related health beliefs and smoking behavior in the National Lung Screening Trial. *Addictive Behaviors*. 2018; 84: 27-32

[168] Loomans-Kropp HA, Dunn BK, Kramer BS, et al. Thyroid incidentalomas in association with low-dose computed tomography in the National Lung Screening Trial. *American Journal of Epidemiology*. 2020; 189 (1): 27-33

[169] Munden RF, Chiles C, Boiselle PM, et al. Micronodules detected on computed tomography during the National Lung Screening Trial: prevalence and relation to positive studies and lung cancer. *Journal of Thoracic Oncology*. 2019; 14 (9): 1538-46

[170] Schreuder A, Jacobs C, Gallardo-Estrella L, et al. Predicting all-cause and lung cancer mortality using emphysema score progression rate between baseline and follow-up chest CT images: a comparison of risk model performances. *PLoS ONE*. 2019; 14 (2): e0212756

[171] Tanner NT, Thomas NA, Ward R, et al. Association of cigarette type with lung cancer incidence and mortality: secondary analysis of the National Lung Screening Trial. *JAMA Internal Medicine*. 21.10.2019 [Epub ahead of print]:

[172] Wang S, Chen A, Yang L, et al. Comprehensive analysis of lung cancer pathology images to discover tumor shape and boundary features that predict survival outcome. *Scientific Reports*. 2018; 8 (1): 10393

[173] Warkentin MT, Tammemagi MC, Freedman MT, et al. Factors associated with small aggressive non-small cell lung cancers in the National Lung Screening Trial: a validation study. *JNCI Cancer Spectrum*. 2018; 2 (1): pkx010

[174] White CS, Dharaiya E, Dalal S, et al. Vancouver Risk Calculator compared with ACR Lung-RADS in predicting malignancy: analysis of the National Lung Screening Trial. *Radiology*. 2019; 291 (1): 205-11

[175] Whittaker Brown SA, Padilla M, Mhango G, et al. Interstitial lung abnormalities and lung cancer risk in the National Lung Screening Trial. *Chest*. 2019; 156 (6): 1195-203

[176] Yong PC, Sigel K, De-Torres JP, et al. The effect of radiographic emphysema in assessing lung cancer risk. *Thorax*. 2019; 74 (9): 858-64

[177] Quaife SL, Ruparel M, Beeken RJ, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach'patients. *BMC Cancer*. 2016; 16: 281

[178] Quaife SL, Ruparel M, Dickson JL, et al. Lung Screen Uptake Trial (LSUT): Randomized Controlled Clinical Trial Testing Targeted Invitation Materials. *American Journal of Respiratory &Critical Care Medicine*. 2020; 201 (8): 965-75

[179] Ruparel M, Quaife SL, Ghimire B, et al. Impact of a Lung Cancer Screening Information Film on Informed Decision-making: A Randomized Trial. *Annals of the American Thoracic Society*. 2019; 16 (6): 744-51

[180] Sferra SR, Cheng JS, Boynton Z, et al. Aiding shared decision making in lung cancer screening: two decision tools. *Journal of Public Health*. 2020; In press: https://doi.org/10.1093/pubmed/fdaa063

[181] Sharma A, Bansal-Travers M, Celestino P, et al. Using a Smoking Cessation Quitline to Promote Lung Cancer Screening. *American Journal of Health Behavior*. 2018; 42 (6): 85-100

[182] Lowenstein LM, Escoto KH, Leal VB, et al. Randomized trial of a patient-centered decision aid for promoting informed decisions about lung cancer screening: Implementation of a PCORI study protocol and lessons learned. *Contemporary Clinical Trials*. 2018; 72: 26-34

[183] Volk RJ, Lowenstein LM, Leal VB, et al. Effect of a Patient Decision Aid on Lung Cancer Screening Decision-Making by Persons Who Smoke: A Randomized Clinical Trial. *JAMA Network Open*. 2020; 3 (1): e1920362

[184] M.D. Anderson Cancer Center. *PCORI-CER-1306-03385 Informed Decisions About Lung Cancer Screening*. 15.07.2019; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02286713 [cited 16.08.2020].

[185] University College London Hospitals. *Lung Screen Uptake Trial (Lung-SCREEN)*. 02.06.2020; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02558101 [cited 16.08.2020].

[186] University College London Hospitals. *Increasing uptake of lung cancer screening in individuals at high risk of lung cancer*. 27.05.2020; Available from: http://www.isrctn.com/ISRCTN21774741 [cited 16.08.2020].

[187] Lowenstein LM, Godoy MCB, Erasmus JJ, et al. Implementing Decision Coaching for Lung Cancer Screening in the Low-Dose Computed Tomography Setting. *JCO Oncol Pract*. 2020; 16 (8): e703-25

[188] Tanner NT, Banas E, Yeager D, et al. In-person and Telephonic Shared Decision-making Visits for People Considering Lung Cancer Screening: An Assessment of Decision Quality. *Chest*. 2019; 155 (1): 236-8

[189] Yoshida M, Kondo K, Nakanishi C, et al. Interventional study for improvement of lung cancer screening rate. *J Med Invest*. 2012; 59 (1-2): 127-35

[190] Hoffman AS, Hempstead AP, Housten AJ, et al. Using a Patient Decision Aid Video to Assess Current and Former Smokers'Values About the Harms and Benefits of Lung Cancer Screening With Low-Dose Computed Tomography. *MDM Policy & Practice*. 2018; 3 (1): 2381468318769886

[191] Housten AJ, Lowenstein LM, Leal VB, et al. Responsiveness of a Brief Measure of Lung Cancer Screening Knowledge. *J Cancer Educ*. 2018; 33 (4): 842-6

[192] Lau YK, Caverly TJ, Cao P, et al. Evaluation of a Personalized, Web-Based Decision Aid for Lung Cancer Screening. *American Journal of Preventive Medicine*. 2015; 49 (6): e125-9

[193] Mazzone PJ, Tenenbaum A, Seeley M, et al. Impact of a Lung Cancer Screening Counseling and Shared Decision-Making Visit. *Chest*. 2017; 151 (3): 572-8

[194] Reuland DS, Cubillos L, Brenner AT, et al. A pre-post study testing a lung cancer screening decision aid in primary care. *BMC Medical Informatics & Decision Making*. 2018; 18 (1): 5

[195] Sakoda LC, Meyer MA, Chawla N, et al. Effectiveness of a Patient Education Class to Enhance Knowledge about Lung Cancer Screening: a Quality Improvement Evaluation. *Journal of Cancer Education*. 2020; 35: 897-904

[196] Studts JL, Thurer RJ, Brinker K, et al. Brief Education and a Conjoint Valuation Survey May Reduce Decisional Conflict Regarding Lung Cancer Screening. *MDM Policy &Practice*. 2020; 5 (1): 2381468319891452

[197] Volk RJ, Linder SK, Leal VB, et al. Feasibility of a patient decision aid about lung cancer screening with low-dose computed tomography. *Preventive Medicine*. 2014; 62: 60-3

[198] M.D. Anderson Cancer Center. *PCORI-CER-1306-03385 Lung Cancer Screening Decision Aid Development and Testing*. 27.09.2019; Available from: https://clinicaltrials.gov/ct2/show/study/NCT02282969 [cited 16.08.2020].

[199] UNC Lineberger Comprehensive Cancer Center. *Pre-Post Study for Supporting Appropriate Implementation of Lung Cancer Screening*. 20.09.2017; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03077230 [cited 16.08.2020].

[200] Autier P. Lung-Cancer screening and the NELSON trial. *N Engl J Med*. 2020; 382 (22): 2165

[201] Gigerenzer G. *Unstatistik des Monats: Lungenkrebs-Screening rettet Leben*. 28.02.2020; Available from: http://www.rwi-essen.de/unstatistik/100 [cited 05.03.2020].

[202] Manhire A, Charig M, Clelland C, et al. Guidelines for radiologically guided lung biopsy. *Thorax*. 2003; 58 (11): 920-36

[203] European Commission. *4-IN THE LUNG RUN: towards INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening*. 02.04.2020; Available from: https://cordis.europa.eu/project/id/848294/de [cited 07.10.2020].

[204] Humphrey L, Deffebach M, Pappas M, et al. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation Rockville (MD): Agency for Healthcare Research and Quality (US); 2013

[205] Richards TB, White MC, Caraballo RS. Lung Cancer Screening with Low-Dose Computed Tomography for Primary Care Providers. *Primary Care: Clinics in Office Practice*. 2014; 41 (2): 307-30

[206] Thomas K, Gould M. *UpToDate: Tumor, Node, Metastasis (TNM) staging system for lung cancer*. 15.10.2019; Available from: http://www.uptodate.com/contents/tumor-node-metastasis-tnm-staging-system-for-non-small-cell-lung-cancer [cited 06.10.2020].

[207] Früh M, Ruysscher D, Popat S, et al. *Scmall-Cell Lung Cancer (SCLC) Guideline*. Available from: http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=3 [cited 01.11.2020].

[208] Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *Journal of Thoracic Oncology*. 2016; 11 (1): 39-51

[209] Rami-Porta R, Asamura H, Travis WD, et al. Lung cancer – major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; 67 (2): 138-55

[210] Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe. *S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms: Langversion 1.0; AWMF-Registernummer 020/007OL*. 02.2018; Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_l_S3_Lungenkarzinom_2018-03.pdf [cited 09.07.2019].

[211] Latimer KM, Mott TF. Lung Cancer: Diagnosis, Treatment Principles, and Screening 2015:

[212] Lung Cancer Europe. *LuCE Report on lung cancer – Challenges in lung cancer in Europe*. 11.2016; Available from: https://www.lungcancereurope.eu/wp-content/uploads/2017/10/LuCE-Report-final.pdf [cited 08.06.2020].

[213] European Respiratory Society. *EUROPEAN LUNG white book; Chapter 9: Tobacco smoking*. Available from: https://www.erswhitebook.org/chapters/tobacco-smoking/ [cited 15.07.2020].

[214] European Respiratory Society. *EUROPEAN LUNG white book; Chapter 19: Lung cancer*. Available from: https://www.erswhitebook.org/chapters/lung-cancer/ [cited 15.07.2020].

[215] European Respiratory Society. *SMOKEHAZ. A scientific review of the health hazards of smoking – Lung cancer; Number of cigarettes*. Available from: https://www.europeanlung.org/en/projects-and-research/projects/smokehaz/lung-conditions/home/adults/lung-cancer/ [cited 15.07.2020].

[216] European Lung Foundation. *Smoking and the lung*. Available from: https://www.europeanlung.org/assets/files/en/publications/smoking-en.pdf [cited 15.07.2020].

[217] European Lung Foundation. *SMOKEHAZ. A scientific review of the health hazards of smoking – Lung cancer; Passive smoking*. 2013; Available from: https://www.europeanlung.org/en/projects-and-research/projects/smokehaz/lung-conditions/home/adults/lung-cancer/ [cited 15.07.2020].

[218] European Lung Foundation. *Passive smoking*. Available from: https://www.europeanlung.org/en/lung-disease-and-information/risk-factors/passive-smoking [cited 15.07.2020].

[219] European Lung Foundation. E-cigarettes, heat-not-burn and smokeless tobacco products. *Breathe* 2020; 16 (1): 161

[220] European Commission. *Smoking of tobacco products by sex, age and country of birth*. Available from: https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_sk1b&lang=en [cited 15 July 2020].

[221] European Commission. *Attitudes of Europeans towards tobacco and electronic cigarettes. Special Eurobarometer 458.* Available from: https://ec.europa.eu/commfrontoffice/publicopinionmobile/index.cfm/Survey/getSurveyDetail/surveyKy/2146 [cited 15 July 2020].

[222] Zhang X, Jiang N, Wang L, et al. Chronic obstructive pulmonary disease and risk of lung cancer: a meta-analysis of prospective cohort studies. *Oncotarget*. 2017; 8 (44): 78044-56

[223] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018; 392 (10159): 1789-858

[224] Global Health Data Exchange. *Global Burden of Disease Study 2017 (GBD 2017) Data Resources,*. Available from: http://ghdx.healthdata.org/gbd-2017 [cited 21.07.2020].

[225] Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health*. 2015; 5 (2): 020415

[226] Varmaghani M, Dehghani M, Heidari E, et al. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J*. 2019; 25 (1): 47-57

[227] Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest*. 2015; 148 (4): 971-85

[228] Ballester B, Milara J, Cortijo J. Idiopathic Pulmonary Fibrosis and Lung Cancer: Mechanisms and Molecular Targets. *Int J Mol Sci*. 2019; 20 (3): 593

[229] EU-IPFF. *The European Idiopathic Pulmonary Fibrosis and Related Disorders Federation*. Available from: https://www.eu-ipff.org/ [cited 21.07.2020].

[230] Nalysnyk L, Cid-Ruzafa J, Rotella P, et al. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev*. 2012; 21 (126): 355-61

[231] Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015; 46 (3): 795-806

[232] Cottin V, Cadranel J, Crestani B, et al. Management of idiopathic pulmonary fibrosis in France: a survey of 1244 pulmonologists. *Respir Med*. 2014; 108 (1): 195-202

[233] Agabiti N, Porretta MA, Bauleo L, et al. Idiopathic Pulmonary Fibrosis (IPF) incidence and prevalence in Italy. *Sarcoidosis Vasc Diffuse Lung Dis*. 2014; 31 (3): 191-7

[234] Harari S, Madotto F, Caminati A, et al. Epidemiology of Idiopathic Pulmonary Fibrosis in Northern Italy. *PLoS One*. 2016; 11 (2): e0147072

[235] Strongman H, Kausar I, Maher TM. Incidence, Prevalence, and Survival of Patients with Idiopathic Pulmonary Fibrosis in the UK. *Adv Ther*. 2018; 35 (5): 724-36

[236] Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018; 16 (4): 412-41

[237] Cote ML, Liu M, Bonassi S, et al. Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. *Eur J Cancer*. 2012; 48 (13): 1957-68

[238] European Respiratory Society. *EUROPEAN LUNG white book; Chapter 3: Genetic susceptibility*. Available from: https://www.erswhitebook.org/chapters/genetic-susceptibility/ [cited 15.07.2020].

[239] Mai PL, Wideroff L, Greene MH, et al. Prevalence of family history of breast, colorectal, prostate, and lung cancer in a population-based study. *Public Health Genomics*. 2010; 13 (7-8): 495-503

[240] Gawelek E, Drozdowska B, Fuchs A. Radon as a risk factor of lung cancer. *Przegl Epidemiol*. 2017; 71 (1): 90-8

[241] Zeeb H, Shannoun S. WHO handbook on indoor radon. a public health perspective. Geneva: World Health Organization; 2009

[242] Darby S, Hill D, Deo H, et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health*. 2006; 32 Suppl 1: 1-83

[243] Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*. 2005; 330 (7485): 223

[244] De Matteis S, Consonni D, Bertazzi PA. Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction. *Acta Biomed*. 2008; 79 Suppl 1: 34-42

[245] GBD 2016 Occupational Carcinogens Collaborators. Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016. *Occup Environ Med*. 2020; 77 (3): 151-9

[246] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part C: Arsenic, metals, fibres and dust*. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100C.pdf [cited 15.07.2020].

[247] Mazzone PJ, Silvestri GA, Patel S, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. *Chest*. 2018; 153 (4): 954-85

[248] Santaballa A, Pinto A, Balanya RP, et al. SEOM clinical guideline for secondary prevention (2019). *Clin Transl Oncol*. 2020; 22 (2): 187-92

[249] Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2017; 28: iv1-iv21

[250] National Institute for Health and Care Excellence (NICE). *Lung cancer: diagnosis and management* Available from: https://www.nice.org.uk/guidance/ng122 [cited 15.07.2020].

[251] National Health Service. *Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography*. Available from: http://www.lungcancercoalition.org/screening-resource/guidelines/guideline-5.html [cited 04.05.2020].

[252] Ma J, Ward EM, Smith R, et al. Annual number of lung cancer deaths potentially avertable by screening in the United States. *Cancer*. 2013; 119 (7): 1381-5

[253] National Cancer Institute. *National Lung Screening Trial*. 08.09.2014; Available from: https://www.cancer.gov/types/lung/research/nlst [cited 27.07.2020].

[254] US Preventive Service Task Force. *Lung Cancer: Screening. An Update for This Topic is In Progress*. 07.07.2020; Available from: https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/lung-cancer-screening-2020 [cited 27.07.2020].

[255] Centers for Medicare & Medicaid Services. *Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N)*. Available from: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274 [cited 27.07.2020].

[256] Wiener RS, Gould MK, Arenberg DA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *Am J Respir Crit Care Med*. 2015; 192 (7): 881-91

[257] American Lung Association. *Is Lung Cancer Screening Right for Me? Questions and Answers About Lung Cancer Screening*. 15.04.2020; Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/saved-by-the-scan/resources/is-lung-cancer-screening-right [cited 27.07.2020].

[258] Demb J, Chu P, Yu S, et al. Analysis of Computed Tomography Radiation Doses Used for Lung Cancer Screening Scans. *JAMA Internal Medicine*. 2019; 179 (12): 1650-7

[259] Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer Journal for Clinicians*. 2019; 69 (3): 184-210

[260] Rivera MP, Tanner NT, Silvestri GA, et al. Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening. An Official American Thoracic Society Research Statement. *Am J Respir Crit Care Med*. 2018; 198 (2): e3-e13

[261] Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. *Cmaj*. 2016; 188 (6): 425-32

[262] Roberts H, Walker-Dilks C, Sivjee K, et al. Screening high-risk populations for lung cancer: guideline recommendations. *J Thorac Oncol*. 2013; 8 (10): 1232-7

[263] Kauczor HU, Baird AM, Blum TG, et al. ESR/ERS statement paper on lung cancer screening. *Eur Radiol*. 2020; 30 (6): 2377-94

[264] Pedersen JH, Rzyman W, Veronesi G, et al. Recommendations from the European Society of Thoracic Surgeons (ESTS) regarding computed tomography screening for lung cancer in Europe. *Eur J Cardiothorac Surg*. 2017; 51 (3): 411-20

[265] Field JK, Dekoning H, Oudkerk M, et al. Implementation of lung cancer screening in Europe: Challenges and potential solutions: Summary of a multidisciplinary roundtable discussion. *ESMO Open*. 2019; 4 (5) (no pagination) (e000577):

[266] Alvarez FV, Trueba IM, Sanchis JB, et al. Recommendations of the Spanish Society of Pneumology and Thoracic Surgery on the diagnosis and treatment of non-small-cell lung cancer. *Arch Bronconeumol*. 2016; 52 Suppl 1: 2-62

[267] Pedersen JH, Sorensen JB, Saghir Z, et al. Implementation of lung cancer CT screening in the Nordic countries. *Acta Oncol*. 2017; 56 (10): 1249-57

[268] Haute Autorité de Santé. *Pertinence du dépistage du cancer broncho-pulmonaire en France – Point de situation sur les données disponibles – Analyse critique des études contrôlées randomisées*. 19.05.2016; Available from: https://www.has-sante.fr/jcms/c_2001613/fr/pertinence-du-depistage-du-cancer-broncho-pulmonaire-en-france-point-de-situation-sur-les-donnees-disponibles-analyse-critique-des-etudes-controlees-randomisees [cited 27.07.2020].

[269] Gray EP, Teare MD, Stevens J, et al. Risk Prediction Models for Lung Cancer: A Systematic Review. *Clin Lung Cancer*. 2016; 17 (2): 95-106

[270] Husing A, Kaaks R. Risk prediction models versus simplified selection criteria to determine eligibility for lung cancer screening: an analysis of German federal-wide survey and incidence data. *Eur J Epidemiol*. 2020; 35 (10): 899-912

[271] Seijo LM, Peled N, Ajona D, et al. Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges. *J Thorac Oncol*. 2019; 14 (3): 343-57

[272] Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA*. 2011; 306 (17): 1865-73

[273] Wender R, Fontham ETH, Barrera E, Jr., et al. American Cancer Society lung cancer screening guidelines. *CA: a cancer journal for clinicians*. 2013; 63 (2): 107-17

[274] Optican RJ, Chiles C. Implementing lung cancer screening in the real world: opportunity, challenges and solutions. *Translational lung cancer research*. 2015; 4 (4): 353-64

[275] Schütte W, Möller M. Früherkennung des Lungenkarzinoms durch CT-Screening – Herausforderungen für die europäische Gesundheitspolitik. *Kompass Onkologie*. 2018; 5 (3): 163-4

[276] Rampinelli C, Origgi D, Bellomi M. Low-dose CT: technique, reading methods and image interpretation. *Cancer Imaging*. 2013; 12 (3): 548-56

[277] Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010: explanation and elaboration; updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010; 340: c869

[278] Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Available from: www.training.cochrane.org/handbook [cited 08.06.2020].

[279] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016; 355: i4919

[280] Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011; 64 (4): 383-94

[281] Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007; 7: 10

[282] Sutton AJ, Abrams KR, Jones DR, et al. Methods for meta-analysis in medical research. Chichester: Wiley; 2000

[283] Veroniki AA, Jackson D, Viechtbauer W, et al. Recommendations for quantifying the uncertainty in the summary intervention effect and estimating the between-study heterogeneity variance in random-effects meta-analysis. *Cochrane Database Syst Rev*. 2015; (Suppl 1): 25-7

[284] Spiro SG, Hackshaw A. Research in progress; LungSEARCH: a randomised controlled trial of surveillance for the early detection of lung cancer in a high-risk group. *Thorax*. 2016; 71 (1): 91-3

[285] Blanchon T, Brechot JM, Grenier PA, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer*. 2007; 58 (1): 50-8

[286] Garg K, Keith RL, Byers T, et al. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. *Radiology*. 2002; 225 (2): 506-10

[287] Istituto Clinico Humanitas. *The DANTE Trial: a randomized study on lung cancer screening with low-dose spiral computed tomography; study details*. 11.01.2007; Available from: https://ClinicalTrials.gov/show/NCT00420862 [cited 06.11.2019].

[288] Danish Lung Cancer Group. *Danish Lung Cancer Screening Trial (DLCST) (DLCST): study details*. 06.07.2007; Available from: https://ClinicalTrials.gov/show/NCT00496977 [cited 06.11.2019].

[289] Cancer Prevention and Research Institute Italy. *Italian Lung Cancer Screening Trial (ITALUNG) (ITALUNG): study details*. 20.05.2016; Available from: https://ClinicalTrials.gov/show/NCT02777996 [cited 06.11.2019].

[290] National Cancer Institute. *Lung Screening Study: study details*. 05.05.2015; Available from: https://ClinicalTrials.gov/show/NCT00006382 [cited 06.11.2019].

[291] German Cancer Research Centre. *Spiral computed tomography scanning for the early detection of lung cancer*. 19.07.2007; Available from: http://isrctn.com/ISRCTN30604390 [cited 06.11.2019].

[292] Fondazione IRCCS Istituto Nazionale dei Tumori Milano. *Early lung cancer detection in high risk individuals (MILD): study details*. 11.05.2017; Available from: https://ClinicalTrials.gov/show/NCT02837809 [cited 06.11.2019].

[293] KWF Kankerbestrijding, ZONMW. *NEderlands Leuvens Longkanker Screenings Onderzoek (NELSON-screening trial) in high risk subjects*. Available from: https://www.trialregister.nl/trial/580 [cited 06.11.2019].

[294] National Cancer Institute. *National Lung Screening Trial (NLST) screening (NLST): study details*. 20.05.2014; Available from: https://ClinicalTrials.gov/show/NCT00047385 [cited 06.11.2019].

[295] National Cancer Institute. *National Lung Screening Trial (NLST) screening (NLST): study results*. 20.05.2014; Available from: https://ClinicalTrials.gov/ct2/show/results/NCT00047385 [cited 06.11.2019].

[296] Royal Liverpool & Broadgreen University Hospital Trust. *UK Lung Cancer Screening Pilot Trial (UKLS)*. 19.10.2017; Available from: http://www.isrctn.com/ISRCTN78513845 [cited 06.11.2019].

[297] National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College. *China national cancer early screening trial: lung and colorectal cancer*. 26.08.2019; Available from: http://www.chictr.org.cn/showproj.aspx?proj=42159 [cited 16.07.2020].

[298] JECS Study Group. *The Japanese randomized trial for evaluating the efficacy of low-dose thoracic CT screening for lung cancer*. 05.01.2017; Available from: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006988 [cited 06.11.2019].

[299] Medical Research Council. *UKCCCR pilot of lung cancer screening using spiral CT*. 09.09.2016; Available from: http://www.isrctn.com/ISRCTN58557945 [cited 06.11.2019].

[300] Jewish Hospital and St. Mary's Healthcare. *Chest X-ray or chest CT scan in patients at high risk of developing lung cancer: study details*. 09.02.2009; Available from: https://ClinicalTrials.gov/show/NCT00006087 [cited 06.11.2019].

[301] Shanghai Chest Hospital. *Early stage lung cancer screening with low-dose computed tomographic: study details*. 13.09.2016; Available from: https://ClinicalTrials.gov/show/NCT02898441 [cited 06.11.2019].

[302] University of Leeds. *The Yorkshire Lung Screening Trial*. 29.07.2019; Available from: http://www.isrctn.com/ISRCTN42704678 [cited 06.11.2019].

[303] Sagawa M, Nakayama T, Tanaka M, et al. A randomized controlled trial on the efficacy of thoracic CT screening for lung cancer in non-smokers and smokers of <30 pack-years aged 50-64 years (JECS study): research design. *Jpn J Clin Oncol*. 2012; 42 (12): 1219-21

[304] Husband JE. Proposals for lung cancer screening in the UK. *Cancer Imaging*. 2001; 2: 6-16

[305] Travis WD, Brambilla E, Müller-Hermelink HK, et al., editors. World Health Organization classification of tumours: pathology and genetics of tumours of the lung, pleura, thymus, and heart. Lyon: IARC Press; 2004.

[306] Seigneurin A, Field JK, Gachet A, et al. A systematic review of the characteristics associated with recall rates, detection rates and positive predictive values of computed tomography screening for lung cancer. *Annals of Oncology*. 2014; 25 (4): 781-91

[307] Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. *Computat Stat Data Anal*. 1994; 17 (5): 555-74

[308] Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. *BMJ*. 2015; 350: g7773

[309] Ripping TM, Ten Haaf K, Verbeek ALM, et al. Quantifying overdiagnosis in cancer screening: a systematic review to evaluate the methodology. *J Natl Cancer Inst*. 2017; 109 (10): djx060

[310] Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015; 10 (9): 1243-60

[311] Bösch D. Lunge und Atemwege. Berlin: Springer; 2014

[312] Barr PJ, Thompson R, Walsh T. The psychometric properties of CollaboRATE: A fast and frugal patient-reported measure of the shared decision-making process. . *J Med Internet Res* 2014; 16 (e2):

[313] Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014; 160 (5): 330-8

[314] RTI International-University of North Carolina at Chapel Hill Evidence-based Practice Center. *Screening for lung cancer with low-dose computed tomography: an evidence review for the U.S. Preventive Services Task Force; AHRQ publication no. 20-05266-EF-1*. 07.2020; Available from: https://www.uspreventiveservicestaskforce.org/home/getfilebytoken/cG_GWGop5EaQtrgdk5SomB [cited 02.09.2020].

[315] Cancer Intervention and Surveillance Modeling Network. *Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: a collaborative modeling study for the U.S. Preventive Services Task Force; AHRQ publication no. 20-05266-EF-2*. 07.2020; Available from: https://www.uspreventiveservicestaskforce.org/home/getfilebytoken/PFx2xFgkPRNxLZP9bSCCSA [cited 02.09.2020].

[316] U.S. Preventive Services Task Force. *Lung cancer: screening; recommendation summary*. 07.07.2020; Available from: https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/lung-cancer-screening-2020 [cited 01.09.2020].

[317] Heijnsdijk EAM, Csanadi M, Gini A, et al. All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: A review and modeling study. *Cancer Med*. 2019; 8 (13): 6127-38

[318] Baker SG, Kramer BS, Prorok PC. Statistical issues in randomized trials of cancer screening. *BMC Med Res Methodol*. 2002; 2: 11

[319] Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst*. 2002; 94 (3): 167-73

[320] Prasad V, Lenzer J, Newman DH. Why cancer screening has never been shown to "save lives"--and what we can do about it. *BMJ*. 2016; 352: h6080

[321] Steele RJ, Brewster DH. Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes? No. *BMJ*. 2011; 343: d6397

[322] Penston J. Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes? Yes. *BMJ*. 2011; 343: d6395

[323] Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2004; 19 (8): 751-60

[324] Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ*. 2017; 356: j347

[325] Cohen SL, Wang JJ, Chan N, et al. Lung cancer screening CT: sex-specific conversion factors to estimate effective radiation dose from dose-length product. *Chest*. 2019; 156 (6): 1214-22

[326] Huang KL, Wang SY, Lu WC, et al. Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis. *BMC Pulmonary Medicine*. 2019; 19 (1): 126

[327] Yang W, Qian F, Teng J, et al. Community-based lung cancer screening with low-dose CT in China: results of the baseline screening. *Lung Cancer*. 2018; 117: 20-6

[328] Maisonneuve P, Rampinelli C, Bertolotti R, et al. Low-dose computed tomography screening for lung cancer in people with workplace exposure to asbestos. *Lung Cancer*. 2019; 131: 23-30

[329] Chu GCW, Lazare K, Sullivan F. Serum and blood based biomarkers for lung cancer screening: a systematic review. *BMC Cancer*. 2018; 18 (1): 181

[330] Lin RS, Plevritis SK. Comparing the benefits of screening for breast cancer and lung cancer using a novel natural history model. *Cancer Causes Control*. 2012; 23 (1): 175-85

[331] Mackintosh JA, Marshall HM, Yang IA, et al. A retrospective study of volume doubling time in surgically resected non-small cell lung cancer. *Respirology*. 2014; 19 (5): 755-62

[332] Sharial M, Teo M, Doherty M, et al. Modern imaging technique assessment of small cell lung cancer doubling time. *Journal of Clinical Oncology*. 2017; 30 (15):

[333] Chien CR, Lai MS, Chen TH. Estimation of mean sojourn time for lung cancer by chest X-ray screening with a Bayesian approach. *Lung Cancer*. 2008; 62 (2): 215-20

[334] Ten Haaf K, Bastani M, Cao P, et al. A comparative modeling analysis of risk-based lung cancer screening strategies. *J Natl Cancer Inst*. 30.09.2019 [Epub ahead of print]:

[335] Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013; 368 (8): 728-36

[336] Volk RJ, Mendoza TR, Hoover DS, et al. Reliability of self-reported smoking history and its implications for lung cancer screening. *Prev Med Rep*. 2020; 17: 101037

[337] Herth FJF, Reinmuth N, Wormanns D, et al. Positionspapier der Deutschen Röntgengesellschaft und der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin zu einem qualitätsgesicherten Früherkennungsprogramm des Lungenkarzinoms mittels Niedrigdosis-CT. *Pneumologie*. 2019; 73 (10): 573-7

[338] American College of Radiology. *Lung-RADS Version 1.1: Assessment Categories*. Available from: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf?la=en [cited 04.05.2020].

[339] Teo BS, Li E, Tan C, et al. Educational pamphlets for improving uptake of cancer screening: a systematic review. *Journal of Primary Health Care*. 2019; 11 (3): 207-16

[340] Fukunaga MI, Halligan K, Kodela J, et al. Tools to promote shared decision making in lung cancer screening using low-dose computerized tomography: a systematic review. *Chest*. 2020; 03: 03

[341] Ustun C, Ceber E. Ethical issues for cancer screenings. Five countries--four types of cancer. *Prev Med*. 2004; 39 (2): 223-9

[342] Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *J Med Libr Assoc*. 2006; 94 (4): 451-5

[343] Lefebvre C, Manheimer E, Glanville J. *Searching for studies*. 03.2011; Available from: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm [cited 05.09.2018].

[344] Black C, Bagust A, Boland A, et al. The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews. *Health Technol Assess*. 2006; 10 (3): 1-90

[345] Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer. *Cochrane Database Syst Rev*. 2013; (6): CD001991

[346] Wormanns D, Kauczor HU, Antoch G, et al. Joint Statement of the German Radiological Society and the German Respiratory Society on a Quality-Assured Early Detection Program for Lung Cancer with Low-Dose CT. *Rofo*. 2019; 191 (11): 993-7

[347] Marzo-Castillejo M, Vela-Vallespín C, Bellas-Beceiro B, et al. Recomendaciones de prevención del cáncer. Actualización PAPPS 2018. *Aten Primaria*. 2018; 50 Suppl 1 (Suppl 1): 41-65

[348] Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. *Lancet Oncol*. 2017; 18 (12): e754-e66

[349] Kauczor HU, Bonomo L, Gaga M, et al. ESR/ERS white paper on lung cancer screening. *Eur Radiol*. 2015; 25 (9): 2519-31

[350] American College of Radiology. *ACR Appropriateness Criteria(R). Lung Cancer Screening*. Available from: https://acsearch.acr.org/docs/3102390/Narrative/ [cited 27.07.2020].

[351] Wender RC, Brawley OW, Fedewa SA, et al. A blueprint for cancer screening and early detection: Advancing screening's contribution to cancer control. *CA Cancer Journal for Clinicians*. 2019; 69 (1): 50-79

[352] Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement. *Am J Respir Crit Care Med*. 2017; 196 (7): e15-e29

[353] Canadian Association of Radiologist. *Guide on screenint for lung cancer*. Available from: https://car.ca/wp-content/uploads/CT-Screening-for-Lung-Cancer-2017.pdf [cited 27.07.2020].

[354] Prabhash K, Advani SH, Batra U, et al. Biomarkers in Non-Small Cell Lung Cancers: Indian Consensus Guidelines for Molecular Testing. *Adv Ther*. 2019; 36 (4): 766-85

[355] Zhou Q, Fan Y, Wang Y, et al. [China National Lung Cancer Screening Guideline with Low-dose Computed Tomography (2018 version)]. *Zhongguo Fei Ai Za Zhi*. 2018; 21 (2): 67-75

[356] Jazieh A, Alghamdi M, Alghanem S, et al. Saudi lung cancer prevention and screening guidelines. *Ann Thorac Med*. 2018; 13 (4): 198-204

[357] Jang SH, Sheen S, Kim HY, et al. The Korean guideline for lung cancer screening. [Korean]. *J Korean Med Sci*. 2015; 58 (4): 291-301

[358] Koegelenberg CFN, Dorfman S, Schewitz I, et al. Recommendations for lung cancer screening in Southern Africa. *J Thorac Dis*. 2019; 11 (9): 3696-703

[359] Standing Committee on Screening, Australian Government Department of Health. *Position Statement: Lung Cancer Screening using Low-Dose Computed Tomography*. Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/EA40B7C67280E5C8CA257CEE00012DA1/$File/Position%20Statement-%20Lung%20Cancer%20Screening%20using%20Low-Dose%20Computed%20Tomography.pdf [cited 27.07.2020].

APPENDIX 1: DOCUMENTATION OF THE SEARCH STRATEGIES

Documentation of the Search Strategies for research question 1 (from S19-02)

1) Focused search for SRs/HTAs

The search lines for population and intervention (in MEDLNE search lines 1 to 13) were taken from Snowsill 2018 [2] and adapted for the other databases.

1. MEDLINE

Search Interface: Ovid

Ovid MEDLINE(R) ALL 1946 to January 28, 2019

The following filter was adopted:

Systematic Review: Wong [342]– High specificity strategy

#	Searches
1	exp Lung Neoplasms/
2	((lung$ or bronch$ or pulmon$) adj3 (cancer$ or neopla$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or small cell or squamous)).ti,ab,ot,kw.
3	(NSLC or NSCLC or SLC or SCLC).ti,ab,ot,kw.
4	1 or 2 or 3
5	exp Tomography, X-Ray Computed/
6	((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw.
7	((computer$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw.
8	(tomogra$ or helix or helical or spiral$ or spiro$).ti,ab,ot,kw.
9	5 or 6 or 7 or 8
10	((low$ adj3 dos$) or LDCT).ti,ab,kw,ot.
11	((ultralow$ or ultra-low$) adj3 dos$).ti,ab,kw,ot.
12	(low-dos$ or ultralow-dos$).ti,ab,kw,ot.
13	10 or 11 or 12
14	4 and 9 and 13
15	Cochrane database of systematic reviews.jn.
16	(search or MEDLINE or systematic review).tw.
17	meta analysis.pt.
18	or/15-17
19	14 and 18
20	screening*.mp.
21	4 and 9 and 18 and 20
22	19 or 21

2. The Cochrane Library

Search Interface: Wiley

Cochrane Database of Systematic Reviews, Issue 1 of 12, January 2019

ID	Search
#1	[mh "Lung Neoplasms"]
#2	((lung* or bronch* or pulmon*) NEAR/3 (cancer* or neopla* or tumor* or tumour* or carcinoma* or

	adenocarcinoma* or small cell or squamous)):ti,ab,kw
#3	(NSLC or NSCLC or SLC or SCLC):ti,ab,kw
#4	#1 or #2 or #3
#5	[mh "Tomography, X-Ray Computed"]
#6	((CT or CAT) NEAR/3 (scan* or screen*)):ti,ab,kw
#7	((computer* NEAR/3 tomogra*) and (scan* or screen*)):ti,ab,kw
#8	(tomogra* or helix or helical or spiral* or spiro*):ti,ab,kw
#9	#5 or #6 or #7 or #8
#10	((low* NEAR/3 dos*) or LDCT):ti,ab,kw
#11	((ultralow* or ultra-low*) NEAR/3 dos*):ti,ab,kw
#12	(low-dos* or ultralow-dos*):ti,ab,kw
#13	#10 or #11 or #12
#14	#4 and #9 and #13
#15	screening*
#16	#4 and #9 and #15
#17	#14 OR #16 in Cochrane Reviews, Cochrane Protocols

3. Health Technology Assessment Database

Search Interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES
2	((lung* or bronch* or pulmon*) AND (cancer* or neopla* or tumor* or tumour* or carcinoma* or adenocarcinoma* or small cell or squamous))
3	#1 OR #2
4	MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES
5	((CT or CAT) AND (scan* or screen*))
6	((computer* AND tomogra*) and (scan* or screen*))
7	(tomogra* or helix or helical or spiral* or spiro*)
8	(#4 OR #5 or #6 or #7)
9	((low* AND dos*) or LDCT)
10	((ultralow* or ultra-low*) AND dos*)
11	(low-dos* or ultralow-dos*)
12	(#9 OR #10 OR #11)
13	(screen*)
14	(#3 AND #8 AND #12)
15	(#3 AND #8 AND #13)
16	(#14 OR #15)
17	(#14 OR #15) IN HTA

2) Additional search for primary studies in bibliographic databases

An update search for studies in bibliographic databases was conducted for the time period not covered by Snowsill 2018 (starting from 2017).

1. MEDLINE

Search Interface: Ovid

Ovid MEDLINE(R) 1946 to June 11, 2020

The following filters were adopted:

RCT: Lefebvre [343] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	exp Lung Neoplasms/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Tomography, X-Ray Computed/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	Mass Screening/
9	Early Detection of Cancer/
10	screen*.mp.
11	or/8-10
12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE).ab,ti.
13	randomized controlled trial.pt.
14	controlled clinical trial.pt.
15	(randomized or placebo or randomly or trial or groups).ab.
16	drug therapy.fs.
17	or/13-16
18	17 not (exp animals/ not humans.sh.)
19	and/3,7,11,18
20	and/3,11-12,18
21	or/19-20
22	21 not (comment or editorial).pt.
23	22 and (english or german).lg.
24	23 and 20161201:3000.(dt).

Search Interface: Ovid

Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations June 11, 2020

#	Searches
1	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
2	(compute* adj3 tomograph*).ab,ti.
3	(ct or ldct).ab,ti.
4	or/2-3
5	screen*.mp.
6	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE).ab,ti.
7	(clinical trial* or random* or placebo).ti,ab. or trial.ti.
8	and/1,4-5,7
9	and/1,5-7
10	or/8-9
11	10 not (comment or editorial).pt.
12	11 and (english or german).lg.
13	12 and 20161201:3000.(dt).

2. Embase

Search Interface: Ovid

Embase 1974 to 2020 June 11

The following filters were adopted:

RCT: Wong [342] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Lung tumor/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Computer assisted tomography/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	exp Mass screening/
9	Early diagnosis/
10	screen*.mp.
11	or/8-10
12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE).ab,ti.
13	(random* or double-blind*).tw.
14	placebo*.mp.
15	or/13-14
16	15 not (exp animal/ not exp human/)

#	Searches
17	and/3,7,11,16
18	and/3,11-12,16
19	or/17-18
20	19 not medline.cr.
21	20 not (Conference Abstract or Conference Review or Editorial).pt.
22	21 and (english or german).lg.
23	22 and 20161230:3000.(dc).

3. The Cochrane Library

Search Interface: Wiley

Cochrane Central Register of Controlled Trials Issue 6 of 12, June 2020

ID	Search
#1	[mh "Lung Neoplasms"]
#2	(lung NEAR/1 (cancer* or tumor* or tumour* or neoplasm*)):ti,ab
#3	#1 or #2
#4	[mh "Tomography, X-Ray Computed"]
#5	(compute* NEAR/3 tomograph*):ti,ab
#6	(ct or ldct):ti,ab
#7	#4 or #5 or #6
#8	[mh ^"Mass Screening"]
#9	[mh ^"Early Detection of Cancer"]
#10	screen*:ti,ab,kw
#11	#8 or #9 or #10
#12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE):ab,ti
#13	#3 AND #7 AND #11
#14	#3 AND #11 AND #12
#15	#13 OR #14 with Publication Year from 2017 to present, in Trials

3) Search in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

URL: http://www.clinicaltrials.gov

Input surface: Advanced Search

Search strategy
lung cancer AND (computed tomography OR CT OR LDCT) AND screening

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

URL: http://apps.who.int/trialsearch/

Input surface: Standard Search

Search strategy
lung cancer AND computed tomography OR lung cancer AND CT OR lung cancer AND LDCT

Documentation of the Search Strategies for research question 2

1) Search in bibliographic databases

1. MEDLINE

Search Interface: Ovid

Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations June 30, 2020

#	Searches
1	(lung adj3 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
2	(compute* adj5 tomograph*).ab,ti.
3	(ct or ldct).ab,ti.
4	or/2-3
5	screen*.mp.
6	dna.mp.
7	(genetic or gene).mp.
8	biomarker*.ab,ti.
9	(antibod* or autoantibod*).ab,ti.
10	((biological* or molecular* or tumor*) adj3 marker*).ab,ti.
11	(microRNA or miRNA).mp.
12	or/6-11
13	and/1,4-5,12

Search Interface: Ovid

Ovid MEDLINE(R) 1946 to June 30, 2020

#	Searches
1	exp Lung Neoplasms/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Tomography, X-Ray Computed/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	Mass Screening/
9	Early Detection of Cancer/
10	screen*.mp.
11	or/8-10
12	exp Biomarkers/
13	Enzyme Linked Immunosorbent Assay/
14	Autoantibodies/
15	dna.mp.
16	(genetic or gene).mp.
17	418
18	(antibod* or autoantibod*).ab,ti.
19	((biological* or molecular* or tumor*) adj3 marker*).ab,ti.
20	(microRNA or miRNA).mp.
21	or/12-20
22	and/3,7,11,21
23	22 not (exp animals/ not humans.sh.)
24	23 not (comment or editorial).pt.

2. Embase

Search Interface: Ovid

Embase 1974 to 2020 June 30

The following filters were adopted:

- Systematic Review: Wong [342] – High specificity strategy
- RCT: Wong [342] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Lung tumor/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Computer assisted tomography/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	exp Mass screening/
9	Early diagnosis/
10	screen*.mp.
11	or/8-10
12	exp Tumor marker/
13	Biological marker/
14	biomarker*.ab,ti.
15	(antibod* or autoantibod*).mp.
16	((biological* or molecular* or tumor*) adj3 marker*).ab,ti.
17	(microRNA or miRNA).mp.
18	dna.mp.
19	(genetic or gene).mp.
20	complement component.mp.
21	or/12-20
22	(random* or double-blind*).tw.
23	placebo*.mp.
24	or/22-23
25	(meta analysis or systematic review or MEDLINE).tw.
26	or/24-25
27	and/3,7,11,21,26
28	27 not medline.cr.
29	28 not (exp animal/ not exp human/)
30	29 not (Conference Abstract or Conference Review or Editorial).pt.

3. The Cochrane Library

Search Interface: Wiley

Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2020

Cochrane Database of Systematic Reviews Issue 7 of 12, July 2020

ID	Search
#1	[mh "Lung Neoplasms"]
#2	(lung NEAR/1 (cancer* or tumor* or tumo?r* or neoplasm*)):ti,ab
#3	#1 or #2
#4	[mh "Tomography, X-Ray Computed"]
#5	(compute* NEAR/3 tomograph*):ti,ab
#6	(ct or ldct):ti,ab
#7	#4 or #5 or #6
#8	[mh ^"Mass Screening"]
#9	[mh ^"Early Detection of Cancer"]
#10	screen*:ti,ab
#11	#8 or #9 or #10
#12	[mh "Biomarkers"]
#13	[mh ^"Enzyme Linked Immunosorbent Assay"]
#14	[mh ^"Autoantibodies"]
#15	dna
#16	genetic or gene
#17	biomarker*:ti,ab
#18	(antibod* or autoantibod*):ti,ab
#19	((biological* or molecular* or tumor*) NEAR/3 marker*):ti,ab
#20	microRNA or miRNA
#21	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#3 and #7 and #11 and #21 in Cochrane Reviews, Cochrane Protocols, Trials

2) Search in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

URL: http://www.clinicaltrials.gov

Input surface: Expert Search

Search strategy
lung cancer AND (computed tomography OR CT OR LDCT) AND screening AND (dna OR genetic OR gene OR biomarker OR marker OR antibody OR autoantibody OR microRNA OR miRNA)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

URL: http://apps.who.int/trialsearch/

Input surface: Advanced Search

Search strategy
lung cancer AND screening AND dna OR lung cancer AND screening AND genetic OR lung cancer AND screening AND gene OR lung cancer AND screening AND biomarker* OR lung cancer AND screening AND marker* OR lung cancer AND screening AND antibod* OR lung cancer AND screening AND autoantibod* OR lung cancer AND screening AND microRNA OR lung cancer AND screening AND miRNA

Documentation of the Search Strategies for research question 4

1) Search in bibliographic databases

1. MEDLINE

Search Interface: Ovid

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July 22, 2020

#	Searches
1	exp Lung Neoplasms/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	1 or 2
4	Mass Screening/
5	Early Detection of Cancer/
6	screen*.mp.
7	4 or 5 or 6
8	3 and 7
9	exp Information Dissemination/
10	exp Decision Making, Shared/
11	exp Consumer Health Information/
12	exp Advertising/
13	exp Health Knowledge, Attitudes, Practice/
14	exp Health Communication/
15	exp Decision Making/
16	exp Informed Consent/
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	(inform* adj3 (patient* or consumer* or customer* or client* or population* or smoker* or person*)).ti,ab.
19	(health adj3 inform*).ti,ab.
20	(inform* adj3 (strateg* or service* or campaign*)).ti,ab.
21	(inform* and (brochure* or leaflet* or handout* or material* or booklet* or pamphlet* or sheet*)).ti,ab.
22	(advert* or communic*).ti,ab.
23	(decision* adj3 (aid* or support* or making)).ti,ab.
24	18 or 19 or 20 or 21 or 22 or 23
25	17 or 24
26	8 and 25

2. Embase

Search Interface: Ovid

Embase 1974 to 2020 July 22

#	Searches
1	exp Lung tumor/
2	(lung adj1 (cancer* or tumor* or tumo?r* or neoplasm*)).ab,ti.
3	1 or 2
4	exp Mass screening/
5	Early diagnosis/
6	screen*.mp.
7	4 or 5 or 6
8	3 and 7
9	exp information dissemination/
10	exp shared decision making/
11	exp consumer health information/
12	exp advertising/
13	exp attitude to health/
14	exp medical information/
15	exp decision making/
16	exp informed consent/
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18	(inform* and (brochure* or leaflet* or handout* or material* or booklet* or pamphlet* or sheet*)).ti,ab.
19	(advert* or communic*).ti,ab.
20	(decision* adj3 (aid* or support* or making)).ti,ab.
21	(inform* adj3 (patient* or consumer* or customer* or client* or population* or smoker* or person*)).ti,ab.
22	(health adj3 inform*).ti,ab.
23	(inform* adj3 (strateg* or service* or campaign*)).ti,ab.
24	18 or 19 or 20 or 21 or 22 or 23
25	17 or 24
26	8 and 25
27	limit 26 to conference abstracts
28	26 not 27

3. The Cochrane Library

Search Interface: Wiley

Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2020

Cochrane Database of Systematic Reviews Issue 7 of 12, July 2020

ID	Search
#1	[mh "Lung Neoplasms"]
#2	(lung NEAR/1 (cancer* or tumor* or tumour* or neoplasm*)):ti,ab
#3	#1 OR #2
#4	[mh ^"Mass Screening"]
#5	[mh ^"Early Detection of Cancer"]
#6	screen*:ti,ab,kw
#7	#4 OR #5 OR #6
#8	#3 AND #7
#9	MeSH descriptor: [Information Dissemination] explode all trees
#10	MeSH descriptor: [Decision Making, Shared] explode all trees
#11	MeSH descriptor: [Consumer Health Information] explode all trees
#12	MeSH descriptor: [Advertising] explode all trees
#13	MeSH descriptor: [Health Knowledge, Attitudes, Practice] explode all trees
#14	MeSH descriptor: [Health Communication] explode all trees
#15	MeSH descriptor: [Decision Making] explode all trees
#16	MeSH descriptor: [Informed Consent] explode all trees
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	(inform* NEAR/3 (patient* or consumer* or customer* or client* or population* or smoker* or person*)):ti,ab
#19	(health NEAR/3 inform*):ti,ab
#20	(inform* NEAR/3 (strateg* or service* or campaign*)):ti,ab
#21	(inform* AND (brochure* or leaflet* or handout* or material* or booklet* or pamphlet* or sheet*)):ti,ab
#22	(advert* or communic*):ti,ab
#23	(decision* NEAR/3 (aid* or support* or making)):ti,ab
#24	#18 OR #19 OR #20 OR #21 OR #22 #23
#25	#17 OR #24
#26	#8 AND #25
#27	(*clinicaltrials*gov* OR *who*trialsearch* OR *clinicaltrialsregister*eu* OR *anzctr*org*au* OR *trialregister*nl* OR *irct*ir* OR *isrctn*org* OR *controlled-trials*com* OR *drks*de*):so
#28	#26 NOT #27

APPENDIX 2: RESEARCH QUESTION 1 – LIST OF CHECKED SYSTEMATIC REVIEWS

1. Coureau G, Salmi LR, Etard C, Sancho-Garnier H, Sauvaget C, Mathoulin-Pelissier S. Low-dose computed tomography screening for lung cancer in populations highly exposed to tobacco: a systematic methodological appraisal of published randomised controlled trials. Eur J Cancer 2016; 61: 146-156.

2. Fu C, Liu Z, Zhu F, Li S, Jiang L. A meta-analysis: is low-dose computed tomography a superior method for risky lung cancers screening population? Clin Respir J 2016; 10(3): 333-341.

3. Humphrey L, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP et al. Screening for lung cancer: systematic review to update the U.S. Preventive Services Task Force; AHRQ publication no. 13-05188-EF-1 [online]. 07.2013 [Zugriff: 23.09.2019]. (Evidence Syntheses; Band 105). URL: https://www.ncbi.nlm.nih.gov/books/NBK154610/pdf/Bookshelf_NBK154610.pdf.

4. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the U.S. Preventive Services Task Force. Ann Intern Med 2013; 159(6): 411-420.

5. Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ et al. Screening for lung cancer. Cochrane Database Syst Rev 2013; (6): CD001991.

6. Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS et al. Screening for lung cancer: CHEST guideline and expert panel report. Chest 2018; 153(4): 954-985.

7. Seigneurin A, Field JK, Gachet A, Duffy SW. A systematic review of the characteristics associated with recall rates, detection rates and positive predictive values of computed tomography screening for lung cancer. Ann Oncol 2014; 25(4): 781-791.

8. Slatore CG, Sullivan DR, Pappas M, Humphrey LL. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. J Thorac Oncol 2014; 9(7): 927-934.

9. Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technol Assess 2018; 22(69): 1-276.

10. Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D et al. Screening for lung cancer: a systematic review and meta-analysis. Prev Med 2016; 89: 301-314.

11. Wang X, Liu H, Shen Y, Li W, Chen Y, Wang H. Low-dose computed tomography (LDCT) versus other cancer screenings in early diagnosis of lung cancer: a meta-analysis. Medicine 2018; 97(27): e11233.

APPENDIX 3: QUALITY ASSESSMENT OF THE SYSTEMATIC REVIEWS INCLUDED IN RESEARCH QUESTION 1

Table A1: Quality assessment of the SRs included in research question 1

Snowsill 2018 [2]	**Yes/No/NA**	**Explanations**
1. Were at least 2 different types of information sources searched (e.g. bibliographic databases and study registries)? Please list all types of information sources reported.	Yes	1. Bibliographic databases 2. Reference lists 3. Study registries (ongoing studies)
2. Were at least 2 different bibliographic databases searched? Please list all bibliographic databases reported.	Yes	MEDLINE, Embase, Health Management Information Consortium, PsycINFO, Web of Science, Cochrane Library, CINAHL
3. Was the search period or search date reported? Please specify.	Yes	The HTA report of Snowsill is an update oft he HTA report of the Aberdeen HTA Group and a supplement of a Cochrane reviews ([344] and [345]) Update search period: January 2004 to January 2017
4. Were at least the most important free-text terms or subject headings of the search strategy reported?	Yes	Presentation of the search strategies in the appendix
Assessment (Questions 1.-4. All questions answered with “yes” = comprehensive information retrieval; one or more questions answered with no = questionable quality) a)	Yes	Comprehensive with restriction to English language publications

Abbreviations: NA=not applicable; SR=systematic review

[a] Information sources listed in report plan S19-02 that were not considered in the SR or were not searched comprehensively (e.g. study registries) were searched in the context of information retrieval without time limit.

APPENDIX 4: LIST OF EXCLUDED STUDIES

Table A2: Research question 1: List of excluded studies (full text level) with reasons for exclusion

Clinical effectiveness and safety

Reference	Main reason for exclusion (full text level)
Ardila D, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng A2:A39 computed tomography. Nature Medicine 2019; 25(6): 954-961.	*wrong study design*
Balagurunathan Y, Beers A, Kalpathy-Cramer J, McNitt-Gray M, Hadjiiski L, Zhao B et al. Semi-automated pulmonary nodule interval segmentation using the NLST data. Medical Physics 2018; 45(3): 1093-1107.	*wrong study design*
Berg CD. Screening with low-dose computed tomography reduced lung cancer mortality in high-risk patients. Annals of Internal Medicine 2011; 155(10): JC5-6.	*wrong study design*
Block JP. Screening for lung cancer with low-dose CT scans reduces lung cancer mortality. Journal of Clinical Outcomes Management 2011; 18(8): 343-345.	*wrong study design*
Bronte G, Rolfo C. Semi-automated volumetric analysis in the NELSON trial for lung cancer screening: is there room for diagnostic experience yet? J Thorac Dis 2016; 8(11): E1490-E1492.	*wrong study design*
Cattaneo SM 2nd, Meisenberg BR, Geronimo MCM, Bhandari B, Maxted JW, Brady-Copertino CJ. Lung cancer screening in the community setting. Annals of Thoracic Surgery 2018; 105(6): 1627-1632.	*wrong study design*
Charbonnier JP, Chung K, Scholten ET, Van Rikxoort EM, Jacobs C, Sverzellati N et al. Automatic segmentation of the solid core and enclosed vessels in subsolid pulmonary nodules. Scientific Reports 2018; 8(1): 646.	*wrong study design*
Chung K, Jacobs C, Scholten ET, Mets OM, Dekker I, Prokop M et al. Malignancy estimation of Lung-RADS criteria for subsolid nodules on CT: accuracy of low and high risk spectrum when using NLST nodules. European Radiology 2017; 27(11): 4672-4679.	*wrong study design*
Ciompi F, Chung K, Van Riel SJ, Setio AAA, Gerke PK, Jacobs C et al. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. Scientific Reports 2017; 7: 46479.	*wrong study design*
Couraud S, Milleron B. Lung cancer screening: what is new since the NLST results? Curr Pulmonol Rep 2016; 5(2): 130-139.	*wrong study design*
Coureau G, Delva F. Lung cancer screening among the smoker population. Bulletin du Cancer 2019; 106(7-8): 693-702.	*wrong language*
Cressman S, Peacock SJ, Tammemagi MC, Evans WK, Leighl NB, Goffin JR et al. The cost-effectiveness of high-risk lung cancer screening and drivers of program efficiency. Journal of Thoracic Oncology 2017; 12(8): 1210-1222.	*wrong study design*
Dawson Q. NELSON trial: reduced lung-cancer mortality with volume CT screening. Lancet Respir Med 2020; 8(3): 236.	*wrong type of publication*

Falaschi F, Romei C, Fiorini S, Lucchi M. Imaging of malignant pleural mesothelioma: it is possible a screening or early diagnosis program?-a systematic review about the use of screening programs in a population of asbestos exposed workers. Journal of Thoracic Disease 2018; 10(Suppl 2): S262-S268.	*wrong population*
Field JK, Duffy SW, Baldwin DR. Patient selection for future lung cancer computed tomography screening programmes: lessons learnt post National Lung Cancer Screening Trial. Transl Lung Cancer Res 2018; 7(Suppl 2): S114-S116.	*wrong type of publication*
Frille A, Hardavella G, Lee R. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. Breathe 2020; 16(1): 190322.	*wrong type of publication*
Fu M, Travier N, Martin-Sanchez JC, Martinez-Sanchez JM, Vidal C, Garcia M. Identifying high-risk individuals for lung cancer screening: going beyond NLST criteria. PLoS ONE 2018; 13(4): e0195441.	*wrong study design*
Fu SS, Rothman AJ, Vock DM, Lindgren B, Almirall D, Begnaud A et al. Program for lung cancer screening and tobacco cessation: study protocol of a sequential, multiple assignment, randomized trial. Contemporary Clinical Trials 2017; 60: 86-95.	*wrong intervention*
Goldwasser DL. Estimation of the tumor size at cure threshold among aggressive non-small cell lung cancers (NSCLCs): evidence from the Surveillance, Epidemiology, and End Results (SEER) Program and the National Lung Screening Trial (NLST). International Journal of Cancer 2017; 140(6): 1280-1292.	*wrong study design*
Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, Oudkerk M. An update on the European lung cancer screening trials and comparison of lung cancer screening recommendations in Europe. Journal of Thoracic Imaging 2019; 34(1): 65-71.	*wrong study design*
Hassannezhad R, Vahed N. Prediction of the risk of malignancy among detected lung nodules in the National Lung Screening Trial. Journal of the American College of Radiology 2018; 15(11): 1529-1535.	*wrong study design*
Hawkins S, Wang H, Liu Y, Garcia A, Stringfield O, Krewer H et al. Predicting malignant nodules from screening CT scans. Journal of Thoracic Oncology 2016; 11(12): 2120-2128.	*wrong study design*
Hekmat K, Bruns CJ. NELSON-Studie 2020: Aufruf zum Lungenkrebs-CT-Screening von Risikopersonen. Chirurg 2020; 91(6): 515.	*wrong type of publication*
Hopkins RJ, Ko J, Gamble GD, Young RP. Airflow limitation and survival after surgery for non-small cell lung cancer: results from a systematic review and lung cancer screening trial (NLST-ACRIN sub-study). Lung Cancer 2019; 135: 80-87.	*wrong study design*
Hostetter JM, Morrison JJ, Morris M, Jeudy J, Wang KC, Siegel E. Personalizing lung cancer risk prediction and imaging follow-up recommendations using the National Lung Screening Trial dataset. Journal of the American Medical Informatics Association 2017; 24(6): 1046-1051.	*wrong study design*
Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis. BMC Pulmonary Medicine 2019; 19(1): 126.	*wrong study design*

Infante M, Sestini S, Galeone C, Marchiano A, Lutman FR, Angeli E et al. Lung cancer screening with low-dose spiral computed tomography: evidence from a pooled analysis of two Italian randomized trials. European Journal of Cancer Prevention 2017; 26(4): 324-329.	*wrong study design*
Lessmann N, Van Ginneken B, Zreik M, De Jong PA, De Vos BD, Viergever MA et al. Automatic calcium scoring in low-dose chest CT using deep neural networks with dilated convolutions. IEEE Transactions on Medical Imaging 2018; 37(2): 615-625.	*wrong study design*
Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ et al. Screening for lung cancer. Cochrane Database of Systematic Reviews 2013; (6): CD001991.	*wrong study design*
Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. Jama 2011; 306(17): 1865-1873.	*wrong intervention*
Ostrowski M, Marjanski T, Rzyman W. Low-dose computed tomography screening reduces lung cancer mortality. Advances in Medical Sciences 2018; 63(2): 230-236.	*wrong study design*
Park JS, Kang B, Park Y, Park SJ, Cheon JH, Jung M et al. Screening for Lung Cancer Using Low-dose Chest Computed Tomography in Korean Long-term Colorectal Cancer Survivors. Journal of Cancer Prevention 2019; 24(1): 48-53.	*wrong population*
Pasquinelli MM, Kovitz KL, Koshy M, Menchaca MG, Liu L, Winn R et al. Outcomes from a minority-based lung cancer screening program vs the National Lung Screening Trial. JAMA Oncology 2018; 4(9): 1291-1293.	*wrong study design*
Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A et al. Erratum: "Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy" (Ann Oncol 2019; 30(7): 1162-1169). Annals of Oncology 05.06.2019 [Epub ahead of print].	*wrong type of publication*
Paul R, Hawkins SH, Schabath MB, Gillies RJ, Hall LO, Goldgof DB. Predicting malignant nodules by fusing deep features with classical radiomics features. J Med Imaging (Bellingham) 2018; 5(1): 011021.	*wrong study design*
Peikert T, Duan F, Rajagopalan S, Karwoski RA, Clay R, Robb RA et al. Novel high-resolution computed tomography-based radiomic classifier for screen-identified pulmonary nodules in the National Lung Screening Trial. PLoS ONE 2018; 13(5): e0196910.	*wrong study design*
Ronit A, Kristensen T, Klitbo DM, Gelpi M, Kalhauge A, Benfield T et al. Incidental lung cancers and positive computed tomography images in people living with HIV. AIDS 2017; 31(14): 1973-1977.	*wrong population*
Rota M, Pizzato M, La Vecchia C, Boffetta P. Efficacy of lung cancer screening appears to increase with prolonged intervention: results from the MILD trial and a meta-analysis. Annals of Oncology 02.05.2019 [Epub ahead of print].	*wrong study design*
Sagawa M, Sugawara T, Ishibashi N, Koyanagi A, Kondo T, Tabata T. Efficacy of low-dose computed tomography screening for lung cancer: the current state of evidence of mortality reduction. Surgery Today 2017; 47(7): 783-788.	*wrong study design*

Schabath MB, Aberle DR. MILD trial, strong confirmation of lung cancer screening efficacy. Nature Reviews: Clinical Oncology 2019; 16(9): 529-530.	*wrong study design*
Shen S, Han SX, Petousis P, Weiss RE, Meng F, Bui AA et al. A Bayesian model for estimating multi-state disease progression. Computers in Biology and Medicine 2017; 81: 111-120.	*wrong study design*
Silva M, Schaefer-Prokop CM, Jacobs C, Capretti G, Ciompi F, Van Ginneken B et al. Detection of subsolid nodules in lung cancer screening: complementary sensitivity of visual reading and computer-aided diagnosis. Investigative Radiology 2018; 53(8): 441-449.	*wrong study design*
Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technology Assessment 2018; 22(69): 1-276.	*wrong study design*
Tammemagi MC, Ten Haaf K, Toumazis I, Kong CY, Han SS, Jeon J et al. Development and validation of a multivariable lung cancer risk prediction model that includes low-dose computed tomography screening results: a secondary analysis of data from the National Lung Screening Trial. JAMA Network Open 2019; 2(3): e190204.	*wrong study design*
Tanner NT, Dai L, Bade BC, Gebregziabher M, Silvestri GA. Assessing the generalizability of the National Lung Screening Trial: comparison of patients with stage 1 disease. American Journal of Respiratory and Critical Care Medicine 2017; 196(5): 602-608.	*wrong study design*
Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK et al. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. PLoS Med 2017; 14(4): e1002277.	*wrong study design*
Van Riel SJ, Ciompi F, Jacobs C, Winkler Wille MM, Scholten ET, Naqibullah M et al. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines. European Radiology 2017; 27(10): 4019-4029.	*wrong study design*
Van Riel SJ, Ciompi F, Winkler Wille MM, Dirksen A, Lam S, Scholten ET et al. Malignancy risk estimation of pulmonary nodules in screening CTs: comparison between a computer model and human observers. PLoS ONE 2017; 12(11): e0185032.	*wrong study design*
Van Riel SJ, Jacobs C, Scholten ET, Wittenberg R, Winkler Wille MM, De Hoop B et al. Observer variability for Lung-RADS categorisation of lung cancer screening CTs: impact on patient management. European Radiology 2019; 29(2): 924-931.	*wrong study design*
Wang X, Liu H, Shen Y, Li W, Chen Y, Wang H. Low-dose computed tomography (LDCT) versus other cancer screenings in early diagnosis of lung cancer: a meta-analysis. Medicine 2018; 97(27): e11233.	*wrong study design*
White CS, Dharaiya E, Campbell E, Boroczky L. The Vancouver Lung Cancer Risk Prediction Model: assessment by using a subset of the National Lung Screening Trial cohort. Radiology 2017; 283(1): 264-272.	*wrong study design*
Winter A, Aberle DR, Hsu W. External validation and recalibration of the Brock model to predict probability of cancer in pulmonary nodules using NLST data. Thorax 2019; 74(6): 551-563.	*wrong study design*

Yang W, Qian F, Teng J, Wang H, Manegold C, Pilz LR et al. Community-based lung cancer screening with low-dose CT in China: results of the baseline screening. Lung Cancer 2018; 117: 20-26.	*wrong population*
Young S, Lo P, Kim G, Brown M, Hoffman J, Hsu W et al. The effect of radiation dose reduction on computer-aided detection (CAD) performance in a low-dose lung cancer screening population. Medical Physics 2017; 44(4): 1337-1346.	*wrong study design*

Table A3: Research question 2: List of excluded studies (full text level) with reasons for exclusion

Clinical effectiveness and safety

Reference	Main reason for exclusion (full text level)
Carozzi, F. M.; Bisanzi, S.; Carrozzi, L.; Falaschi, F.; Lopes Pegna, A.; Mascalchi, M.; Picozzi, G.; Peluso, M.; Sani, C.; Greco, L.; Ocello, C.; Paci, E.; Italung Working Group Multimodal lung cancer screening using the ITALUNG biomarker panel and low dose computed tomography. Results of the ITALUNG biomarker study. International Journal of Cancer 2017; 141(1):94-101	*wrong comparison*
Chu, G. C. W.; Lazare, K.; Sullivan, F. Serum and blood based biomarkers for lung cancer screening: a systematic review. BMC Cancer 2018; 18(1):181	*wrong comparison*
Clark, M. E.; Bedford, L. E.; Young, B.; Robertson, J. F. R.; das Nair, R.; Vedhara, K.; Littleford, R.; Sullivan, F. M.; Mair, F. S.; Schembri, S.; Rauchhaus, P.; Kendrick, D. Lung cancer CT screening: Psychological responses in the presence and absence of pulmonary nodules. Lung Cancer 2018; 124():160-167	*wrong comparison*
Gyoba, J.; Shan, S.; Roa, W.; Bedard, E. L. Diagnosing Lung Cancers through Examination of Micro-RNA Biomarkers in Blood, Plasma, Serum and Sputum: A Review and Summary of Current Literature. International Journal of Molecular Sciences 2016; 17(4):494	*wrong comparison*
Heuvelmans, M. A.; Vonder, M.; Rook, M.; Groen, H. J. M.; De Bock, G. H.; Xie, X.; Ijzerman, M. J.; Vliegenthart, R.; Oudkerk, M. Screening for Early Lung Cancer, Chronic Obstructive Pulmonary Disease, and Cardiovascular Disease (the Big-3) Using Low-dose Chest Computed Tomography: Current Evidence and Technical Considerations. Journal of Thoracic Imaging 2019; 34(3):160-169	*wrong study design*
Hubers, A. J.; Heideman, D. A.; Duin, S.; Witte, B. I.; de Koning, H. J.; Groen, H. J.; Prinsen, C. F.; Bolijn, A. S.; Wouters, M.; van der Meer, S. E.; Steenbergen, R. D.; Snijders, P. J.; Uyterlinde, A.; Berkhof, H.; Smit, E. F.; Thunnissen, E. DNA hypermethylation analysis in sputum of asymptomatic subjects at risk for lung cancer participating in the NELSON trial: argument for maximum screening interval of 2 years. Journal of Clinical Pathology 2017; 70(3):250-254	*wrong comparison*
Seijo, L. M.; Peled, N.; Ajona, D.; Boeri, M.; Field, J. K.; Sozzi, G.; Pio, R.; Zulueta, J. J.; Spira, A.; Massion, P. P.; Mazzone, P. J.; Montuenga, L. M. Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2019; 14(3):343-357	*wrong study design*
Sullivan, F. M.; Farmer, E.; Mair, F. S.; Treweek, S.; Kendrick, D.; Jackson, C.; Robertson, C.; Briggs, A.; McCowan, C.; Bedford, L.; Young, B.; Vedhara, K.; Gallant, S.; Littleford, R.; Robertson, J.; Sewell, H.; Dorward, A.; Sarvesvaran,	*wrong comparison*

J.; Schembri, S. Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT R- Lung Test (ECLS): study protocol for a randomized controlled trial. BMC Cancer 2017; 17(1):187	
Takx, R. A.; Vliegenthart, R.; Mohamed Hoesein, F. A.; Isgum, I.; de Koning, H. J.; Mali, W. P.; van der Aalst, C. M.; Zanen, P.; Lammers, J. W.; Groen, H. J.; van Rikxoort, E. M.; Schmidt, M.; van Ginneken, B.; Oudkerk, M.; Leiner, T.; de Jong, P. A. Pulmonary function and CT biomarkers as risk factors for cardiovascular events in male lung cancer screening participants: the NELSON study. European Radiology 2015; 25(1):65-71	*wrong intervention*
Wang, Z.; Wang, Y.; Huang, Y.; Xue, F.; Han, W.; Hu, Y.; Wang, L.; Song, W.; Jiang, J. Challenges and research opportunities for lung cancer screening in China. Cancer Communications 2018; 38(1):34	*wrong study design*
Yang, B.; Li, X.; Ren, T.; Yin, Y. Autoantibodies as diagnostic biomarkers for lung cancer: A systematic review. Cell Death Discovery 2019; 5():126	*wrong comparison*

Table A4: Research question 4: List of excluded studies (full text level) with reasons for exclusion

Clinical effectiveness and safety

Reference	**Main reason for exclusion (full text level)**
Begnaud, A.; Lindgren, B. Randomized electronic promotion of lung cancer screening. Chest 2016; 150(4):28A	*wrong type of publication*
Bellinger, Christina; Pinsky, Paul; Foley, Kristie; Case, Douglas; Dharod, Ajay; Miller, David Lung Cancer Screening Benefits and Harms Stratified by Patient Risk: Information to Improve Patient Decision Aids. Annals of the American Thoracic Society 2019; 16(4):512-514	*wrong intervention*
Darling, G.; Sandhu, N.; Mora, L. Recruitment Strategies for the Lung Cancer Screening. Journal of Thoracic Oncology 2018; 13(10):S273S274	*wrong type of publication*
Erkmen, Cherie P.; Mitchell, Mark; Randhawa, Simran; Sferra, Shelby; Kim, Rachel; DiSesa, Verdi; Kaiser, Larry R.; Ma, Grace X. An Enhanced Shared Decision Making Model to Address Willingness and Ability to Undergo Lung Cancer Screening and Follow-Up Treatment in Minority Underserved Populations. Journal of Community Health 2018; 43(1):27-32	*wrong intervention*
Fabbrini, Angela E.; Lillie, Sarah E.; Partin, Melissa R.; Fu, Steven S.; Clothier, Barbara A.; Bangerter, Ann K.; Nelson, David B.; Doro, Elizabeth A.; Bell, Brian J.; Rice, Kathryn L. Initial results of a lung cancer screening demonstration project: a local program evaluation. American Journal of Managed Care 2018; 24(6):272-277	*wrong outcomes*
Fagan, Heather Bittner; Fournakis, Nicole A.; Jurkovitz, Claudine; Petrich, Anett M.; Zhang, Zugui; Katurakes, Nora; Myers, Ronald E. Telephone-Based Shared Decision-making for Lung Cancer Screening in Primary Care. Journal of Cancer Education 2020; 35(4):766-773	*wrong outcomes*
Fraenkel, Liana; Peters, Ellen; Tyra, Shea; Oelberg, David Shared Medical Decision Making in Lung Cancer Screening: Experienced versus Descriptive Risk Formats. Medical Decision Making 2016; 36(4):518-25	*wrong intervention*
Fukunaga MI, Halligan K, Kodela J, Toomey S, Furtado V, Luckmann R, et al. Tools to promote shared decision making in lung cancer screening using low-dose computerized tomography: a systematic review. Chest. 2020;03:03	*wrong type of publication*

Golden, Sara E.; Ono, Sarah S.; Thakurta, Sujata G.; Wiener, Renda Soylemez; Iaccarino, Jonathan M.; Melzer, Anne C.; Datta, Santanu K.; Slatore, Christopher G. "I'm Putting My Trust in Their Hands": A Qualitative Study of Patients' Views on Clinician Initial Communication About Lung Cancer Screening. Chest 2020; 09():09	*wrong intervention*
Han, Paul K. J.; Lary, Christine; Black, Adam; Gutheil, Caitlin; Mandeville, Hayley; Yahwak, Jason; Fukunaga, Mayuko Effects of Personalized Risk Information on Patients Referred for Lung Cancer Screening with Low-Dose CT. Medical Decision Making 2019; 39(8):950-961	*wrong outcomes*
Hill, Paul Armstrong Current State of Shared Decision-Making for CT Lung Cancer Screening and Improvement Strategies. Journal of Patient Experience 2020; 7(1):49-52	*wrong intervention*
Hinshaw, Lisa B.; Jackson, Sharon A.; Chen, Michael Y. Direct mailing was a successful recruitment strategy for a lung-cancer screening trial. Journal of Clinical Epidemiology 2007; 60(8):853-7	*wrong outcomes*
Hudson, Janella N.; Quinn, Gwendolyn P.; Wilson, Lauren E.; Simmons, Vani N. Evaluation of Promotional Materials To Promote Low-Dose Computed Tomography (LDCT) Screening to High- Risk Consumers and Health Care Providers. Journal of Cancer Education 2018; 33(5):1043-1051	*wrong outcomes*
Lau, Yan Kwan; Caverly, Tanner J.; Cherng, Sarah T.; Cao, Pianpian; West, Mindy; Arenberg, Douglas; Meza, Rafael Development and validation of a personalized, web-based decision aid for lung cancer screening using mixed methods: a study protocol. JMIR Research Protocols 2014; 3(4):e78	*wrong study design*
Li, Chien-Ching; Matthews, Alicia K.; Wu, Tingqing Adaptation and Preliminary Evaluation of a Lung Cancer Screening Decision Tool for Older Chinese American Populations. Journal of the National Medical Association 2020; 27():27	*wrong intervention*
McDonnell, Karen Kane; Strayer, Scott M.; Sercy, Erica; Campbell, Callie; Friedman, Daniela B.; Cartmell, Kathleen B.; Eberth, Jan M. Developing and testing a brief clinic-based lung cancer screening decision aid for primary care settings. Health Expectations 2018; 21(4):796-804	*wrong outcomes*
Parker, A.; Knapp, P.; Treweek, S.; Madhurasinghe, V.; Littleford, R.; Gallant, S.; Sullivan, F.; Schembri, S.; Rick, J.; Graffy, J.; Collier, D. J.; Eldridge, S.; Kennedy, A.; Bower, P. The effect of optimised patient information materials on recruitment in a lung cancer screening trial: An embedded randomised recruitment trial 11 Medical and Health Sciences 1117 Public Health and Health Services. Trials [Electronic Resource] 2018; 19 (1) (no pagination)(503):	*wrong outcomes*
Parker, Adwoa; Knapp, Peter; Treweek, Shaun; Madhurasinghe, Vichithranie; Littleford, Roberta; Gallant, Stephanie; Sullivan, Frank; Schembri, Stuart; Rick, Jo; Graffy, Jonathan; Collier, David J.; Eldridge, Sandra; Kennedy, Anne; Bower, Peter The effect of optimised patient information materials on recruitment in a lung cancer screening trial: an embedded randomised recruitment trial. Trials [Electronic Resource] 2018; 19(1):503	*wrong outcomes*
Percac-Lima, Sanja; Ashburner, Jeffrey M.; Rigotti, Nancy A.; Park, Elyse R.; Chang, Yuchiao; Kuchukhidze, Salome; Atlas, Steven J. Patient navigation for lung cancer screening among current smokers in community health centers a randomized controlled trial. Cancer Medicine 2018; 7(3):894-902	*wrong intervention*
Ruco, Arlinda; Dossa, Fahima; Tinmouth, Jill; Llovet, Diego; Kishibe, Teruko; Baxter, Nancy N. M. D. PhD Social media and mobile health technology for cancer screening: a systematic review and meta-analysis protocol. BMJ Open	*wrong outcomes*

2020; 10(2):e035411	
Ruparel, M.; Quaife, S; .; Ghimire, B.; Dickson, J.; Horst, C.; Tisi, S.; Bhowmik, A.; Navani, N.; Baldwin, D.; Duffy, S.; et al., Impact of an Information-Film to Promote Informed Decision-Making in Individuals Taking Part in a Lung Cancer Screening Demonstration Pilot. Journal of Thoracic Oncology 2018; 13(10):S790	*wrong type of publication*
Sferra, S.; Erkmen, C.; Ma, G.; Cheng, J.; Kaiser, L.; DiSesa, V. Online decision aid vs option grid in shared decision making prior to lung cancer screening. Chest 2017; 152(4):A1122	*wrong type of publication*
Studts, J.; Brinker, K.; Tannenbaum, S.; Byrne, M. LuCaS DA: a lung cancer screening decision aid to improve screening decisions. Journal of Thoracic Oncology 2017; 12(1):S577	*wrong type of publication*
Teo BS, Li E, Tan C, Munro YL. Educational pamphlets for improving uptake of cancer screening: a systematic review. J Prim Health Care. 2019;11(3):207-16	*wrong type of publication*
Williams LB, Looney SW, Joshua T, McCall A, Tingen MS. Promoting Community Awareness of Lung Cancer Screening Among Disparate Populations: Results of the cancer-Community Awareness Access Research and Education Project. Cancer Nurs. 2019;10:10.	*wrong population*

APPENDIX 5: EVIDENCE GAPS

Table A5: Additional evidence generation needs

ADDITIONAL EVIDENCE GENERATION NEEDS	
Research question 1: *What is the benefit/harm of screening for lung cancer using low-dose computed tomography (LDCT) compared to no screening in individuals with risk factors for lung cancer other than tobacco smoking*	
Evidence	*No data from (randomised) controlled trials currently available*
Population	*Adult persons (age 18 and older) without lung cancer (confirmed or suspected) (ICD-10 code C34), who are no current or former tobacco smokers but have at least one other risk factor for lung cancer: e.g. exposure to occupational or environmental toxins (e.g. radon, asbestos or fine particle exposure), COPD (ICD-10 code J44), idiopathic pulmonary fibrosis (ICD-10 code J84.1), family history of lung cancer (ICD-10 code C34)*
Intervention	*Screening for lung cancer using low-dose computed tomography (LDCT)*
Comparator	*No screening (usual care).*
Outcome(s)	• *Mortality (overall mortality, lung cancer mortality)* • *Morbidity* • *Health-related quality of life* • *Harms resulting from screening itself (e.g. consequences from radiation exposure) or from subsequent diagnostic interventions (e.g. invasive biopsy) including overdiagnoses, consequences resulting from false screening results (false positive and false negative)* • *(Serious) adverse events*
Time stamp	*23.09.2020*
Study design	*Observational studies (to examine the risk associated with a suspected exposure) or RCTs (if exposure is a proven risk factor)*
Research question 2: *What is the benefit/harm of screening for lung cancer using biomarkers in addition to LDCT compared to screening using LDCT alone in individuals at elevated risk of lung cancer?*	
Evidence	*No (randomised) controlled trials currently available*
Population	*Current or former tobacco smokers aged 18 years or older without lung cancer (confirmed or suspected) (ICD-10 code C34)*
Intervention	*Screening for lung cancer using biomarkers in addition to low-dose computed tomography (LDCT)*
Comparator	*Screening for lung cancer using low-dose computed tomography (LDCT) alone*
Outcome(s)	• *Mortality (overall mortality, lung cancer mortality)* • *Morbidity* • *Health-related quality of life* • *Harms resulting from screening itself (e.g. consequences from radiation exposure) or from subsequent diagnostic interventions (e.g. invasive biopsy) including overdiagnoses, consequences resulting from false screening results (false positive and false negative)* • *(Serious) adverse events*
Time stamp	*23.09.2020*
Study design	*Observational studies (regarding prognostic and/or diagnosticproperties to find a biomarker most suitable for the use as an additional screening tool) or RCTs (as soon as sufficient knowledge about suitable and valid biomarkers exists)*

Research question 3: *What is the benefit/harm of screening for lung cancer in increased screening intervals (> 1 year) using LDCT compared to annual screening for lung cancer in individuals at elevated risk of lung cancer?*	
Evidence	*Very low quality evidence from 1 RCT for annual vs biennial screening*
Population	*Current or former tobacco smokers aged 18 years or older without lung cancer (confirmed or suspected) (ICD-10 code C34)*
Intervention	*Annual screening for lung cancer using low-dose computed tomography (LDCT)*
Comparator	*Screening for lung cancer using LDCT with screening interval longer than one year*
Outcome(s)	• *Mortality (overall mortality, lung cancer mortality)* • *Morbidity* • *Health-related quality of life* • *Harms resulting from screening itself (e.g. consequences from radiation exposure) or from subsequent diagnostic interventions (e.g. invasive biopsy) including overdiagnoses, consequences resulting from false screening results (false positive and false negative)* • *(Serious) adverse events*
Time stamp	*23.09.2020*
Study design	*RCTs (design ideally based on modelling studies)*
Ongoing studies	*4-IN THE LUNG RUN (https://cordis.europa.eu/project/id/848294/de)*
Research question 4: *What is the effectiveness of a shared-decision-making process in the context of a lung cancer-screening program compared to no shared-decision-making process on informed choice regarding participation?*	
Evidence	*No (randomised) controlled trials currently available*
Population	*Current or former tobacco smokers aged 18 years or older without lung cancer (confirmed or suspected) (ICD-10 code C34)*
Intervention	*Shared-decision-making counselling prior to initial LDCT scan within a lung cancer-screening program*
Comparator	*No shared-decision-making counselling prior to initial LDCT scan within a lung cancer-screening program*
Outcome(s)	• *Participant empowerment* • *Increased knowledge* • *Informed decision-making* • *Participant satisfaction* • *Screening participation rate* • *Smoking cessation rate*
Time stamp	*23.09.2020*
Study design	*RCTs*

APPENDIX 6: GUIDELINE RECOMMENDATIONS ON LUNG CANCER SCREENING

Table A6: Overview of guidelines

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Europe				
European Society of Radiology (ESR) and European Respiratory Society (ERS) joint white paper on lung cancer screening (LCS) [263]	2020	Europe	The ESR and ERS agree that Europe's health systems need to adapt to allow citizens to benefit from organised pathways, rather than unsupervised initiatives, to allow early diagnosis of lung cancer and reduce the mortality rate. Now is the time to set up and conduct demonstration programmes focusing, among other points, on methodology, standardisation, tobacco cessation, education on healthy lifestyle, cost-effectiveness and a central registry.	Statement paper. Updated expert opinion.
SEOM (Spanish Society of Medical Oncology) [248]	2020	Spain	Lung cancer screening in high-risk patients, as long as smoking cessation and LDCT, is recommended. Individuals at high risk (who currently smoke or have quit within the past 15 years; minimum 30 packs/year, and 55–74 years of age): Low dose computerized tomography + advice to quit smoking.	B/I
German Radiological Society (GRS), German Respiratory Society (GRS) [346]	2019	Germany	The involved professional societies strongly recommend that low-dose CT examinations for early detection of lung cancer should only be performed within a quality-assured program	Joint Statement
European Society For Medical Oncology (ESMO) ESMO [265]	2019	Europe	The panel concluded that national health policy groups in Europe should start to implement CT screening as adequate evidence is available. It was recognised that there are opportunities to improve the screening process through 'Implementation Research Programmes'. Implementation of LC screening should be a priority in Europe. It needs to be driven scientifically, politically and also using patient advocacy. Europe needs to plan 'Implementation Research Programmes'.	The expert panel reviewed the current evidence for LC screening with low-dose CT

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			Investment is needed into recruitment challenges especially in 'hard to reach' communities. Ensure thoracic radiologists reporting on CT-screened individuals use volume and VDT and are provided with the necessary training and work, with QA procedures in place. The issues around current GDPR need to be resolved, in order to enable the development of a European registry for collection of LC CT screening data. Secondary care pathways are aligned with the imminent implementation of LC screening, together with service provision and availability of screening platforms. Develop a collegiate approach to the workup and treatment of patients with LC in multidisciplinary clinics, identified through CT screening programmes. All clinical specialties should be fully engaged, including medical oncologists. The role of non-imaging early detection biomarkers is still in an early phase; however, the LC screening community should be fully engaged and participate in the developing integrated research programmes using molecular/radiomics and artificial intelligence approaches. Innovative research programmes (eg, ELIC and iDNA) provide enormous potential which can impact on LC screening and save lives. LC CT screening will happen in Europe. It is up to the community to make it happen now.	
AWMF (DE) – Association of Scientific Medical Societies, DKG (DE) – German Cancer Society [210]	2018	Germany	1. X-ray thorax: In asymptomatic individuals at risk for lung cancer, early detection by chest X-ray should not be done alone or in combination with cytological sputum exams.	A/1a

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
*Full text in German			2. Computed tomography (CT): Asymptomatic people at risk for lung cancer between the ages of 55 and 74 years and a smoking history of ≥ 30 pack years and less than 15 years of nicotine withdrawal can be an annual screening for lung cancer using low-dose CT under the recommendation 5.4. framework mentioned Tobe offered.	0/1a
			2. Computed tomography (CT): In asymptomatic persons at risk for lung cancer aged ≥ 50 years and a smoking history of ≥ 20 pack years and one of the following additional risk factors, an early detection of lung cancer by means of low-dose CT can be carried out under the recommendations given in 5.4. framework conditions are offered. Risk factors: Lung carcinoma, positive family history for a lung carcinoma, ENT malignancy or other smoking-related malignancies, lymphoma disease, asbestos exposure, COPD, pulmonary fibrosis.	0/1a
			2. Computed tomography (CT): Annual early detection of lung cancer using low-dose CT should be carried out for at least 2 years and under the following conditions: • Multidisciplinary treatment team with at least the participation of specialists in radiology, pneumology, thoracic surgery, oncology, and Radiotherapy, ideally in a certified lung cancer center (DKG); • Accompanying smoking cessation, • Continuous documentation and comparison of findings, • Within a quality-assured early detection program.	B, 1a

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Prevención del Cáncer del Programa de Prevención y Promoción de la Salud (PAPPS) [347]	2018	Spain	Primary care professionals should take clear and personalized advice to quit smoking to all smokers.	A/I
			Chest X-ray or sputum cytology should not be recommended as lung cancer screening tests.	B/I
			TCBD should not be recommended as a lung cancer screening test.	B/III
European Position Statement on Lung Cancer Screening [348]	2017	Europe	1. Low-dose CT is the only evidence-based method for the early detection of lung cancer shown to provide a mortality reduction. On the basis of this evidence from randomised controled trials, the EU position statement recommends that we start to plan for the implementation of lung cancer screening in Europe while cognisant of future publications that include the awaited NELSON trial data on mortality and cost-effectiveness and data from the six smaller European studies for developing implementation strategies in each of their own countries. 2. Future lung cancer low-dose CT programmes should use a validated risk stratification approach so that only individuals deemed to be at high enough risk are screened. In the near future, incorporation of potential biomarkers and susceptibility genes into lung cancer risk models should be considered to improve the accuracy of risk stratification models. 3. Although only evidence for annual low-dose CT lung cancer screening is available, recent research suggests the possibility of using a more personalised approach to lung cancer screening with a risk-based approach on the results of baseline and first screening rounds. 4. The EU position statement expert group recommends that the planning for low-dose CT screening should be started throughout Europe because low-dose CT lung cancer screening has the potential to save lives."	Joint Statement

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Nordic Thoracic Oncology Group [267]	2017	Nordic countries (Denmark, Norway, Sweden, Finland, Iceland)	"We would recommend for the Nordic countries that the NLST criteria are used: 55–75 years of age, more than 30 pack years smoking history, current smoker or having quit smoking within last 15 years, and having no substantial comorbidity. However, we would also suggest that the use of risk stratification, as done in the UKLS, is tested beforehand in pilot projects in the Nordic countries, as this may increase cost-effectiveness. The suggested screening interval in the Nordic countries therefore should be one baseline screening followed by a single annual screening, and thereafter biennial screening in participants without pulmonary nodules. Participants with nodules should be followed annually or as specified in the management flowchart. It is our recommendation in the Nordic Countries that the inclusion of incidental findings in a screening protocol should only be done in a separate formalized trial, and not as a part of the general public screening offered. Any incidental findings detected during screening should be reported and discussed with the participant, together with a referral to a relevant physician or multidisciplinary tumor (MDT) board. Furthermore, the potential for making these incidental findings should be discussed with the participating individuals when screening is prepared and offered. It is recommended that a national authorization of LDCT screening centers is established and a plan for the number and geographical distribution of these is made. It is recommended that an evaluation of what the expected demand for radiologists and other LC specialists will be and if there is a risk that there will be a shortage of qualified staff. It is recommended that LDCT screening is introduced in a gradual phased manner in each country. This could be by the establishment of one or a few multidisciplinary screening centers to gain knowledge and experience in this new field, prior to	Expert consensus

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			subsequent expansion of the activity. Based on experience from the European screening trials it is recommended that the initial screened cohort in a center should not be less than 2000 individuals.	
European Society For Medical Oncology (ESMO) [249]	2017	Europe	"Screening with LDCT reduces lung cancer-related mortality. It is not yet ready for large-scale implementation, mainly because the lung cancer mortality reduction rate lacks definite proof of a second study result, and partly because of remaining questions regarding definition of the at-risk population, timing, interval and method of computed tomography (CT, especially 2D versus 3D evaluation), how to handle (false) positive findings and especially cost-effectiveness, notably in relation to smoking cessation.	A/I
			• LDCT screening can be carried out outside a clinical trial provided it is offered within a dedicated programme with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of suspicious findings. Candidates are current or former heavy smokers (30 pack-years or 15 years since smoking cessation) aged 55–74 years, who are well informed about potential benefits and risks. Individuals offered LDCT screening should be referred to a smoking cessation programme.	B/I
			• LDCT screening should not be offered on an ad hoc individual basis, but patients requesting screening should be referred to a dedicated programme, as recommended above.	B/V
			• Other screening methods, such as chest X-ray, sputum analysis or biomarkers, are not recommended for clinical use.	C/I
European Society of Thoracic Surgeons (ESTS) [264]	2017	Europe	Ten recommendations have been prepared that cover the essential aspects to be taken into account when considering implementation of CT screening in Europe. These issues are:	Working group with eight experts in the field (based on the current situation regarding CT screening in Europe and the available

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			1. Implementation of CT screening in Europe, 2. Participation of thoracic surgeons in CT screening programs, 3. Training and clinical profile for surgeons participating in screening programs, 4. the use of minimally invasive thoracic surgery and other relevant surgical issues 5. Associated elements of CT screening programs (i.e. smoking cessation programs, radiological interpretation, nodule evaluation algorithms and pathology reports). Thoracic Surgeons will play a key role in this process and therefore the ESTS is committed to providing guidance and facilitating this process for the benefit of patients and surgeons.	evidence)
French National Authority for Health (HAS) [268]	2016	France	HAS considers that the conditions of quality, efficacy and safety necessary for the detection of bronchopulmonary cancer by thoracic computed tomography with a dose of X-rays classified low in people highly exposed or smoked were not met in France in 2016. In France, a taskforce edited a common statement recommending screening smokers or ex-smokers, from 55 to 75 years old who have smoked at least 30 packs/year. The taskforce also underlined the need for clinical trials aiming to translate screening strategy to the French setting. However, the French Health Authority recently claimed that lung cancer screening was not relevant in the current setting.	Expert group (critical analysis and synthesis of evidence)
Spanish Society of Pneumology and Thoracic Surgery (SEPAR) [266]	2016	Spain	Annual chest X-ray screening in high-risk patients is not effective, and is therefore, not recommended.	A/I
			Annual screening using TCBD in high-risk individuals reduces lung cancer mortality.	B/I

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			The definition of high risk is not clearly established, but the only randomized and controlled study that has shown reduction in mortality used the following criteria of inclusion: age between 55 and 74 years, at least 30 packages-year smoking and a maximum period of smoking withdrawal of 15 years.	B/I
			There is insufficient evidence to recommend the number of screenings, nor the time interval between them, to which the high-risk individual should undergo. Most of the studies from which evidence has been obtained for the recommendations has been done with 1 screening per year for at least 3 years.	-
			Lung cancer screening provides an excellent opportunity to offer a smoking cessation program.	B/I
			The incorporation of smoking cessation programs into screening programs can improve the cost-effectiveness ratio.	C/2
European Society of Radiology (ESR) and the European Respiratory Society (ERS) [349]	2015	Europe	"The European Society of Radiology and the European Respiratory Society are recommending lung cancer screening in comprehensive, quality-assured programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres. • Inclusion criteria: age between 55 and 80 years, tobacco smoking history of at least 30 pack-years, and current smoker or ex-smoker who has quit smoking within the last 15 years. • Exclusion criteria: comorbidities precluding curative therapy and lack of consent to undergo curative therapy."	-
America				

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
U.S. Preventive Service Task Force [254] (in review: public comment)	2020	USA	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults ages 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Population: Adults ages 50 to 80 years who have a 20 pack-year smoking history, currently smoke, or have quit within the past 15 years.	B/I
American College of Radiology ACR Appropriateness Criteria® [350]	2020	USA	1. Lung cancer screening with low-dose CT chest without IV contrast is usually appropriate in patients 55 to 80 years of age and 30 or more packs per year smoking history and currently smokes or have quit within the past 15 years. 2. The panel did not agree on recommending lung cancer screening with low-dose CT chest without IV contrast in patients 50 years of age or older and 20 or more packs per year history of smoking plus one additional risk factor. There is insufficient medical literature to conclude whether or not these patients would benefit from CT screening for lung cancer. Screening in this patient population is controversial but may be appropriate. 3. Lung cancer screening is usually not appropriate in patients younger than 50 years of age or older than 80 years of age; or in patients of any age with less than 20 packs per year history of smoking and no additional risk factors.	Expert Panel (Although there are references that report on studies with design limitations, 14 well-designed or good-quality studies provide good evidence)
American Cancer Society (ACS) [258]	2019	USA	Annual screening with low-dose helical CT in adults who: • currently smoke or have quit within the past 15 years; and	-----

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			• have at least a 30 pack-year smoking history; and • receive evidence-based smoking cessation counseling, if they are current smokers; and • have undergone a process of informed/shared decision making that included information about the potential benefits, limitations, and harms of screening with low-dose CT; and • have access to a high-volume, high quality lung cancer screening and treatment center Population: Current or former smokers aged 55-74 y in good health with at least a 30-pack-y history of smoking.	

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
American Cancer Society (ACS) [259]	2019	USA	Population: current or former smokers aged 55-74 y in good health with at least a 30–pack-y history of smoking. Annual screening in adults who: -Currently smoke or have quit within the past 15 y; and -Have at least a 30–pack-y smoking history; and -Receive evidence-based smoking cessation counseling, if they are current smokers; and -Have undergone a process of informed/shared decision making that included information about the potential benefits, limitations, and harms of screening with low-dose CT; and Have access to a high-volume, high-quality lung cancer screening and treatment center.	Available evidence
American College of Chest Physicians (CHEST) [247]	2018	USA	For asymptomatic smokers and former smokers age 55 to 77 who have smoked 30 pack years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low dose CT should be offered.	"Weak recommendation "moderate-quality evidence
National Comprehensive Cancer Network (NCCN) [236]	2019	USA	The NCCN panel recommends lung cancer screening using LDCT for individuals with high-risk factors; 2 groups of individuals qualify as high risk: Group 1: Aged 55 to 74 years; 30 or more pack-year history of smoking tobacco; and currently smoke or, if former smoker, have quit within 15 years (category 1). This is a category 1 recommendation, because these individuals are selected based on the NLST inclusion criteria. An NCCN category 1 recommendation is based on high-level evidence (ie, randomized controlled trial) and uniform consensus (≥85%) among panel members. Annual screening is recommended for these high-risk individuals for 2 years (category 1) based on the NLST. Annual screening is recommended until the individual is	Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			no longer eligible for definitive treatment (category 2A). Uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate	
			Group 2: Aged 50 years or older, 20 or more pack-year history of smoking tobacco, and one additional risk factor (other than second-hand smoke) (category 2A). This is a category 2A recommendation, because these individuals are selected based on lower level evidence, such as nonrandomized studies, observational data, and ongoing randomized trials.40,54–60 Most panel members (85%) would recommend LDCT for these individuals.61 Additional risk factors include cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure to carcinogens. The NCCN panel does not believe that exposure to second hand smoke is an independent risk factor, because the data are either weak or variable.	Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
American Cancer Society [351]	2019	USA	Lung cancer screening with low-dose helical CT: Current or former smokers aged 55-74 years in good health with at least a 30–pack-y history of smoking Annual screening in adults who: currently smoke or have quit within the past 15 y; and have at least a 30–pack-y smoking history; and receive evidence-based smoking-cessation counseling, if they are current smokers; and have undergone a process of informed/shared decision making that included information about the potential benefits, limitations, and harms of screening with low-dose CT; and have access to a high-volume, high-quality lung cancer screening and treatment center	Available evidence

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
American Thoracic Society (ATS) [260]	2018	USA	1) Juxtaposing lung cancer risk and competing risk of death. -Better selection of those at high risk for lung cancer may improve the harm-tobenefit ratio of screening; however, benefits and harms of LCS may not be linearly related to risk of developing lung cancer. -The complex interplay between baseline risk of developing lung cancer, treatment-related harms, and competing causes of death substantially affects the balance of harms and benefits of LCS. -Research is needed to identify the optimal threshold where the benefits of reducing lung cancer death (LCD) outweigh the risk of dying of a competing cause and serve to prolong survival. 2) COPD, lung cancer risk, and potential harms of LDCT screening. -Although individuals with COPD have a higher risk than smokers without COPD of developing lung cancer, the presence of advanced COPD may pose a significant risk for harms of LCS and downstream evaluation and treatment of screen-detected nodules. - The benefit of screening those with advanced-stage COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] classes 3 and 4) is uncertain, and how best to risk stratify these patients using functional status information should be an area of research	Statement
American Thoracic Society (ATS) Policy Statement [352]	2017	USA	Conclusions The application of molecular biomarkers to assist with the early detection of lung cancer has the potential to substantially improve our ability to select patients for lung cancer screening, and to assist with the characterization of indeterminate lung nodules. To support the application of molecular biomarkers in these	--

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			clinical settings there must be evidence that the molecular biomarker leads to clinical decisions whose benefits outweigh their harms. Although it is tempting to apply novel testing based on promising discovery or validation level studies, the lung cancer community should insist on additional evidence of clinical utility before changing practice. We have described relevant considerations and have suggested standards to apply when determining whether a molecular biomarker for the early detection of lung cancer is ready for clinical use.	
Canadian Task Force on Preventive Health Care (CTFPHC) [261]	2016	Canada	Adults between 55 and 74 years of age who are at high risk for lung cancer (i.e., those who smoke or who quit smoking within the past 15 years and who have at least a 30 pack-year smoking history) may benefit from screening for lung cancer with low-dose computed tomography (CT) every year for three consecutive years (weak recommendation).	Weak recommendation, low-quality evidence
			There is no clear benefit of low-dose CT screening for lung cancer in adults younger than 55 years and older than 74 years, or in those at a lower risk based on smoking history (i.e., adults who smoke with less than a 30 pack-year smoking history or adults who quit smoking more than 15 years prior).	Weak recommendation, low-quality evidence
			There is no benefit of screening for lung cancer with chest radiography (with or without sputum cytology), but there are known harms (e.g., false-positive results, adverse effects of invasive follow-up testing and overdiagnosis).	Strong recommendation, low-quality evidence.
Canadian Association Radiologists (CAR) [353]	2016	Canada	Only patients that can be defined as “high risk” are likely to benefit from lung cancer screening with LDCT. We recommend screening patients who have a 1.5% or higher risk of developing lung cancer over the next six years. Recommend routine annual screening for high risk patients until such time as they no longer meet eligibility criteria. In addition,	These recommendations are based on a review of best available literature and stakeholder consultation outreach and consultation, according to the CAR process.

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			screening should be discontinued in those who develop health problems that substantially limit life expectancy or would preclude curative treatment. Exclusion criteria: Serious comorbid conditions, persons who are unwilling to undergo curative treatment, individuals with symptoms requiring clinical evaluation (hemoptysis or unexplained weight loss of more than 6.8 kg (15lb) in the preceding year), currently undergoing workup or surveillance CT for any clinically or incidentally detected abnormalities in the thorax (participants who have had a CT of the chest within the past year should wait to begin screening until 12 months after the last CT of the chest), patients with a previous history of lung cancer diagnosed and treated within the last five years, individuals who are unable to undergo CT scanning due to inability to lie flat, unmanageable claustrophobia, inability to breath-hold, or weight over CT scanner limit .	
American Thoracic Society (ATS), American College of Chest Physicians (CHEST) [256]	2015	USA	Implementation of LDCT screening begins with several planning steps, including formation of a multidisciplinary steering committee, engaging and educating primary care providers (PCPs), engaging local leadership, establishing a business model, and marketing the program. During the implementation phase, programs should be attentive to establishing systems to screen the right patients at the right time, to performing shared decision making to help eligible patients decide whether to undergo screening, and to standardizing processes for performing LDCT scans, reporting LDCT results, evaluating screen-detected nodules, communicating results to patients and their providers, and managing incidentally detected abnormalities. Smoking cessation is a critical corollary to LDCT screening, and	Official Statement

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			LDCT screening programs should either incorporate counseling into the program or refer current smokers and recent quitters to external smoking cessation resources. To maintain performance, programs should collect data on patients undergoing LDCT screening in a registry that should be periodically reviewed to ensure the program is achieving quality metrics.	
Cancer Care Ontario (CCC) [262]	2013	Canada	Recommendation 1: Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years who currently smoke or have quit within the past 15 years and are disease free at the time of screening. Recommendation 2: Positive Result and Follow-up Screening modality: Screening for lung cancer should be done using an LDCT multidetector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv). -Collimation should be ≤2.5 mm. -Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy. -Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). The Lung Cancer Diagnosis Pathway should be consulted for guidance on clinical workup.	The core methodology of the Program in Evidence-Based Care's guideline development process is systematic review.

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			Recommendation 3: Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative scan. "	
Asia				
Indian Consensus Guidelines for Molecular Testing (Biomarkers in Non-Small Cell Lung Cancers) [354]	2019	India	The guideline summarizes the importance of targetable mutations in NSCLC such as epidermal growth factor receptor (EGFR), rearrangements in anaplastic lymphoma kinase and receptor tyrosine kinase encoded by ROS-1 gene, overexpression of programmed cell death ligand-1 and resistant EGFR mutations. It reaffirms recommendations from international working groups, discusses vulnerable pre-analytical procedures and provides a balanced review on the pros and cons of different diagnostic tests (immunohistochemistry, fluorescence in situ hybridization, polymerase chain reaction-based testing and next-generation sequencing). The document also provides an algorithm to aid diagnostic decision-making and a checklist to assess the quality of testing laboratories that will help the medical oncologists make an informed choice. Overall, these recommendations are based on evidence and clinical experience and will aid policymakers, oncologists, health care practitioners and pathologists who strive to implement molecular strategies and make informed decisions for improved care in NSCLC in India.	Consensus guideline
China lung cancer early detection and treatment expert group (CLCEDTEG) [355] * Full article in Chinese	2018	China	Annual lung cancer screening with LDCT is recommended for high risk individuals aged 50-74 years who have at least a 20 pack-year smoking history and who currently smoke or have quit within the past five years.	

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Saudi Lung Cancer Association of Saudi Thoracic Society [356]	2018	Saudi Arabia	Asymptomatic patients: (symptomatic patients should be worked up properly according to standards of care). Age 55–77 years Smoking history >30 PY (number of packs smoked per day X year of smoking) Active smoker or quit smoking less than 15 years ago. Did not have chest CT scan the last year Do not perform screening for individuals with comorbidities that could adversely influence their ability to tolerate the evaluation of screen-detected findings or tolerate treatment of early-stage screen-detected lung cancer or that substantially limit their life expectancy. We recommend that low-dose CT (LDCT) screening should not be performed in these situations (strong recommendation, low-quality evidence) (e.g., advanced liver disease, COPD with hypoventilation and hypoxia, NYHA class IV heart failure).	Expert group
The Korean guideline for lung cancer screening (A Korean multisociety group) [357] *Full article in Korean	2015	Korea	Annual LDCT screening should be recommended to current smokers and ex-smokers (if less than 15 years have elapsed after smoking cessation) who are aged 55 to 74 years with 30 pack-years or more of smoking-history. LDCT can discover non-calcified lung nodules in 20 to 53% of the screened population, depending on the nodule positivity criteria. Individuals may undergo regular LDCT follow-up or invasive diagnostic procedures that lead to complications. Radiation-associated malignancies associated with repetitive LDCT, as well as overdiagnosis, should be considered the harms of screening.	high-level evidence

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			LDCT should be performed in qualified hospitals and interpreted by expert radiologists. Education and actions to stop smoking must be offered to current smokers. Chest radiograph, sputum cytology at regular intervals, and serum tumor markers should not be used as screening methods.	
Africa				
South African Thoracic Society [358]	2019	South African	Annual LDCT should be offered to patients between 55–74 years of age who are current or former smokers (having quit within the preceding 15 years), with at least a 30-pack year smoking history and with no history of lung cancer. Patients should be in general good health, fit for surgery, and willing to undergo further investigations if deemed necessary. Given the high local prevalence of tuberculosis (TB) infection and post-TB lung disease, which can radiographically mimic lung cancer, a conservative threshold (nodule size ≥6 mm) should be used to determine whether the baseline LDCT screen is positive (thus nodules <6 mm require no action until the next annual screen). If a non-calcified, solid or partly solid nodule is ≥6 mm, but <10 mm with no malignant features (e.g., distinct spiculated margins), the LDCT should be repeated in 6 months. If a solid nodule or the largest component of a non-solid nodule is ≥10 or ≥6 mm and enlarging or with additional malignant features present, definitive action to exclude lung cancer is warranted. Patients should be screened annually until 15 years have	Expert group. Based on numerous international guidelines

Name of society/organisation issuing guidance (reference)	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			elapsed from date of smoking cessation, they turn 80, become unfit for a curative operation or significant changes are observed.	
Oceania				
Standing Committee on Screening Endorsed by Cancer Australia, Cancer Council, and the Community Care and Population. Health Principal Committee of the Australian Health Ministers' Advisory Council [359]	2015	Australia	On the basis of the current evidence and in line with the Population Based Screening Framework, the Standing Committee on Screening does not support an Australian lung cancer screening program, either for the general population or for high risk populations. The Standing Committee on Screening will continue to evaluate and advise on emerging evidence on lung cancer screening.	Position Statement

Abbreviations: EGFR=epidermal growth factor receptor; LDCT=low density computed tomography; NI=no indicated; NSCLC=non-small cell lung cancer.

APPENDIX 7: RISK OF BIAS TABLES OF RCTS INCLUDED IN RESEARCH QUESTION 1

Table A7: Risk of bias – overall mortality (research question 1)

Study	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
LDCT screening versus no screening						
DANTE	High	NA	NA	NA	NA	High
DLCST	Low	Yes	Yes	Yes	Yes	Low
ITALUNG	Low	Yes	Yes	Yes	Yes	Low
LUSI	Low	Unclear	Yes	No[a]	No[b]	High
MILD	High	NA	NA	NA	NA	High
NELSON	Low	No	Yes	Yes	Yes	Low
LDCT screening versus chest X-ray screening						
LSS	High	NA	NA	NA	NA	High
NLST	High	NA	NA	NA	NA	High

Abbreviations: ITT=intention to treat; NA=not applicable.
[a] The stratification factors do not match the adjustment factors used.
[b] Discrepancies between the publications

Table A8: Risk of bias – lung cancer mortality (research question 1)

Study	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
LDCT screening versus no screening						
DANTE	High	NA	NA	NA	NA	High
DLCST	Low	Yes	Yes	Yes	Yes	Low
ITALUNG	Low	Yes	Yes	Yes	Yes	Low
LUSI	Low	Yes	Yes	No [a]	Yes	High
MILD	High	NA	NA	NA	NA	High
NELSON	Low	Unclear [b]	Yes	Yes	Yes	Low [c]
LDCT screening versus chest X-ray screening						
LSS	High	NA	NA	NA	NA	High
NLST	High	NA	NA	NA	NA	High

Abbreviations: ITT=intention to treat; NA=not applicable.

[a] The stratification factors do not match the adjustment factors used

[b] Only 296 medical records of 426 deceased Dutch male patients with lung cancer were reviewed blindly by a committee and the cases assigned to a cause of death (for a follow-up period of 10 years). For all other deceased persons, the cause of death was documented as on the official death certificate.

[c] An investigation comparing the possibly unblinded determination of the cause of death lung cancer from official death certificates with the blinded committee assessment did not reveal a significant discrepancy. In summary, the risk of bias was therefore considered low.

Table A9: Risk of bias – adverse events (research question 1)

Study	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
LDCT screening versus no screening						
DANTE	High	NA	NA	NA	NA	High

Abbreviations: ITT=intention to treat; NA=not applicable.

Table A10: Risk of bias – consequences resulting from false positive screening results (research question 1)

Study	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
LDCT screening versus no screening						
DANTE	High	NA	NA	NA	NA	High
DLCST	Low	No	Yes	Yes	Yes	Low
ITALUNG	Low	No	Yes	Yes	Yes	Low
LUSI	Low	No	Yes	Yes	No [a]	High
MILD	High	NA	NA	NA	NA	High
NELSON	Low	No	Yes	Yes	Yes	Low

Abbreviations: ITT=intention to treat; NA=not applicable
[a] Discrepancies between the publications

Table A11: Risk of bias – overdiagnosis (research question 1)

Study	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
LDCT screening versus no screening						
DANTE	High	NA	NA	NA	NA	High
DLCST	Low	No	Yes	Yes	Yes	Low
ITALUNG	Low	Unclear	Yes	Yes	Yes	Low
LUSI	Low	No	Yes	Yes	No [a]	High
MILD	High	NA	NA	NA	NA	High
NELSON	Low	No	Yes	Yes	Yes	Low
LDCT screening versus chest X-ray screening						
NLST	High	NA	NA	NA	NA	High
LSS	High	NA	NA	NA	NA	High

Abbreviations: ITT=intention to treat; NA=not applicable.
[a] Discrepancies between the publications

APPENDIX 8: GRADE EVIDENCE PROFILES

Research question 1

Table A12: GRADE assessment – overall mortality (research question 1)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI] [a]		Quality	Impor-tance
						Screening	No Screening		Risk without screening [b]	Risk with screening [c]		
Mortality												critical
Overall mortality												
6	Low [d]	Not serious	Not serious	Not serious	None	17,234	16,469	IRR: 0.95, [0.88; 1.03]; p = 0.164	8 to 11 years after randomisation: 5 [-3; 12] less 101 per 1000	96 per 1000	High ++++	

Abbreviations: CI=confidence interval; IRR=incidence rate ratio.
[a] To calculate the absolute effects, the incidence rate ratio from the meta-analysis was applied to the median risk in the control group (baseline risk).
[b] Median risk of the control group per 1000 persons
[c] Median risk of the intervention group per 1000 invited screening participants
[d] Low risk of bias in over 70% of the weight of relevant studies

Table A13: GRADE assessment – lung cancer mortality (research question 1)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI] [a]		Quality	Impor-tance
						Screening	No Screening		Risk without screening [b]	Risk with screening [c]		
Mortality												critical
Lung cancer mortality												

Number of	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI] [a]	Quality	Impor-tance
6	Low [d]	Not serious	Not serious	Serious[e]	None	17,234	16,469	IRR: 0.81, [0.72; 0.91]; p = 0.004	8 to 11 years after randomisation: 5 [3; 8] less 28 per 1000 23 per 1000	Moderate +++O	

Abbreviations: CI=confidence interval; IRR=incidence rate ratio.
[a] To calculate the absolute effects, the incidence rate ratio from the meta-analysis was applied to the median risk in the control group (baseline risk).
[b] Median risk of the control group per 1000 persons
[c] Median risk of the intervention group per 1000 invited screening participants
[d] Low risk of bias in over 70% of the weight of relevant studies
[e] Downgraded by 1 level because the evaluation of the studies with a low risk of bias alone showed no statistically significant difference between the groups.

Table A14: GRADE assessment – Adverse events after surgery for suspicious findings (research question 1)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening [a]	Risk with screening [b]		
Morbidity												important
Adverse events after surgery for suspicious findings												
1	High [c]	NA (only 1 trial)	Not serious	Serious [d]	None	1264	1186	OR: 3.48 [1.41; 8.62]; p = 0.004	Maximum 8 years: 12 [2; 37] more 5 per 1000	17 per 1000	Low ++OO	

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio.
[a] Median risk of the control group per 1000 persons
[b] Median risk of the intervention group per 1000 screening participants
[c] High risk of bias on study level
[d] Downgraded by 1 level due to a large CI.

Table A15: GRADE assessment – Adverse events after surgery with a serverity level ≥ 3 (research question 1)

Number of	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider	Number of patients	Relative effect (95% CI)	Anticipated absolute effects [95% CI]	Quality	Impor-tance

studies					ations	Screening	No Screening		Risk without screening [a]	Risk with screening [b]		
Morbidity												important
Adverse events after surgery with a severity level ≥ 3												
1	High [c]	NA (only 1 trial)	Not serious	Serious [d]	None	1264	1186	OR: 4.25, [0.92; 19.69]; p = 0.046	Maximum 8 years: 6 [0; 36] more 2 per 1000	8 per 1000	Low ++OO	

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio.
[a] Median risk of the control group per 1000 persons
[b] Median risk of the intervention group per 1000 screening participants
[c] High risk of bias on study level
[d] Downgraded by 1 level due to a large CI.

Table A16: GRADE assessment – Consequences of false positive screening results (research question 1)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening [a]	Risk with screening [b]		
Morbidity												important
Consequences of false positive screening results												
6	Low [c]	Not serious	Not serious	Not serious	None	17,234	-	See Table 4.15	1 to 15 per 1000 --	--	High ++++	

Abbreviations: CI=confidence interval.
[a] Median risk of the control group per 1000 persons
[b] Median risk of the intervention group per 1000 screening participants
[c] Low risk of bias in over 70% of the weight of relevant studies

Table A17: GRADE assessment – Overdiagnosis (research question 1)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening [a]	Risk with screening [b]		
Morbidity												important
Overdiagnosis												
6	Low [c]	Serious [d]	Not serious	Not serious	Outcome can only occure with screening [e]	15,917	15,189	Range [minimum; maximum] of point estimates for the overdiagnosis risk of the individual studies in relation to the persons invited for screening: 0 to 2.2%.	0[f] to 22 [1; 42][g] per 1000 -	 --	High ++++	

Abbreviations: CI=confidence interval.
[a] Median risk of the control group per 1000 persons
[b] Median risk of the intervention group per 1000 screening participants
[c] Low risk of bias in over 70% of the weight of relevant studies
[d] Downgraded by 1 level for heterogeneous results
[e] Upgrading by 1 level.
[f] Based on the results of the ITALUNG study. Fewer lung cancer cases were diagnosed in the intervention group than in the control group. Thus, no overdiagnosis is detectable.
[g] Based on the results of the DANTE study

Research question 3

Table A18: GRADE assessment – Annual versus biennial screening/Mortality (research question 3)

Number of studies	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI] [a]		Quality	Impor-tance
						Biennial Screening	Annual Screening		Risk with biennial screening [b]	Risk with annual screening [c]		
Mortality												critical
Overall mortality												
1	High [d]	NA (only 1 trial)	Not serious	Very serious [e]	None	1,186	1,190	HR: 0.80, [0.57; 1.12]; p = 0.191	10 years after randomisation: 13 [-8; 28] less 51 per 1000	64 per 1000	Very Low +000	
Lung cancer mortality												
1	High [d]	NA (only 1 trial)	Not serious	Very serious [e]	None	1,186	1,190	HR: 1.10, [0.59; 2.05]; p = 0.760	10 years after randomisation: 2 [-7; 17] more 18 per 1000	16 per 1000	Very Low +000	

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable.
[a] To calculate the absolute effects, the hazard ratio was applied to the risk in the control group.
[b] Median risk of the group with biennial screening
[c] Median risk of the group with annual screening
[d] High risk of bias on study level
[e] Downgraded by 2 levels because i) an independent replication by a second study is lacking and ii) results lack the necessary statistical precision, as they fail to exclude important benefit or important harm (95% CI is consistent with a doubling of lung cancer mortality).

Research question 4

Table A19: GRADE assessment – Information leaflets (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Information leaflet	No leaflet	Relative (95% CI)	Absolute (95% CI)		
Screening participation rate												
1	Observational study	Very serious [a]	NA (only 1 trial)	Serious [b]	Very serious [c]	None	240	244	93 (38.8) % vs 92 (37.7)% , p=n.r.	-	Very low	not important

Abbreviations: CI=confidence interval; NA=not applicable; n.r.=not reported.
[a] Observational study with high risk of bias
[b] Study located in Japan
[c] Only one small observational study

Table A20: GRADE assessment – Targeted screening invitation (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Targeted invitation	Standard information	Relative (95% CI)	Absolute (95% CI)		
Increased knowledge												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Very serious [a]	None	388	415	5.7 (2.3) vs 5.5 (2.3) [b], p=ns	-	Low	important/
Participant empowerment												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Very serious [a]	None	388	415	≥ 83.2% vs ≥ 76.2% [c],	-	Low	important

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Targeted invitation	Standard information	Relative (95% CI)	Absolute (95% CI)		
									p=ns			
Participant satisfaction												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Very serious [a]	None	388	415	≥ 98.7% vs ≥ 97.3% [d], p=n.r.	-	Low	important/
Screening participation rate												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Very serious [a]	None	416	429	OR: 1.47 [0.91-2.40], p=0.177	-	Low	not important

Abbreviations: CI=confidence interval; NA=not applicable; n.r.=not reported; ns=not significant; OR=odds ratio; RCT=randomised controlled trial; SD=standard deviation.
[a] Only one RCT
[b] Knowledge score; mean (SD)
[c] % participants with low decisional conflict
[d] 5 participants satisfied with decision

Table A21: GRADE assessment – Couselling for screening invitation (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Telephone counselling + brochure	Brochure alone	Relative (95% CI)	Absolute (95% CI)		
Screening participation rate												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Very serious [b]	None	213	218	OR: 1.10 [0.70 to 1.72] , p=0.98	-	Very low	not important

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; RCT=randomised controlled trial.

[a] RCT with high risk of bias
[b] Only one RCT

Table A22: GRADE assessment – Decision aid vs no decision aid (research question 4)

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Decision aid	Standard information material	Relative (95% CI)	Absolute (95% CI)		
Increased knowledge												
2	1 RCT/1 observational study	Not serious	Not serious	Not serious	Serious [a]	None	265	284	Significant benefit for decision aid (details see Table 4.29)	-	Moderate	important
5	Single-arm pre-post	Very serious [b]	Not serious	Not serious	Serious [a]	None	305	-	See Table 4.30	-	Very low	important
Informed decision making												
2	1 RCT/1 observational study	Not serious	Not serious	Not serious	Serious [a]	None	257	275	Significant benefit for decision aid (details see Table 4.31)	-	Moderate	important
1	Single-arm pre-post	Serious [c]	NA (only 1 trial)	Not serious	Very serious [d]	None	30	-	See Table 4.32	-	Very low	important
Participant empowerment												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Serious [a]	None	234	233	−14.9 (−20.1 to −9.7) [e], p<0.001	-	Moderate	important
4	Single-	Serious [c]	Not	Not serious	Serious [a]	None	351	-	See Table	-	Low	important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other considera-tions	Decision aid	Standard information material	Relative (95% CI)	Absolute (95% CI)		
	arm pre-post		serious						4.35			
Participant satisfaction												
1	Observational study	Very serious [f]	NA (only 1 trial)	Not serious	Very serious [d]	None	30	51	4.8 (0.8) vs 4.7 (0.6) [g], p<0.001	-	Very low	important
Screening participation rate												
1	RCT	Not serious	NA (only 1 trial)	Not serious	Serious [a]	None	237	238	OR: 0.70 [0.47 to 1.03]; p=0.07 [h], p=0.07	-	Moderate	not important
2	Single-arm pre-post	Very serious[i]	Not serious	Not serious	Serious[a]	None	80	-	See Table 4.40	-	Very low	not important

Abbreviations: CI=confidence interval; MD=mean difference; NA=not applicable; OR=odds ratio; RCT=randomised controlled trial; SD=standard deviation; vs=versus.
[a] Low number of participants
[b] Single-arm studies with low and high risk of bias
[c] Single-arm study with low risk of bias
[d] Only one small study
[e] Decisional Conflict Scale; MD [95% CI]
[f] Single-arm studies with high risk of bias
[g] Satisfaction score; mean (SD)
[h] Scheduled for screening within 1 year
[i] Single-arm studies with low and high risk of bias

Table A23: GRADE assessment – Option grid vs decision aid (research question 4)

Quality assessment	Summary of findings			Importance
	Number of patients	Effect	Quality	

Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other con-siderations	Option grid	Web-based decision aid	Relative (95% CI)	Absolute (95% CI)		
Increased knowledge												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Serious [b]	None	128	109	64.7% vs 62.4% [c], p=0.43	-	Low	important
Informed decision making												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Serious [b]	None	128	109	97.4 vs 98.6 [d], p=0.60	-	Low	important
Participant empowerment												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Serious [b]	None	128	109	6.0 vs 10.2 [e], p=0.0198	-	Low	important

Abbreviations: CI=confidence interval; NA=not applicable; RCT=randomised controlled trial; SMD=shared decision making.
[a] RCT with high risk of bias
[b] Only one RCT
[c] % participant with correct answers
[d] Mean CollaboRATE SDM score
[e] Mean score on Decisional Conflict Scale

Table A24: GRADE assessment – Information film (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other con-siderations	Film + booklet	Booklet	Relative (95% CI)	Absolute (95% CI)		
Increased knowledge												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Serious [b]	None	120	109	0.62 [0.17-1.08] [c], p=0.007	-	Low	important
Participant empowerment												
1	RCT	Serious [a]	NA (only 1	Not	Serious [b]	None	120	109	8.5 (1.25)	-	Low	important

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecis ion	Other con-siderations	Film + booklet	Booklet	Relative (95% CI)	Absolute (95% CI)		
			trial)	serious					vs 8.24 (1.49) [d], p=0.007			
Screening participation rate												
1	RCT	Serious [a]	NA (only 1 trial)	Not serious	Serious [b]	None	120	109	76.7% vs 78.9% [e], p=0.66	-	Low	not important

Abbreviations: CI=confidence interval; LDCT=low-dose computed tomography; MD=mean difference; NA=not applicable; OR=odds ratio; RCT=randomised controlled trial; SD=standard deviation; vs=versus.
[a] RCT with high risk of bias
[b] Only one RCT
[c] Objective knowledge score; MD [95% CI]
[d] Decisional Conflict scale; MD (SD)
[e] % participants with LDCT completion

Table A25: GRADE assessment – Shared decision-making counselling (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecis ion	Other con-siderations	In-person SDM	Telephon e SDM	Relative (95% CI)	Absolute (95% CI)		
Participant empowerment												
1	Observatio nal study	Very serious [a]	NA (only 1 trial)	Not serious	Very serious [b]	None	69	68	11.3 (3.4) vs 12.1 (3.4) [c], p=n.r.	-	Very low	important
Participant satisfaction												
1	Observatio nal study	Very serious[a]	NA (only 1 trial)	Not serious	Very serious [b]	None	69	68	26.7 (2.8) vs 24.6	-	Very low	important

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecis ion	Other con-siderations	In-person SDM	Telephon e SDM	Relative (95% CI)	Absolute (95% CI)		
									(5.6) [d]; p=n.r.			
Screening participation rate												
1	Observatio nal study	Very serious [a]	NA (only 1 trial)	Not serious	Very serious [b]	None	69	68	88.4% vs 88.2 [e], p=n.r.	-	Very low	not important

Abbreviations: CI=confidence interval; LDCT=low-dose computed tomography; MD=mean difference; NA=not applicable; n.r.=not reported; SD=standard deviation; vs=versus.
[a] Observational study with high risk of bias
[b] Only one small study
[c] Decisional Conflict scale; mean (SD)
[d] Decisional satisfaction score; mean (SD)
[e] % participants with LDCT completion

Table A26: GRADE assessment – Education classes for screening information (research question 4)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impres-sion	Other con-siderations	Educatio n class	None	Relative (95% CI)	Absolute (95% CI)		
Informed decision making												
1	Single-arm pre-post	Very serious [a]	NA (only 1 trial)	Not serious	Very serious [b]	None	269	-	78% [c]	-	Very low	important

Abbreviations: CI=confidence interval; NA=not applicable.
[a] Single-arm study with high risk of bias
[b] Only one small study
[c] % of participants having all information needed after intervention

APPENDIX 9: MISCELLANEOUS

Table A27: Documentation of queries to study authors in the assessment report

Study reference/ID	Content of query	Reply received yes/no	Content of reply
Depiscan 2007	Current status of the study Results for further endpoints	no	--
Garg 2002	Current status of the study Results for further endpoints	no	--

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts, as well as responses from the author, is available on the EUnetHTA website.