IQWiG Reports – Commission No. S19-02

Lung cancer screening with low-dose computed tomography[1]

Extract

[1] Translation of Chapters 1 to 6 of the final report S19-02 *Lungenkrebsscreening mittels Niedrigdosis-Computertomografie* (Version 1.0; Status: 19 October 2020 [German original], 23 December 2020 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Lung cancer screening with low-dose computed tomography

Commissioning agency
Federal Joint Committee

Commission awarded on
18 July 2019

Internal Commission No.
S19-02

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A9 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Jürgen Behr, University Hospital of the Ludwig-Maximilians University Munich, Comprehensive Pneumology Center Munich (CPC-M), Munich, Germany
- Hans-Hermann Dubben, Institute und Polyclinic for General Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany
- Dagmar Lühmann, Institute und Polyclinic for General Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany

IQWiG thanks the external experts for their collaboration in the project.

IQWiG employees

- Mareike Störchel
- Thorsten Busan
- Elke Hausner
- Moritz Felsch
- Daniel Fleer
- Simone Ohlwein
- Sibylle Sturtz

Keywords: Mass Screening, Tomography – X-Ray Computed, Lung Neoplasms, Benefit Assessment, Systematic Review

Key statement

Research question

The objective of this investigation is to

- assess the benefit of lung cancer screening with low-dose computed tomography (LDCT) in comparison with no (systematic) screening

with regard to patient-relevant outcomes in people at elevated risk of lung cancer due to current or past heavy tobacco use.

Conclusion

There is no proof of any effect of lung cancer screening with LDCT on overall survival when compared with no screening. For lung cancer-specific mortality, there is an indication of a benefit of LDCT screening. Since the respective estimators and associated confidence intervals (CIs) for the absolute effect are of a similar magnitude, screening can be reasonably assumed to also have a favourable effect on all-cause mortality. The joint analysis of these two sub-outcomes therefore results in a hint of benefit of LDCT screening for the outcome of mortality.

However, lung cancer screening with LDCT can cause adverse events (hint of harm) and lead to negative consequences via false-positive screening results (proof of harm). Some overdiagnoses occur as well (proof of harm). The studies did not report any data on consequences of false-negative screening results. Their impact on the weighing of benefit and harm is viewed as low. Data from only 1 study were available on the outcome of adverse events, and no usable data were available for the outcome of health-related quality of life. However, the effect of screening on the AE rate and on health-related quality of life is likely reflected in the outcome of overdiagnoses.

In comparison with no screening, within 10 years, LDCT screening for lung cancer spares an estimated 5 of 1000 persons (95% CI: [3;8]) death by lung cancer and may possibly extend the life of some of these screening participants. Mortality-related benefits are primarily countered by harm from false-positive screening results and overdiagnoses. Due to false-positive screening results, a minimum of 1 of 1000 persons and a maximum of 15 of 1000 persons undergo invasive procedures which would not have been performed without the screening. These procedures can cause complications, such as pneumothorax. Overdiagnosis are to be considered harm as a result of the associated unnecessary follow-up diagnostics and therapy, including the resulting complications. In the individual studies, the risk of overdiagnosis was between 0 and 22 of 1000 persons invited to the screening. The risk of overdiagnosis based on the people diagnosed with lung cancer during the screening phase is between 0% and 63% in the individual studies. This highlights the importance of maintaining a low risk of overdiagnosis for a favourable benefit-harm relationship.

In summary, there is a hint of benefit of LDCT screening versus no screening, and hence, the benefit of LDCT screening outweighs its harm in (former) heavy smokers.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
COPD	chronic obstructive pulmonary disease
IDR	incidence density rate
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDCT	low-dose computed tomography
NSCLC	non-small cell lung cancer
PLCO	Prostate, Lung, Colorectal, and Ovarian
RCT	randomized controlled trial
SCLC	small cell lung cancer
UICC	Union for International Cancer Control
VATS	video-assisted thoracoscopic surgery

1 Background

Lung cancer is an epithelial malignant neoplasm in the lung or in the bronchial system [1]. According to the Robert-Koch Institute, in 2016, lung cancer was second only to prostate cancer among the most commonly diagnosed cancers in men in Germany, and it was the most common cancer-related cause of death. In women, lung cancer was among the most commonly diagnosed cancers after breast cancer and colon cancer, and it was the second most common cause of death (after breast cancer). The median age of onset was 70 years for men and 69 years for women [2]. In a joint examination of both sexes, the International Agency for Research on Cancer estimated that, in 2018, lung cancer was the most commonly diagnosed cancer and the most common cancer-related cause death worldwide [3].

The most important risk factor for lung cancer is smoking. In about 9 out of 10 men with lung cancer and at least 6 out of 10 women with lung cancer, the disease was attributed to active smoking. Second-hand smoking increases the risk as well [2]. Environmental exposures such as to radon, particulate matter, or asbestos are further risk factors for lung cancer [2]. The symptoms of the disease are unspecific. Persistent cough and dyspnoea are among the most common symptoms. In advanced disease, patients also experience fatigue, weight loss, chest pain, bone pain, and haemoptysis [1].

A basic distinction is made between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This distinction is based on differences in therapy and prognosis since SCLC progresses rapidly and leads to systemic spread at an early stage. The most important histologic types for further classification of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1]. Further subtypes, which can determine appropriate treatment concepts, can be defined on the basis of additional criteria, e.g. immunohistochemistry or molecular pathology [4].

Moreover, lung cancer is categorized using the TNM Classification (8th edition) from the Union for International Cancer Control (UICC) [5], which stages the disease based on the size of the primary tumour, lymph node involvement, and the degree of metastasis [6]. In 2015 and 2016, a total of 76% of men and 75% of women with initial lung cancer diagnoses were classified in UICC stages III and IV. This is associated with low 5-year survival rates of 15% (men) and 21% (women) [2]. Early detection of lung cancer might therefore improve its prognosis. As early as in 1993, the large-scale U.S. study “Prostate, Lung, Colorectal, and Ovarian” (PLCO) was started, investigating whether lung cancer mortality can be reduced by annual screening with chest radiographs. More than 150 000 individuals participated in the study. Following the 4-year screening phase and a total study duration of 13 years, no statistically significant difference in lung cancer mortality was found when compared with standard care. At the time of diagnosis, the groups were similar in terms of stage distribution. Screening by chest radiographs did not reduce lung cancer tumours in later stages. There was no shift to earlier disease stages [7].

Currently, low-dose computed tomography (LDCT) represents a procedure that might be suitable for the early detection of lung cancer. The image quality of CT has been continuously advanced. By modifying various CT parameters such as tube voltage and tube current, low-dose protocols can be used to reduce the radiation dose, while ensuring sufficient image quality for diagnostics [8]. The S3 guideline of the German Guideline Program in Oncology gives a "can be considered" recommendation for lung cancer screening with LDCT for people aged 55 to 74 years who have consumed more than 30 pack-years and have been smoke-free for less than 15 years as well as for people 50 years of age or older who have consumed more than 20 pack-years and have an additional risk factor, such as asbestos exposure or a family history of lung cancer. The authors of the S3 guideline point out that data from ongoing studies should be awaited before any further recommendations are made [5].

A known problem of lung cancer screening with LDCT is the high rate of false-positive results [5]. Lung nodules are a common finding in CT imaging. Size and morphology are important factors when determining a lung nodule's probability of malignancy. However, other factors, such as localization, growth rate, and the person's age and sex must be considered as well to estimate the probability of malignancy [10]. In case of abnormal screening results, further examinations are conducted for diagnostic clarification. Methods available for this purpose include purely diagnostic procedures such as bronchoscopic transbronchial biopsy and CT-guided percutaneous biopsy as well as video-assisted thoracoscopic biopsy, which can also be performed with a therapeutic objective. Following the pathological confirmation of malignancy, differentiation of the tumour type (grading) and extent (staging) determines the subsequent therapy as well as the prognosis [5].

In Germany, no systematic screening for lung cancer is currently in place. In this health services context, studies comparing LDCT screening versus no screening are therefore relevant for this assessment. Current systematic reviews [11-13] which investigate lung cancer screening with LDCT include studies with the comparator intervention of "no screening" as well as studies in which the comparator intervention was screening with another diagnostic procedure, particularly chest radiographs. This approach is supported by the results of the PLCO study [7], which suggest that "no screening" is comparable with "chest radiograph screening", at least in terms of their effect on lung cancer-specific mortality.

2 Research question

The objective of this investigation is to

- assess the benefit of lung cancer screening with LDCT in comparison with no (systematic) screening

with regard to patient-relevant outcomes in people at elevated risk of lung cancer due to current or past heavy tobacco use.

3 Methods

The target population of the benefit assessment is current or past male and female smokers without suspected lung cancer. The experimental intervention is lung cancer screening with LDCT. The comparator intervention is no screening (or no systematic screening). For a sensitivity analysis of the outcomes of mortality and overdiagnoses, lung cancer screening with chest radiograph was also looked at as a comparator intervention.

The investigation examined the following patient-relevant outcomes:

- Mortality, particularly all-cause mortality and lung cancer-specific mortality
- Morbidity
- Health-related quality of life
- Adverse events (AEs)
- Harm resulting from the screening measure or subsequent diagnostic examinations (e.g. invasive procedures such as biopsies), including the consequences of incorrect screening results (false positive or false negative) and overdiagnoses.

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

The publication had to be written in German or English.

In an effort to identify relevant screening studies as efficiently as possible and to use existing scientific evidence at the highest evidence level, in a 1st step, focused information retrieval was conducted for systematic reviews. The goal was to select 1 or more high-quality, current systematic reviews from which to identify and then select primary studies in accordance with the report's specific inclusion criteria. In a 2nd step, the information retrieval was updated to include the time period not covered by the systematic review(s).

The search for systematic reviews was done as part of the focused information retrieval in the MEDLINE database as well as Cochrane Database of Systematic Reviews and Health Technology Assessment Database, restricting the publication period to the past 6 years.

The supplementary search for primary studies was done as part of the comprehensive information retrieval for the time period not covered by the systematic reviews in the databases of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were additionally used: study registries, screening of reference lists, documents and requests to authors made available from commenting procedures.

The selection of relevant systematic reviews as part of the focused information retrieval was done by 1 reviewer. Relevant primary studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, the risk of bias at study and outcome levels was assessed and rated as high or low. The results of the individual studies were organized according to outcomes and described.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites were met.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter is the case if no data are available or the available data do not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn. Finally, the benefit and harm of lung cancer screening with LDCT was assessed across outcomes.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval found 9 randomized controlled trials to be relevant for the research question of this benefit assessment. Two ongoing studies and 1 planned study were found through the search in study registries. Further, 1 completed study without reported results and 4 studies of unclear status were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 12 June 2020.

Table 1: Study pool of the benefit assessment

Study	Available documents	
	Full publication (in professional journals)	**Registry entry / results report from the study registries**
DANTE	Yes [14-18]	Yes [19] / no
DLCST	Yes [20-35]	Yes [36] / no
ITALUNG	Yes [37-47]	Yes [48] / no
LSS	Yes [49-52]	Yes [53] / no
LUSI	Yes [54-58]	Yes [59] / no
MILD	Yes [60-67]	Yes [68] / no
NELSON	Yes [69-108]	Yes [109] / no
NLST	Yes [110-184]	Yes [185] / yes [186]
UKLS[a]	Yes [187-196]	Yes [197] / no

a: This is a feasibility study in which morbidity and mortality data are to be recorded over a 10-year follow-up period. The study was not used in the benefit assessment since no usable results have been reported so far. Therefore, the tables below do not present UKLS [191].

4.2 Characteristics of the studies included in the assessment

One study, UKLS [187-196], is a feasibility study which generally meets the report's inclusion criteria, but has not reported any results usable for the benefit assessment. Therefore, the tables below do not include UKLS.

The remaining 8 studies (number of randomized persons: 90 836) differed with regard to the screening strategies applied: In 6 studies, participants were allocated to either LDCT screening or no screening. In DLCST [20-35], ITALUNG [37-47], LUSI [54-58], MILD [60-67], and NELSON [69-108], control-group participants were offered no imaging at baseline or in the further course of the study, unless lung cancer was suspected. In DANTE [14-18], a chest radiograph was taken at baseline. Since this scan was taken in both the intervention and comparator groups and no further screening was conducted over the course of the study in the comparator group, this study was deemed suitable for comparing LDCT versus no screening.

In contrast, the 2 studies LSS [49-52] and NLST [110-184] compare LDCT screening versus screening using chest radiography. Both of these studies were RCTs conducted in the USA.

For all no-screening study groups, outcome-specific data were collected via registries. Depending on the study, postal or phone surveys as well as clinical examinations were additionally used. All studies were conducted in Europe (Italy, Denmark, Germany, Netherlands, and Belgium).

Six studies had 3000 to 4000 participants, while NELSON had some 16 000 and NLST 53 500. The screening phase lasted 1 to 6 years, and the planned follow-up was between 5 and 10 years (for LSS, no data were available on follow-up duration). Except in the MILD and NELSON studies, the screening interval was 1 year for all screening rounds. The MILD study was the only 3-arm study, with people in the intervention group being screened either annually or biennially. In the beginning, the study randomized participants to annual or biennial screening. Random allocation to an additional control group started at a later stage, thereby leading to different group sizes. In the NELSON study, the screening interval was increased after each screening round, from 1 year to 2 years and then 2.5 years.

The studies included men and women who smoked at baseline (at least 20 or 30 pack years) or had stopped smoking less than 10 years ago (15 years in NLST). Exceptions were the DANTE study, which included only men, and the NELSON study, which initially recruited only men and started including women only in the later course of the study. The authors justify this approach by the fact that the Dutch population includes relatively few women with long-term exposure to cigarette smoke, resulting in a greater recruitment effort required to achieve the desired case numbers. Therefore, only 16% of participants of the NELSON study are women, while women make up at least 31% of participants in the other studies. The studies specified a participant age of ≥ 49 to 75 years, with the MILD study being the only one not defining an upper age limit.

Screening adherence in the various intervention groups was between 81% and 96%. Of the studies comparing against no screening, 3 reported a contamination of between 1% and 7%, although the validity of these data is unclear. One study comparing against chest radiography screening reports a contamination of 4%. No contamination data were available for the other 4 studies.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 8 studies. Table 2 presents an overview of the available usable data on patient-relevant outcomes from the included studies. All studies reported usable data on the outcome of mortality (all-cause mortality and lung cancer-specific mortality). Chest radiography screening is not viewed as an adequate comparator for investigating the effect of LDCT screening in terms of the consequences of false screening results, health-related quality of life, and AEs in comparison with no screening. For the outcomes of consequences of false screening results, health-related quality of life, and AEs,

only the 6 studies comparing LDCT screening versus no screening were therefore considered. All 6 studies reported usable results on the outcome of consequences of false screening results. Usable results on the outcome of AEs were available from the DANTE study. On the outcome of health-related quality of life, the studies provided either no data or no usable data.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes				
	Mortality	Morbidity			HRQoL
			Screening-related harm		
	All-cause mortality and lung cancer-specific mortality	AEs	Consequences of false screening results	Overdiagnoses	HRQoL
LDCT screening vs. no screening					
DANTE	●	●	●	●	–
DLCST	●	–	●	●	–
ITALUNG	●	–	●	●	–
LUSI	●	–	●	●	–
MILD	●	–	●	●	–
NELSON	●	–	●	●	–
LDCT screening vs. chest radiography screening					
LSS	●	x	x	●	x
NLST	●	x	x	●	x

●: Data were reported and were usable.
–: Either no data were reported, or the data were not usable for the benefit assessment.
x: For this outcome, chest radiography screening is not an adequate comparator for assessing the effect of LDCT screening versus no screening.
AE: adverse event; HRQoL: health-related quality of life; LDCT: low-dose computed tomography

4.4 Assessment of the risk of bias of results

Risk of bias across outcomes

The risk of bias across outcomes was rated as low for 4 studies (DLCST, ITALUNG, LUSI, and NELSON) and as high for the other 4 studies. In the studies with a high risk of bias across outcomes, it was unclear whether the randomization sequence was adequately generated (MILD and NLST) or whether the allocation was appropriately concealed (DANTE, MILD, and NLST). For LSS, it was unclear whether the reporting was independent of results (e.g. missing information on planned outcomes). For the MILD study, significant differences in baseline

characteristics (age, sex, smoking status, and pack-years) between the intervention and control groups led to a high risk of bias.

Risk of bias on the outcome level

In the DLCST, ITALUNG, and NELSON studies, the outcome-specific risk of bias for the outcomes of all-cause mortality, lung cancer-specific mortality, consequences of false screening results, and overdiagnoses was rated as low. While the LUSI study was found to have a low risk of bias on the study level, discrepant information on results provided in the publications led to a high risk of bias for all outcomes. The risk of bias for the outcome of AE was rated as high for the DANTE study, the only study reporting results on AEs.

In all studies (DANTE, MILD, NLST, and LSS) with a high risk of bias across outcomes, the outcome-specific risk of bias was consequently high as well; therefore, no further outcome-specific assessment was conducted for these studies.

4.5 Results on patient-relevant outcomes

4.5.1 Results on mortality

4.5.1.1 Results on all-cause mortality

For the outcome of all-cause mortality, data from 3 studies of high qualitative certainty of results (DLCST, ITALUNG, NELSON) and 3 studies of moderate qualitative certainty of results (DANTE, MILD, LUSI) were available for comparison with no screening. For all studies, the data on the longest follow-up were used, which was between 8 and 11 years from randomization.

Random-effects model metaanalyses were used since the designs of the included studies were insufficiently comparable (e.g. in terms of screening intervals, participant selection criteria, and results analysis) for basing a metaanalysis on a model with fixed effect. The pooled estimator from 3 studies with high qualitative certainty of results was not statistically significant (incidence density rate [IDR]: 0.93; 95% CI: [0.69; 1.26]; p = 0.434). The joint analysis of the studies with high and moderate qualitative certainty of results likewise resulted in no statistically significant effect of screening (IDR: 0.95; 95% CI: [0.88; 1.03]; p = 0.164).

For the comparison of LDCT screening versus chest radiography screening, 2 studies (LSS and NLST) provided data of moderate qualitative certainty of results on the outcome of all-cause mortality. The sensitivity analysis, which took into account these 2 studies with the data for the longest follow-up period, does not contradict the results of the comparison of LDCT screening versus no screening (IDR: 0.97; 95% CI: [0.92; 1.02]; p = 0.168).

For the outcome of all-cause mortality, there is consequently no hint of benefit or harm of lung cancer screening with LDCT.

Subgroup analyses on all-cause mortality

The 6 included studies comparing LDCT screening versus no screening (DANTE, DLCST, ITALUNG, MILD, LUSI, and NELSON) and the 2 studies comparing LDCT screening versus chest radiography screening (LSS and NLST) investigated scanner age (old: use of LDCT scanners < 16 slices versus new: exclusive use of LDCT scanners ≥ 16 slices) and screening centre size (small versus large centres: < versus ≥ 3000 recruited participants) as potential effect modifiers. Where a study switched from old to new scanners over its course, it was classified based on the scanners predominantly used in the study. The breakdowns of studies into subgroups based on the age of the CT scanners and the size of the screening centres were identical. Studies with older CT scanners were conducted in smaller centres, while studies with newer CT scanners were conducted in larger centres. Furthermore, the available data from 4 studies (DANTE, LUSI, NELSON, and NLST) allowed investigating participants' sex as a potential effect modifier. Within the 3-arm MILD study, the length of the screening interval was investigated as an effect modifier since the 2 intervention groups received screening either annually or biennially.

The test for interaction did not show statistical significance in any of the subgroup analyses for the studies comparing to no screening. The results remained unchanged after inclusion of the studies comparing against chest radiography screening as part of a sensitivity analysis.

For all-cause mortality, no effect modification was therefore found by the age of CT scanners or centre size, participant sex, or length of screening interval.

4.5.1.2 Results on lung cancer-specific mortality

For the comparison of LDCT screening versus no screening with regard to lung cancer-specific mortality, data of high qualitative certainty of results were available from 3 studies (DLCST, ITALUNG, and NELSON) and data of moderate qualitative certainty of results from 3 other studies (DANTE, LUSI, MILD). For all studies, the data on the longest follow-up were used, which was between 8 and 11 years from randomization.

The pooled estimator from 3 studies with high qualitative certainty of results was not statistically significant (IDR: 0.80; 95% CI: [0.60; 1.06]; p = 0.076). The collective analysis of studies with moderate and high qualitative certainty of results showed a statistically significant difference (IDR: 0.81; 95% CI: [0.72; 0.91]; p = 0.004) in favour of LDCT screening.

For the comparison of LDCT screening versus chest radiography screening, 2 studies (LSS and NLST) provided data of moderate qualitative certainty of results on lung cancer-specific mortality. The data from the 2 studies on the longest follow-up (5 and 12 years since randomization) were taken into account as part of a sensitivity analysis. Said analysis does not contradict the result of the analysis from the studies comparing against no screening (IDR: 0.89; 95% CI: [0.82; 0.96]; p = 0.010).

For the outcome of lung cancer-specific mortality, there is therefore an indication of a benefit of lung cancer screening with LDCT in comparison with no screening.

Subgroup analyses on lung cancer-specific mortality

For the 6 included studies comparing LDCT screening versus no screening (DANTE, DLCST, ITALUNG, MILD, LUSI, and NELSON) and the 2 studies comparing LDCT screening versus chest radiography screening, the age of the CT scanners used in the studies and the screening centre size (small versus large centres: < versus ≥ 3000 recruited participants) were investigated as potential effect modifiers for lung cancer-specific mortality. Multislice CT scanners with 16 slices or more were defined as new, while all other CT scanners with fewer slices were considered old. Where a study switched from old to new scanners over its course, it was classified based on the scanners predominantly used in the study. The breakdowns of studies into subgroups based on the age of the CT scanners and the size of the screening centres were identical. Studies with older CT scanners were conducted in smaller centres, while studies with newer CT scanners were conducted in larger centres. The subgroup analysis for the studies comparing to no screening showed no effect modification. Even when the studies were included in the comparison against chest radiography screening, no effect modification was found.

For the outcome of lung cancer-specific mortality, available subgroup analyses or correspondingly stratified analyses of multiple studies allowed investigating the following additional effect modifiers: the presence of chronic obstructive pulmonary disease (COPD) at baseline (DLSCT), sex (DANTE, LUSI, NELSON, NLST), participant age (NELSON), and length of screening interval (MILD: annual versus biannual screening).

The test for interaction showed no statistical significance for any of the subgroup analyses. If possible, a sensitivity analysis was conducted, adding the studies comparing LDCT screening versus chest radiography screening. These sensitivity analyses did not contradict the results. For lung cancer-specific mortality, there was no effect modification with regard to the attributes of age of the CT scanner or centre size, presence of COPD at baseline, participant sex and age, or length of the screening interval.

4.5.1.3 Overall analysis for the outcome of mortality

For all-cause mortality, there was no hint of benefit or harm of LDCT screening, but the results of the metaanalyses suggest a decrease in all-cause mortality. An indication of benefit was found for lung cancer-related mortality.

The estimator for absolute effect is 5 of 1000 persons (95% CI: [−3; 12]) for all-cause mortality and 5 of 1000 persons (95% CI: [3; 8]) for lung cancer-specific mortality within about 10 years. Since the respective estimators and associated confidence intervals for absolute effect are of a similar magnitude, overall, a hint of benefit of lung cancer screening with LDCT in comparison with no screening is therefore derived for the outcome of mortality, taking into account the conclusions on benefit on the suboutcomes of lung cancer-specific mortality and all-cause mortality.

4.5.2 Results on adverse events

AEs can occur in the intervention group or in the no-screening comparator group; this distinguishes them from the outcomes reported in Section 4.5.3. A complete survey of this outcome is very resource-intensive since systematic recording is necessary even in the no-screening comparator group.

Usable data on AEs were available only from the DANTE study with moderate qualitative certainty of results, specifically for the occurrence of postoperative AEs as well as for the occurrence of AEs with a severity ≥ 3. No further results on AEs were reported. Presented are the results for the longest follow-up since randomization (maximum of 8 years). The analysis revealed a statistically significant difference in the occurrence of AEs following surgery to address an abnormal finding (OR: 3.48; 95% CI: [1.41; 8.62]; p = 0.004). Hence, there is an effect to the disadvantage of LDCT screening.

Further restriction to AEs of a severity level ≥ 3 likewise revealed a statistically significant difference between the two study groups (OR: 4.25; 95% CI: [0.92; 19.69]; p = 0.046). Hence, there is an effect to the disadvantage of LDCT screening.

For the outcome of AEs, there is overall a hint of harm from lung cancer screening with LDCT in comparison with no screening.

4.5.3 Results on harm directly or indirectly resulting from the screening, including the consequences of false screening results and overdiagnoses

4.5.3.1 Results on the consequences of false-negative screening results

No results were available regarding the consequences of false-negative screening results.

4.5.3.2 Results on the consequences of false-positive screening results

The outcome of consequences of false-positive screening results was assessed using the data of screening participants who had positive screening results, but whose subsequent invasive diagnostics did not confirm the suspected lung cancer. Invasive diagnostics are defined as methods used for histological or cytological confirmation of the diagnosis. This outcome was investigated using both data on purely diagnostic interventional clarification as well as data on surgical therapeutic procedures performed when the treatment and diagnostics of lung tissue of unclear dignity were not readily distinguishable from one another. This is the case if both can be done during one and the same procedure, such as in video-assisted thoracoscopic surgery (VATS). Complications associated with these procedures in patients for whom the subsequent findings were benign were also included in this outcome. The chosen follow-up period was the one at which the screening phase in the respective studies was completed.

Data of high qualitative certainty of results were available from 3 studies (DLCST, ITALUNG, and NELSON) and data with moderate qualitative certainty of results from 3 other studies (DANTE, LUSI, and MILD).

The need for invasive diagnostics was recorded only for the intervention groups in all studies except the DANTE study. While all studies compared LDCT screening versus no screening, the DANTE study conducted chest radiography and 3-day sputum cytology in all participants, regardless of group allocation at baseline. Therefore, it remains unclear whether the intergroup difference is due solely to LDCT screening.

The studies differed in the way they presented the invasive diagnostics: in some studies, procedures and biopsies were presented together, while in others, procedures were reported separately. Multiple operationalizations are available for some studies; these operationalizations strongly affect the number of events. Therefore, no overall estimate was reported for this outcome, but a range [minimum; maximum] of the effect estimators from the individual studies is provided below.

Between 0.1% and 1.5% of the participants invited to the studies underwent invasive diagnostics, which became necessary only due to the false positive result in the screening. Surgery on individuals with benign findings was conducted in 0.1% to 1.3% of the participants invited to the screening. A total of between 0.1% and 1.5% of study participants experienced a consequence from false-positive results.

Complications in individuals who underwent surgery and ended up having benign results were reported in 2 studies (DLCST and NELSON). In DLCST, 2 of 7 people who underwent surgery and ended up having benign findings experienced minor complications; hence, among all participants invited to the screening, 0.1% suffered minor complications after surgery to address benign findings. In the NELSON study, complications were reported not for all persons with benign findings who underwent surgery, but only for those who received either thoracotomy or VATS. These operated patients with benign findings experienced a total of 3 serious complications and 20 minor complications. Hence, serious complications arose in 0.04% of all participants invited to the screening, and minor complications, in 0.3% of them.

Consequently, there is proof of harm from lung cancer screening with LDCT in comparison with no screening as regards the consequences of false-positive screening results.

4.5.3.3 Results of overdiagnoses

The 8 studies in question were RCTs which typically followed up on participants in both groups for about 5 years after the screening phase. The studies reported a high participation rate and low contamination. Overall, all studies were deemed suitable for calculating a risk of overdiagnoses of lung cancer. Data of high qualitative certainty of results were available from the 3 studies DLCST, ITALUNG, and NELSON, and data of moderate qualitative certainty of results from the other 5 studies, DANTE, LUSI, MILD, NLST, and LSS.

Overdiagnoses based on the individuals invited to the screening

From all 8 included studies, the risk of overdiagnosis was calculated for all participants invited to the screening.

Among the 6 included studies comparing LDCT screening versus no screening, the ITALUNG study is the only one where in the total follow-up, fewer lung cancer cases were diagnosed in the intervention group than in the control group. Hence, no overdiagnoses were demonstrated in this study. No overdiagnoses were found for the biennial screening in the MILD study, either. The highest overdiagnosis risk was found in DANTE at 2.2% and DLCST at 2.1%. The calculated risk of overdiagnosis of study participants was 0.9% in LUSI, 0.6% in NELSON and 1.4% for annual screening in the MILD study. In the 2 studies comparing LDCT screening versus chest radiography screening, an overdiagnosis risk of 1.2% was calculated for LSS and 0.1% for NLST.

Overdiagnoses calculated for individuals diagnosed with lung cancer during the screening phase

Data suitable for calculating the risk of overdiagnosis in patients with lung cancer diagnosis were available from 5 studies, 4 of which compared against no screening (DLCST, ITALUNG, LUSI, and NELSON). The result of the DLCST study was particularly notable since it had a calculated risk of overdiagnosis of 63.2%. The overdiagnosis risk in LUSI was 28.6% and in NELSON 16.2%. No overdiagnoses were found for ITALUNG. In the NLST study comparing against chest radiography screening, an overdiagnosis risk of 2.8% was calculated.

In this report, no overall estimate was determined for overdiagnoses. With regard to the overdiagnoses calculated for individuals with a lung cancer diagnosis during the screening phase, the between-study percentages differed so widely that it was impossible to meaningfully interpret an overall estimate. It was not possible to identify specific reasons for the heterogeneity of results, e.g. individual aspects on screening design and characteristics of the study population. For the percentage of overdiagnoses calculated for the persons invited to the screening, heterogeneity was less pronounced, and it was possible to arrive at an overall estimate for the studies comparing against no screening. However, the associated confidence interval is about as broad as the range of the individual point estimators in the studies. Hence, the pooled estimator with confidence interval provides no additional information. To achieve a transparent and uniform presentation of results, the percentage of overdiagnoses was provided as a range [minimum; maximum] of point estimators from the individual studies for both reference quantities.

Since metaanalyses were foregone, no interaction tests were calculated, either. Thus, the subgroup results were presented in tabular form and qualitatively assessed.

For the DANTE and NELSON studies, data were available only on men. For the LUSI study, data were available broken down by men and women. These data do not suggest an effect modification by sex. The NLST study comparing against chest radiography screening reported data broken down by sex which suggest that there is no such effect modification.

For the MILD study, data were available on both annual and biennial screenings. Regarding the screening intervals, the numerical differences in percentages of overdiagnoses between the two

screening groups are likely due to chance since the 95% CIs of the two estimators overlap and each contain the point estimators of the other group. Therefore, this result likewise does not suggest any effect modification by the screening interval.

The diagnosis of lung cancer requires the histological or cytological confirmation of the diagnosis. It is safe to assume that virtually all patients receiving a lung cancer diagnosis also received treatment Any diagnostics and treatment are associated with a risk of adverse events and complications. Hence, there is proof of harm of lung cancer screening with LDCT in comparison with no screening in terms of overdiagnoses, that is, from the resulting invasive diagnostics and treatment, including the associated complications and AEs.

4.5.4 Results on health-related quality of life

Data on health-related quality of life were either not available from the studies or were unusable for the benefit assessment.

4.6 Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

Mortality	Morbidity				HRQoL
All-cause mortality and lung cancer-specific mortality	AEs	Screening-related harm			
		Consequences of false-negative screening results	Consequences of false-positive screening results	Overdiagnoses	
⇗[a]	⇘	–	⇓⇓	⇓⇓	–

⇓⇓: Proof of harm of LDCT screening
⇗: Hint of benefit of LDCT screening
⇘: Hint of harm of LDCT screening
-: No (usable) data reported

a: Based on an indication of benefit in lung cancer-specific mortality and an effect on all-cause mortality which is consistent with it, but statistically not significant.

AE: adverse event; HRQoL: health-related quality of life; LDCT: low-dose computed tomography

4.7 Overview and discussion of the results on all patient-relevant outcomes for weighing benefit and harm

Table 4 below shows an overview and discussion of all patient-relevant outcomes.

Table 4: Overview of and discussion of the results on all patient-relevant outcomes for weighing benefit and harm (multi-page table)

Patient-relevant outcome	Results	Baseline risk[a] per 1000 people	Risk[b] per 1000 invited screening participants	Absolute effect per 1000 invited screening participants [95% CI]	Note
Mortality					
All-cause mortality	IDR: 0.95; 95% CI: [0.88; 1.03]; p = 0.164	101	96	5 [-3; 12]	There is no proof of LDCT screening either decreasing or increasing all-cause mortality. However, the estimator and the confidence interval for absolute effect are of a similar magnitude as those for lung cancer-specific mortality.
Lung cancer-specific mortality	IDR: 0.81; 95% CI: [0.72; 0.91]; p = 0.004	28	23	5 [3; 8]	Without LDCT screening, 28 of 1000 persons die of lung cancer. With LDCT screening, 23 of 1000 persons die of lung cancer. Within 10 years, LDCT screening spares about 5 of 1000 persons from death due to lung cancer.
Morbidity					
AEs[d]	AE after surgery: OR: 3.48; 95% CI: [1.41; 8.62]; p = 0.004	5	17	-12 [-37; -2]	Without LDCT screening, 5 of 1000 persons suffer an AE after surgery, 2 of them an AE of severity ≥ 3. With LDCT screening, 17 of 1000 persons suffer an AE after surgery, 8 of them an AE of severity ≥ 3.
	AE of severity ≥ 3 after surgery: OR: 4.25; 95% CI: [0.92; 19.69]; p = 0.046	2	8	-6 [-36; 0]	LDCT screening leads to 1 additional AE after surgery in 12 persons, in 6 of them with a severity of ≥ 3.
Consequences of false-negative screening results	No data reported	-	-	-	-

Table 4: Overview of and discussion of the results on all patient-relevant outcomes for weighing benefit and harm (multi-page table)

Patient-relevant outcome	Results	Baseline risk[a] per 1000 people	Risk[b] per 1000 invited screening participants	Absolute effect per 1000 invited screening participants [95% CI]	Note
Consequences of false-positive screening results	See Table 25 of the full report	-	-	1 to 15	1–15 of 1000 persons receive invasive diagnostics or surgery with subsequent benign findings[e].
Overdiagnoses	Range [minimum; maximum] of the individual studies' point estimators for overdiagnosis risk of the persons invited to the screening: 0 to 2.2%	-	-	0[f] [0; 1.1] to 22 [1; 42][g]	In 0 to 22 of 1000 persons, the screening detects lung cancer that would not have caused any symptoms during the person's remaining lifetime. These persons undergo diagnostic and therapeutic procedures which are unnecessary, and some of which are associated with complications. The overdiagnosis risk calculated from the individual studies for persons diagnosed with lung cancer during the screening phase is between 0% and 63%.
HRQoL					
HRQoL	No usable data	-	-	-	-

a: Median risk in the control group.
b: Median risk in the intervention group.
c: Mean of follow-up period since randomization.
d: Results of the DANTE study, which was the only study reporting usable data on this outcome.
e: Among all participants invited to the screening, 0.1% to 0.3% (0.04%) had a (serious) complication following surgery on benign findings.
f: Based on the results of the ITALUNG study. Fewer lung cancer cases were diagnosed in the intervention group than in the control group. Hence, no overdiagnoses can be demonstrated.
g: Based on the results of the DANTE study.

AE: adverse event; CI: confidence interval; HRQoL: health-related quality of life; IDR: incidence density rate; LDCT: low-dose computed tomography; OR: odds ratio

5 Classification of the assessment result

Publication bias

Usable results for the report came from 8 studies with over 90 000 participants. However, the results of 3 other studies were missing: The publications of 2 studies (Depiscan 2007 and Garg 2002) were incomplete. Only results at baseline were found. Both studies had low case numbers of 400 [198] and 1000 [199] participants. Another study without published results was referred to as a completed 2000-participant pilot study intended to investigate the feasibility, compliance, and cost of a large RCT [200]. Nevertheless, the available information does not suggest publication bias.

Range for estimating overdiagnoses

The risk of overdiagnosis of the persons diagnosed with lung cancer during the screening phase varied greatly between the studies (0% to 63%). No overdiagnoses were demonstrated in the ITALUNG study, whereas DLCST had the highest rates. The inclusion and exclusion criteria of the two studies as well as their study designs are largely equivalent. Both studies started in 2004, but the ITALUNG study also included some older CT scanners (single slice), while the DLCST study used exclusively multislice technology (16-slice detector systems). The LUSI and NELSON studies, where the risk of overdiagnosis was 29% or 16%, respectively, used newer CT scanners as well. In the NLST study (comparing with chest radiography screening), the risk of overdiagnosis was relatively low, at 2.8%. Like the ITALUNG study, NLST predominantly used older CT scanners. The screening strategies in the ITALUNG and DLCST studies are comparable in terms of the cut-off for new lung nodule diameter defined as a positive finding (≥ 5 mm in diameter). Unlike the ITALUNG study, DLCST included computer-aided volume measurement, thus allowing follow-up CT imaging to be used for determining the volume increase of a lung nodule and estimating the malignancy based on the volume growth. Such software-based analysis for assessing the lung nodule was also used in the LUSI and NELSON studies. A potential explanation is that the use of modern CT scanners and computer-aided calculation of the lung module's growth rate can lead to more true-positive findings and hence to more overdiagnoses.

The risk of overdiagnosis for all participants invited to the screening ranged from 0% to 2.2% in the studies. No relationships between the risk of overdiagnosis and the screening strategies can be derived from these figures.

Weighing of benefits versus harm

Any screening causes harm as a result of false screening results and overdiagnoses. Screening is justified only if its associated benefits outweigh its harms. When weighing benefit versus harm, it must be noted further that the results for the various outcomes are weighted differently.

Benefit

The studies have shown that LDCT screening in (former) heavy smokers reduces the risk of lung cancer-related mortality. Within about 10 years, LDCT screening spares about 5 of 1000

persons (95% CI: [3; 8]) death from lung cancer. On the basis of the study results, however, there is no statistical evidence for screening improving all-cause mortality. Due to competing causes of death, particularly other diseases associated with tobacco use such as other cancer types or cardiovascular diseases, some of the screening participants spared lung cancer death might conceivably die at a similar point in time, resulting in their lives not being substantially prolonged.

This problem was particularly highlighted by the NELSON study [70], which was most recently published: Despite a statistically significant reduction in lung cancer-related death (IDR: 0.76; 95% CI: [0.61; 0.94]) the main analysis showed no appreciable change in all-cause mortality (IDR: 1.01; 95% CI: [0.92; 1.11]). Instead, it was found that other causes of death tended to be more common. Gigerenzer summarized this result as follows: “Simply put, this means that no lives were saved overall” [201]. However, the figures provided by the NELSON study are based on men only, while in the metaanalysis of this report, a reduction of all-cause mortality was certainly numerically recognizable in women (see Figure 4 of the full report). In this report, data for both men and women (16% of the study population) were included from the NELSON study.

The overall results on all-cause mortality do not contradict the results on all-cause mortality either. For instance, the two estimators of the respective metaanalyses point in the same direction. In addition, the estimator and the confidence interval for the absolute effect with respect to all-cause mortality are of a similar magnitude as the effect for lung cancer-specific mortality (see Table 4). The effect of the LDCT screening on lung cancer-specific mortality is likely to be reflected in all-cause mortality as well. Overall, this results in a hint of benefit of low-dose-CT screening for the outcome of mortality.

Harm

Viewed in isolation, the occurrence of an AE as a result of surgery suggests harm. However, very little data on AEs (of all treatment forms) were available for the intervention and control groups; therefore, the actual harm done remains unclear on the basis of these data (see Section A4.3.6 of the full report). Nevertheless, it is reasonable to assume that the screening’s effect on the AE rate will be reflected by the outcome of overdiagnoses.

No results were available on the consequences of false-negative screening results. Individuals with false-negative screening findings are erroneously reassured of having no lung cancer. The most important consequence would be symptoms being ignored, which could delay diagnostics and subsequent treatment. However, if this resulted in higher mortality, it should be reflected by the outcome of lung cancer-specific mortality. Overall, the lack of specific data on this outcome is thought to have only a minor impact on the weighing of benefits and harms. In case of false-positive screening results, individuals experience harm from the notification of a distressing result, from the subsequent diagnostics, and from the associated complications. According to the results of this assessment, out of 1000 participants invited to lung cancer screening, 1 to 15 people undergoes invasive diagnostics or surgery which reveal benign

findings. The most common complication of lung biopsy is pneumothorax [202]. The risk of pneumothorax occurring depends on the biopsy method and location of the lung nodule. Some pneumothorax patients will not need thoracic drainage. Conceivably, the removal of a benign lung nodule might also provide information about other diagnoses and prevent future complications (e.g. retention pneumonia). For instance, the NELSON study documented incidental findings in the screening group [88]. For the present report, no systematic investigation of incidental findings of LDCT screening was conducted since data on such events and their consequences are available only for the screening group. Therefore, it is unclear whether these findings are of benefit or harm to the individuals. While the NLST study considered incidental findings in both groups, once again, chest radiography screening does not represent an adequate comparator for investigating the effect in comparison with no screening. Loomans et al. [176] investigated, for instance, whether incidental findings may lead to a rise in incidence and overdiagnosis of thyroid carcinoma. From the authors' point of view, the data may suggest that. After a median follow-up of 6.6 years in the intervention group and 6.5 years in the comparator group, 35 thyroid carcinomas were diagnosed in the LDCT screening group (n = 26 457) and 25 in the chest radiography screening group (n = 26 238). A total of 7 of the 60 patients with thyroid cancer died, 6 of them from the LDCT screening group, although thyroid cancer was listed as the cause of death for only 3 people. Other causes of death were other cancer diagnoses or heart disease.

The risk of overdiagnosis for people diagnosed with lung cancer during the screening phase varied greatly among studies and was between 0% (no overdiagnoses in the ITALUNG study) and 63% (in the DLCST study). The studies showed that an estimated 0 to 22 of 1000 persons invited to lung cancer screening are diagnosed with lung cancer which would not have caused any symptoms for the remaining lifespan. A comparison with data from the benefit assessment on prostate cancer screening with the PSA test shows that the risk of overdiagnosis is lower for lung cancer screening. In prostate cancer screening, an estimated 35 to 60 of 1000 men invited to screening are overdiagnosed within 16 years [203]. Here, it seems plausible for the higher overdiagnosis rate to be due to the fact that prostate cancer tends to grow markedly more slowly than lung cancer. This assumption is confirmed by the estimator for lung cancer overdiagnosis being lower, with the follow-up period in the studies being only about half as long. It is also worth noting, however, that unlike PSA screening, lung cancer screening targets a high-risk population rather than all men of a specific age group. When looking at cancer-specific mortality as well, the benefit-harm relationship is more favourable for LDCT screening. Prostate cancer screening spares only about half as many men (3 of 1000) from death by the screened-for cancer within about 16 years.

For the outcome of health-related quality of life, no usable data were available. The notification of abnormal findings can be reasonably assumed to adversely impact the health-related quality of life of screening participants. Since this effect is likely short-lived in case of false-positive results, only screening participants with true-positive results are likely to experience a relevant

impact. The effect of screening on health-related quality of life is therefore likely to be largely depicted by the outcome of overdiagnoses.

The German Ministry for the Environment, Nature Conservation, and Nuclear Safety (BMU) is currently assessing whether radiation exposure from multiple years of LDCT screening, including follow-up diagnostics, is permissible.

Considerations regarding the screening programme design

The introduction of lung cancer screening with LDCT would require criteria to be defined for the high-risk population. The 6 European studies show considerable overlap in their study populations. For instance, they all included active smokers as well as nonsmokers who stopped smoking less than 10 years ago. Most studies required a history of more than 20 pack-years. The age of the study participants was about 50 years to 75 years. The German S3 guideline "Prevention, diagnosis, therapy, and follow-up of lung cancer", which takes into account the NLST study from the United States, defines the high-risk population somewhat more narrowly and recommends screening for asymptomatic persons without additional risk factors who are 55 to 74 years of age with a total tobacco use of more than 30 pack-years and less than 15 years of smoking abstinence [5]. Various risk prediction models are currently being proposed to enable a more precise selection of high-risk persons [204,205]. Alongside age and smoking history, criteria which might be used to select high-risk persons include low body mass index (BMI), a family history of lung cancer, other cancers, a self-reported history of COPD, chest radiographs within the past 3 years, low education level, and African descent [205].

The information on smoking status is both self-reported and decisive for the screening selection, begging the question of its reliability. Asking active and past smokers about their smoking habits twice has shown that, across short time periods, self-reports are typically reliable when using standard questions about smoking history [206].

The screening design in the studies predominantly involved an annual LDCT scan. Alongside the screening, participants were often offered consultation or a smoking cessation programme. With regard to the examination strategy, the included studies exhibited considerable heterogeneity. Screening findings were placed into either 2 or 3 categories ("positive", "negative" and, "indeterminate"), and these categories were defined differently. The subsequent follow-up diagnostics and further examination intervals were defined based on the lung nodule category. The studies also used different scanner types. Most studies had the CT scans read by 2 radiologists independently from one another. Some studies employed volumetry software with which follow-up CT images are compared to determine the lung nodule's growth rate and estimate the risk of malignancy. Using volumetry software, Seigneurin et al. [207] observed low recall rates at similar lung cancer detection rates. In the authors' view, this suggests that a volume-based assessment of lung nodules permits more precise distinctions between benign and malignant ones than an assessment based on diameter alone.

In case of an introduction of LDCT screening, quality assurance measures must be taken, including uniform protocols for the evaluation of CT images and the subsequent follow-up and diagnostics. The Lung Imaging Reporting and Data System (Lung RADS System) developed by the American College of Radiology is deemed suitable by the German Radiological Society and German Society for Pneumology and Respiratory Medicine [208]. This system is used for the classification of lung nodules. It also defines the follow-up and further diagnostics necessary depending on the findings [209]. In addition, both societies favour the consistent use of volumetry software [208]. Since radiation exposure can be considerably reduced with the new device generation, screening should be performed exclusively with multislice CT scanners. The quality of lung cancer screening should be continuously reviewed and improved. For this purpose, particularly findings requiring follow-up, i.e. recall rates and the percentage of positive biopsies out of all biopsies, should be recorded [210].

In case of introduction of this screening, it would be important to provide appropriate information materials providing a balanced presentation of advantages and disadvantages of LDCT screening to the target group to enable shared decision making [210].

A recently started European study examines issues related to implementation of the screening [211]. The EU-funded 4-IN THE LONG RUN (INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening) project is coordinated by Erasmus University Medical Centre in Rotterdam, Netherlands. Alongside Germany, the United Kingdom, Spain, Italy, and France are involved in the study. The RCT aims to include a total of 24 000 persons with the goal of investigating the safety of risk-based examination intervals. Further, strategies for recruitment, smoking cessation, and reduction of comorbidities are examined by using a calcium score for cardiovascular disease as well as biomarkers. The study is planned to end in December 2024.

6 Conclusion

There is no proof of any effect of lung cancer screening with LDCT on overall survival when compared with no screening. For lung cancer-specific mortality, there is an indication of a benefit of LDCT screening. Since the respective estimators and associated confidence intervals for the absolute effect are of a similar magnitude, screening can be reasonably assumed to also have a favourable effect on all-cause mortality. The joint analysis of these two sub-outcomes therefore results in a hint of benefit of LDCT screening for the outcome of mortality.

However, lung cancer screening with LDCT can cause adverse events (hint of harm) and lead to negative consequences via false-positive screening results (proof of harm). Some overdiagnoses occur as well (proof of harm). The studies did not report any data on consequences of false-negative screening results. Their impact on the weighing of benefit and harm is viewed as low. Data from only 1 study were available on the outcome of AEs, and no usable data were available for the outcome of health-related quality of life. However, the effect of screening on the AE rate and on health-related quality of life is likely reflected in the outcome of overdiagnoses.

In comparison with no screening, within 10 years, LDCT screening for lung cancer spares an estimated 5 of 1000 persons (95% CI: [3;8]) death by lung cancer and may possibly extend the life of some of these screening participants. Mortality-related benefits are primarily countered by harm from false-positive screening results and overdiagnoses. Due to false-positive screening results, a minimum of 1 of 1000 persons and a maximum of 15 of 1000 persons undergo invasive procedures which would not have been performed without the screening. These procedures can cause complications, such as pneumothorax. Overdiagnosis are to be considered harm as a result of the associated unnecessary follow-up diagnostics and therapy, including the resulting complications. In the individual studies, the risk of overdiagnosis was between 0 and 22 of 1000 persons invited to the screening. The risk of overdiagnosis based on the people diagnosed with lung cancer during the screening phase is between 0% and 63% in the individual studies. This highlights the importance of maintaining a low risk of overdiagnosis for a favourable benefit-harm relationship.

In summary, there is a hint of benefit of LDCT screening versus no screening, and hence, the benefit of LDCT screening outweighs its harm in (former) heavy smokers.

References for English extract

Please see full final report for full reference list.

1. Bösch D. Lunge und Atemwege. Berlin: Springer; 2014.

2. Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland (Ed). Krebs in Deutschland für 2015/2016. Berlin: RKI; 2019. URL: https://www.rki.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2019/krebs_in_deutschland_2019.pdf?__blob=publicationFile

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424.

4. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB 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): 1243-1260.

5. 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 [online]. 02.2018 [Accessed: 09.07.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_l_S3_Lungenkarzinom_2018-03.pdf.

6. Wittekind C (Ed). TNM-Klassifikation maligner Tumore. Weinheim: Wiley-VCH; 2017.

7. 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.

8. Diederich S, Lenzen Z, Puskas A, Koch AT, Yelbuz TM, Eameri M et al. Low dose computerized tomography of the thorax: experimental and clinical studies. Radiologe 1996; 36(6): 475–482

9. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005; 237(2): 395-400.

10. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR et al. Guidelines for management of incidental pulmonary nodules detected on ct images: from the Fleischner Society 2017. Radiology 2017; 284(1): 228-243.

11. 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.

12. 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.

13. 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 (Baltimore) 2018; 97(27): e11233.

14. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G 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): 445-453.

15. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G 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): 1166-1175.

16. Infante M, Chiesa G, Solomon D, Morenghi E, Passera E, Lutman FR 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): 327-335.

17. Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer 2008; 59(3): 355-363.

18. Lopci E, Castello A, Morenghi E, Tanzi D, Cavuto S, Lutman F 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. Nucl Med Commun 2019; 40(5): 508-516.

19. Istituto Clinico Humanitas. The DANTE Trial: a randomized study on lung cancer screening with low-dose spiral computed tomography; study details [online]. In: ClinicalTrials.gov. 11.01.2007 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00420862.

20. Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences of allocation to lung cancer screening: a randomised controlled trial. BMJ Open 2012; 2(2): e000663.

21. Ashraf H, Saghir Z, Dirksen A, Pedersen JH, Thomsen LH, Dossing M 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): 574-579.

22. Ashraf H, Tonnesen P, Holst Pedersen J, Dirksen A, Thorsen H, Dossing M. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). Thorax 2009; 64(5): 388-392.

23. Bons LR, Sedghi Gamechi Z, Thijssen CGE, Kofoed KF, Pedersen JH, Saghir Z et al. Growth of the thoracic aorta in the smoking population: the Danish Lung Cancer Screening Trial. Int J Cardiol 2020; 299: 276-281.

24. 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 Intern Med 2018; 178(10): 1420-1422.

25. Hoyer N, Wille MMW, Thomsen LH, Wilcke T, Dirksen A, Pedersen JH et al. Interstitial lung abnormalities are associated with increased mortality in smokers. Respir Med 2018; 136: 77-82.

26. Jensen MD, Siersma V, Rasmussen JF, Brodersen J. Direct and indirect healthcare costs of lung cancer CT screening in Denmark: a registry study. BMJ Open 2020; 10(1): e031768.

27. Malmqvist J, Siersma V, Thorsen H, Heleno B, Rasmussen JF, Brodersen J. 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.

28. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P et al. The Danish Randomized Lung Cancer CT Screening Trial: overall design and results of the prevalence round. J Thorac Oncol 2009; 4(5): 608-614.

29. Petersen RH, Hansen HJ, Dirksen A, Pedersen JH. Lung cancer screening and video-assisted thoracic surgery. J Thorac Oncol 2012; 7(6): 1026-1031.

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

31. Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). Lung Cancer 2015; 87(1): 65-72.

32. Roe OD, Markaki M, Tsamardinos I, Lagani V, Nguyen OTD, Pedersen JH 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.

33. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF 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.

34. Sorensen L, Nielsen M, Petersen J, Pedersen JH, Dirksen A, De Bruijne M. Chronic obstructive pulmonary disease quantification using CT texture analysis and densitometry: results from the Danish Lung Cancer Screening Trial. AJR Am J Roentgenol 2020; 214(6): 1269-1279.

35. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J 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): 542-551.

36. Danish Lung Cancer Group. Danish Lung Cancer Screening Trial (DLCST) (DLCST): study details [online]. In: ClinicalTrials.gov. 06.07.2007 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00496977.

37. Carozzi FM, Bisanzi S, Carrozzi L, Falaschi F, Lopes Pegna A, Mascalchi M et al. Multimodal lung cancer screening using the ITALUNG biomarker panel and low dose computed tomography: results of the ITALUNG biomarker study. Int J Cancer 2017; 141(1): 94-101.

38. Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol 2013; 8(7): 866-875.

39. Lopes Pegna A, Picozzi G, Mascalchi M, Carozzi MF, Carrozzi L, Comin C 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.

40. Mascalchi M, Belli G, Zappa M, Picozzi G, Falchini M, Della Nave R 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): 421-429.

41. Mascalchi M, Comin CE, Bertelli E, Sali L, Maddau C, Zuccherelli S et al. Screen-detected multiple primary lung cancers in the ITALUNG trial. J Thorac Dis 2018; 10(2): 1058-1066.

42. Mascalchi M, Mazzoni LN, Falchini M, Belli G, Picozzi G, Merlini V et al. Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT. Br J Radiol 2012; 85(1016): 1134-1139.

43. Mascalchi M, Picozzi G, Falchini M, Vella A, Diciotti S, Carrozzi L et al. Initial LDCT appearance of incident lung cancers in the ITALUNG trial. Eur J Radiol 2014; 83(11): 2080-2086.

44. Paci E, Puliti D, Carozzi FM, Carrozzi L, Falaschi F, Pegna AL et al. Prognostic selection and long-term survival analysis to assess overdiagnosis risk in lung cancer screening randomized trials. J Med Screen 2020: 969141320923030.

45. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017; 72(9): 825-831.

46. Pistelli F, Aquilini F, Falaschi F, Puliti D, Ocello C, Lopes Pegna A et al. Smoking cessation in the ITALUNG lung cancer screening: what does “teachable moment” mean? Nicotine Tob Res 2019; 23: 23.

47. Puliti D, Mascalchi M, Carozzi FM, Carrozzi L, Falaschi F, Paci E et al. Decreased cardiovascular mortality in the ITALUNG lung cancer screening trial: analysis of underlying factors. Lung Cancer 2019; 138: 72-78.

48. Cancer Prevention and Research Institute Italy. Italian Lung Cancer Screening Trial (ITALUNG) (ITALUNG): study details [online]. In: ClinicalTrials.gov. 20.05.2016 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT02777996.

49. Croswell JM, Baker SG, Marcus PM, Clapp JD, Kramer BS. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. Ann Intern Med 2010; 152(8). 505-512, w176-w180.

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

51. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P. 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): 114-121.

52. Gohagan JK, Marcus PM, Fagerstrom RM, Pinsky PF, Kramer BS, Prorok PC 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.

53. National Cancer Institute. Lung Screening Study: study details [online]. In: ClinicalTrials.gov. 05.05.2015 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00006382.

54. Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H 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): 890-896.

55. Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H 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): 1475-1486.

56. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA et al. Lung cancer mortality reduction by LDCT screening: results from the randomized German LUSI trial. Int J Cancer 2020; 146(6): 1503-1513.

57. Gonzalez Maldonado S, Delorme S, Husing A, Motsch E, Kauczor HU, Heussel CP 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.

58. Sommer G, Tremper J, Koenigkam-Santos M, Delorme S, Becker N, Biederer J 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): 600-605.

59. German Cancer Research Centre. Spiral computed tomography scanning for the early detection of lung cancer [online]. In: ISRCTN Registry. 19.07.2007 [Accessed: 06.11.2019]. URL: http://isrctn.com/ISRCTN30604390.

60. Pastorino U, Rossi M, Rosato V, Marchiano A, Sverzellati N, Morosi C 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): 308-315.

61. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial. Ann Oncol 2019; 30(7): 1162-1169.

62. Pastorino U, Sverzellati N, Sestini S, Silva M, Sabia F, Boeri M et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. Eur J Cancer 2019; 118: 142-148.

63. Pozzi P, Munarini E, Bravi F, Rossi M, La Vecchia C, Boffi R et al. A combined smoking cessation intervention within a lung cancer screening trial: a pilot observational study. Tumori 2015; 101(3): 306-311.

64. Silva M, Prokop M, Jacobs C, Capretti G, Sverzellati N, Ciompi F et al. Long-term active surveillance of screening detected subsolid nodules is a safe strategy to reduce overtreatment. J Thorac Oncol 2018; 13(10): 1454-1463.

65. Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E 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): 460-467.

66. Sverzellati N, Guerci L, Randi G, Calabro E, La Vecchia C, Marchiano A et al. Interstitial lung diseases in a lung cancer screening trial. Eur Respir J 2011; 38(2): 392-400.

67. Sverzellati N, Silva M, Calareso G, Galeone C, Marchiano A, Sestini S et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. Eur Radiol 2016; 26(11): 3821-3829.

68. Fondazione IRCCS Istituto Nazionale dei Tumori Milano. Early lung cancer detection in high risk individuals (MILD): study details [online]. In: ClinicalTrials.gov. 11.05.2017 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT02837809.

69. Bunge EM, Van den Bergh KAM, Essink-Bot ML, Van Klaveren RJ, De Koning HJ. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. Lung Cancer 2008; 62(3): 385-390.

70. De Koning HJ, Van der Aalst CM, De Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020; 382(6): 503-513.

71. Gietema HA, Schilham AM, Van Ginneken B, Van Klaveren RJ, Lammers JW, Prokop M. 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): 890-897.

72. Gietema HA, Zanen P, Schilham A, Van Ginneken B, Van Klaveren RJ, Prokop M et al. Distribution of emphysema in heavy smokers: impact on pulmonary function. Respir Med 2010; 104(1): 76-82.

73. Han D, Heuvelmans MA, Van der Aalst CM, Van Smoorenburg LH, Dorrius MD, Rook M et al. New fissure-attached nodules in lung cancer screening: a brief report from the NELSON Study. J Thorac Oncol 2020; 15(1): 125-129.

74. Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, De Jonge GJ et al. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening. Br J Radiol 2018; 91(1090): 20170405.

75. Heuvelmans MA, Oudkerk M, De Bock GH, De Koning HJ, Xie X, Van Ooijen PM 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): 1836-1845.

76. Heuvelmans MA, Vliegenthart R, De Koning HJ, Groen HJM, Van Putten MJAM, Yousaf-Khan U et al. Quantification of growth patterns of screen-detected lung cancers: the NELSON study. Lung Cancer 2017; 108: 48-54.

77. Heuvelmans MA, Walter JE, Peters RB, Bock GH, Yousaf-Khan U, Aalst CMV 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.

78. Heuvelmans MA, Walter JE, Vliegenthart R, Van Ooijen PMA, De Bock GH, De Koning HJ et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. Thorax 2018; 73(8): 779-781.

79. Horeweg N, Scholten ET, De Jong PA, Van der Aalst CM, Weenink C, Lammers JW 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): 1342-1350.

80. Horeweg N, Van der Aalst CM, Thunnissen E, Nackaerts K, Weenink C, Groen HJ 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): 848-854.

81. Horeweg N, Van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J 2013; 42(6): 1659-1667.

82. Horeweg N, Van Rosmalen J, Heuvelmans MA, Van der Aalst CM, Vliegenthart R, Scholten ET 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): 1332-1341.

83. Hubers AJ, Heideman DAM, Duin S, Witte BI, De Koning HJ, Groen HJM 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. J Clin Pathol 2017; 70(3): 250-254.

84. Oudkerk M, Heuvelmans MA. Screening for lung cancer by imaging: the Nelson study. JBR-BTR 2013; 96(3): 163-166.

85. Ru Zhao Y, Xie X, De Koning HJ, Mali WP, Vliegenthart R, Oudkerk M. NELSON lung cancer screening study. Cancer Imaging 2011; 11(Spec No A): S79-S84.

86. Takx RA, Vliegenthart R, Mohamed Hoesein FA, Isgum I, De Koning HJ, Mali WP 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.

87. Takx RAP, Isgum I, Willemink MJ, Van der Graaf Y, De Koning HJ, Vliegenthart R 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): 50-57.

88. Van de Wiel JCM, Wang Y, Xu DM, Van der Zaag-Loonen HJ, Van der Jagt EJ, Van Klaveren RJ 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): 1474-1482.

89. Van den Bergh KAM, Essink-Bot ML, Borsboom GJ, Scholten ET, Van Klaveren RJ, De Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011; 38(1): 154-161.

90. Van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, Prokop M, De Koning HJ 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.

91. Van den Bergh KAM, Essink-Bot ML, Bunge EM, Scholten ET, Prokop M, Van Iersel CA 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.

92. Van den Bergh KAM, Essink-Bot ML, Van Klaveren RJ, De Koning HJ. Informed participation in a randomised controlled trial of computed tomography screening for lung cancer. Eur Respir J 2009; 34(3): 711-720.

93. Van der Aalst CM, De Koning HJ, Van den Bergh KAM, Willemsen MC, Van Klaveren RJ. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. Lung Cancer 2012; 76(2): 204-210.

94. Van der Aalst CM, Van den Bergh KAM, Willemsen MC, De Koning HJ, Van Klaveren RJ. 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): 600-605.

95. Van der Aalst CM, Van Klaveren RJ, Van den Bergh KAM, Willemsen MC, De Koning HJ. The impact of a lung cancer computed tomography screening result on smoking abstinence. Eur Respir J 2011; 37(6): 1466-1473.

96. Van Iersel CA, De Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K 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): 868-874.

97. Van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361(23): 2221-2229.

98. Van't Westeinde SC, Horeweg N, De Leyn P, Groen HJ, Lammers JW, Weenink C et al. Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial. Eur J Cardiothorac Surg 2012; 42(3): 420-429.

99. Walter JE, Heuvelmans MA, De Bock GH, Yousaf-Khan U, Groen HJM, Van der Aalst CM 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): 741-747.

100. Walter JE, Heuvelmans MA, De Bock GH, Yousaf-Khan U, Groen HJM, Van der Aalst CM 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: 103-108.

101. Walter JE, Heuvelmans MA, De Jong PA, Vliegenthart R, Van Ooijen PMA, Peters RB 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): 907-916.

102. Walter JE, Heuvelmans MA, Ten Haaf K, Vliegenthart R, Van der Aalst CM, Yousaf-Khan U et al. Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study. Thorax 2019; 74(3): 247-253.

103. Walter JE, Heuvelmans MA, Yousaf-Khan U, Dorrius MD, Thunnissen E, Schermann A et al. New subsolid pulmonary nodules in lung cancer screening: the NELSON Trial. J Thorac Oncol 2018; 13(9): 1410-1414.

104. Xu DM, Gietema H, De Koning H, Vernhout R, Nackaerts K, Prokop M et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer 2006; 54(2): 177-184.

105. Yousaf-Khan AU, Van der Aalst CM, Aerts JGJV, Den Bakker MA, De Koning HJ. Uniform and blinded cause of death verification of the NELSON lung cancer screening participants. Lung Cancer 2017; 111: 131-134.

106. Yousaf-Khan U, Horeweg N, Van der Aalst C, Ten Haaf K, Oudkerk M, De Koning H. 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): 747-753.

107. Yousaf-Khan U, Van der Aalst C, De Jong PA, Heuvelmans M, Scholten E, Lammers JW 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.

108. Yousaf-Khan U, Van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Walter J et al. Risk stratification based on screening history: the NELSON lung cancer screening study. Thorax 2017; 72(9): 819-824.

109. KWF Kankerbestrijding, ZONMW. NEderlands Leuvens Longkanker Screenings Onderzoek (NELSON-screening trial) in high risk subjects [online]. In: Netherlands Trial Register. [Accessed: 06.11.2019]. URL: https://www.trialregister.nl/trial/580.

110. Aberle DR, Adams AM, Berg CD, Clapp JD, Clingan KL, Gareen IF et al. Baseline characteristics of participants in the randomized National Lung Screening Trial. J Natl Cancer Inst 2010; 102(23): 1771-1779.

111. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013; 369(10): 920-931.

112. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS 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.

113. Chudgar NP, Bucciarelli PR, Jeffries EM, Rizk NP, Park BJ, Adusumilli PS et al. Results of the National Lung Cancer Screening Trial: where are we now? Thorac Surg Clin 2015; 25(2): 145-153.

114. Clark MA, Gorelick JJ, Sicks JD, Park ER, Graham AL, Abrams DB 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.

115. Dillard TA, Patel RR, Schroeder C. Uneven distribution of cancer histology in the National Lung Screening Trial. Am J Med Sci 2015; 350(3): 219-221.

116. Gareen IF, Duan F, Greco EM, Snyder BS, Boiselle PM, Park ER 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): 3401-3409.

117. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. J Natl Cancer Inst 2014; 106(11): dju284.

118. Horeweg N, Nackaerts K, Oudkerk M, De Koning HJ. Low-dose computed tomography screening for lung cancer: results of the first screening round. J Comp Eff Res 2013; 2(5): 433-436.

119. Jin GY, Lynch D, Chawla A, Garg K, Tammemagi MC, Sahin H et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. Radiology 2013; 268(2): 563-571.

120. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013; 369(3): 245-254.

121. Kruger R, Flynn MJ, Judy PF, Cagnon CH, Seibert JA. Effective dose assessment for participants in the National Lung Screening Trial undergoing posteroanterior chest radiographic examinations. AJR Am J Roentgenol 2013; 201(1): 142-146.

122. Larke FJ, Kruger RL, Cagnon CH, Flynn MJ, McNitt-Gray MM, Wu X 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): 1165-1169.

123. Marcus PM, Doria-Rose VP, Gareen IF, Brewer B, Clingan K, Keating K 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): 434-438.

124. 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.

125. National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013; 368(21): 1980-1991.

126. Park ER, Gareen IF, Jain A, Ostroff JS, Duan F, Sicks JD et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. Cancer 2013; 119(7): 1306-1313.

127. Patz EF Jr, Greco E, Gatsonis C, Pinsky P, Kramer BS, Aberle DR. 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): 590-599.

128. Patz EF Jr, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemagi MC et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014; 174(2): 269-274.

129. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer 2013; 119(22): 3976-3983.

130. Pinsky PF, Gierada DS, Black W, Munden R, Nath H, Aberle D et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. Ann Intern Med 2015; 162(7): 485-491.

131. Pinsky PF, Gierada DS, Hocking W, Patz EF Jr, Kramer BS. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. Ann Intern Med 2014; 161(9): 627-633.

132. Pinsky PF, Gierada DS, Nath H, Kazerooni EA, Amorosa J. ROC curves for low-dose CT in the National Lung Screening Trial. J Med Screen 2013; 20(3): 165-168.

133. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National Lung Screening Trial: variability in nodule detection rates in chest CT studies. Radiology 2013; 268(3): 865-873.

134. Pinsky PF, Nath PH, Gierada DS, Sonavane S, Szabo E. Short- and long-term lung cancer risk associated with noncalcified nodules observed on low-dose CT. Cancer Prev Res (Phila) 2014; 7(12): 1179-1185.

135. Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. J Natl Cancer Inst 2014; 106(6): dju084.

136. Tanner NT, Gebregziabher M, Hughes Halbert C, Payne E, Egede LE, Silvestri GA. Racial differences in outcomes within the National Lung Screening Trial: implications for widespread implementation. Am J Respir Crit Care Med 2015; 192(2): 200-208.

137. Tanner NT, Kanodra NM, Gebregziabher M, Payne E, Halbert CH, Warren GW et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. Am J Respir Crit Care Med 2016; 193(5): 534-541.

138. Yip R, Henschke CI, Yankelevitz DF, Smith JP. 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): 591-596.

139. Yip R, Yankelevitz DF, Hu M, Li K, Xu DM, Jirapatnakul A et al. Lung cancer deaths in the National Lung Screening Trial attributed to nonsolid nodules. Radiology 2016; 281(2): 589-596.

140. Young RP, Duan F, Chiles C, Hopkins RJ, Gamble GD, Greco EM 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): 1060-1067.

141. 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 Rev Respir Med 2019; 13(6): 585-591.

142. 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.

143. Brown D, Zingone A, Yu Y, Zhu B, Candia J, Cao L et al. Relationship between circulating inflammation proteins and lung cancer diagnosis in the National Lung Screening Trial. Cancer Epidemiol Biomarkers Prev 2019; 28(1): 110-118.

144. Cherezov D, Hawkins SH, Goldgof DB, Hall LO, Liu Y, Li Q 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): 6340-6356.

145. De-Torres JP, Wisnivesky JP, Bastarrika G, Wilson DO, Celli BR, Zulueta JJ. 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): 641-644.

146. Gallardo-Estrella L, Pompe E, De Jong PA, Jacobs C, Van Rikxoort EM, Prokop M et al. Normalized emphysema scores on low dose CT: validation as an imaging biomarker for mortality. PLoS One 2017; 12(12): e0188902.

147. Gierada DS, Pinsky PF, Duan F, Garg K, Hart EM, Kazerooni EA et al. Interval lung cancer after a negative CT screening examination: CT findings and outcomes in National Lung Screening Trial participants. Eur Radiol 2017; 27(8): 3249-3256.

148. Gu F, Cheung LC, Freedman ND, Katki HA, Caporaso NE. Potential impact of including time to first cigarette in risk models for selecting ever-smokers for lung cancer screening. J Thorac Oncol 2017; 12(11): 1646-1653.

149. Hopkins RJ, Duan F, Chiles C, Greco EM, Gamble GD, Aberle D 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.

150. 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): 965-971.

151. Kamel MK, Lee B, Harrison S, Port JL, Pua B, Altorki NK et al. Do the surgical results in the National Lung Screening Trial reflect modern thoracic surgical practice? J Thorac Cardiovasc Surg 2019; 157(5). 2038-2046.e1.

152. Kumar V, Cohen JT, Van Klaveren D, Soeteman DI, Wong JB, Neumann PJ et al. Risk-targeted lung cancer screening: a cost-effectiveness analysis. Ann Intern Med 2018; 168(3): 161-169.

153. Lee C, Flynn MJ, Judy PF, Cody DD, Bolch WE, Kruger RL. Body size-specific organ and effective doses of chest CT screening examinations of the National Lung Screening Trial. AJR Am J Roentgenol 2017; 208(5): 1082-1088.

154. Li Q, Balagurunathan Y, Liu Y, Qi J, Schabath MB, Ye Z et al. Comparison between radiological semantic features and Lung-RADS in predicting malignancy of screen-detected lung nodules in the National Lung Screening Trial. Clin Lung Cancer 2018; 19(2). 148-156.e3.

155. Liu Y, Wang H, Li Q, McGettigan MJ, Balagurunathan Y, Garcia AL 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.

156. Lu H, Mu W, Balagurunathan Y, Qi J, Abdalah MA, Garcia AL 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.

157. National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. J Thorac Oncol 2019; 14(10): 1732-1742.

158. Nguyen XV, Davies L, Eastwood JD, Hoang JK. Extrapulmonary findings and malignancies in participants screened with chest CT in the National Lung Screening Trial. J Am Coll Radiol 2017; 14(3): 324-330.

159. 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. J Med Screen 2018; 25(2): 110-112.

160. Pinsky PF, Gierada DS, Nath PH, Munden R. Lung cancer risk associated with new solid nodules in the National Lung Screening Trial. AJR Am J Roentgenol 2017; 209(5): 1009-1014.

161. Pompe E, De Jong PA, Lynch DA, Lessmann N, Isgum I, Van Ginneken B et al. Computed tomographic findings in subjects who died from respiratory disease in the National Lung Screening Trial. Eur Respir J 2017; 49: 1601814.

162. Robbins HA, Katki HA, Cheung LC, Landy R, Berg CD. Insights for management of ground-glass opacities from the National Lung Screening Trial. J Thorac Oncol 2019; 14(9): 1662-1665.

163. Rojewski AM, Tanner NT, Dai L, Ravenel JG, Gebregziabher M, Silvestri GA 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): 110-118.

164. Sonavane SK, Pinsky P, Watts J Jr, Gierada DS, Munden R, Singh SP et al. The relationship of cancer characteristics and patient outcome with time to lung cancer diagnosis after an abnormal screening CT. Eur Radiol 2017; 27(12): 5113-5118.

165. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and outcomes of small cell lung cancer detected by CT screening. Chest 2018; 154(6): 1284-1290.

166. Wong JYY, Bassig BA, Seow WJ, Hu W, Ji BT, Blair A et al. Lung cancer risk in welders and foundry workers with a history of heavy smoking in the USA: the National Lung Screening Trial. Occup Environ Med 2017; 74(6): 440-448.

167. Yip R, Henschke CI, Xu DM, Li K, Jirapatnakul A, Yankelevitz DF. Lung cancers manifesting as part-solid nodules in the National Lung Screening Trial. AJR Am J Roentgenol 2017; 208(5): 1011-1021.

168. Zhu J, Nelson K, Toth J, Muscat JE. Nicotine dependence as an independent risk factor for atherosclerosis in the National Lung Screening Trial. BMC Public Health 2019; 19(1): 103.

169. National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. Radiology 2011; 258(1): 243-253.

170. Bahl M. Incidental thyroid nodules in the National Lung Screening Trial: estimation of prevalence, malignancy rate, and strategy for workup. Acad Radiol 2018; 25(9): 1152-1155.

171. De-Torres JP, Wisnivesky JP, Bastarrika G, Wilson DO, Celli BR, Zulueta JJ. Exploring the impact of lung cancer screening on lung cancer mortality of smokers with obstructive lung disease: analysis of the NLST-ACRIN Cohort. Arch Bronconeumol 12.05.2020 [Epub ahead of print].

172. Gareen IF, Black WC, Tosteson TD, Wang Q, Sicks JD, Tosteson ANA. 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. Med Care 2018; 56(5): 403-409.

173. Hammer MM, Palazzo LL, Kong CY, Hunsaker AR. Cancer risk in subsolid nodules in the National Lung Screening Trial. Radiology 2019; 293(2): 441-448.

174. Kaminsky DA, Daphtary N, Estepar RSJ, Ashikaga T, Mikulic L, Klein J et al. Ventilation heterogeneity and its association with nodule formation among participants in the National Lung Screening Trial: a preliminary investigation. Acad Radiol 2020; 27(5): 630-635.

175. Kaufman AR, Dwyer LA, Land SR, Klein WMP, Park ER. Smoking-related health beliefs and smoking behavior in the National Lung Screening Trial. Addict Behav 2018; 84: 27-32.

176. Loomans-Kropp HA, Dunn BK, Kramer BS, Pinsky P. Thyroid incidentalomas in association with low-dose computed tomography in the National Lung Screening Trial. Am J Epidemiol 2020; 189(1): 27-33.

177. Munden RF, Chiles C, Boiselle PM, Sicks JD, Aberle DR, Gatsonis CA. Micronodules detected on computed tomography during the National Lung Screening Trial: prevalence and relation to positive studies and lung cancer. J Thorac Oncol 2019; 14(9): 1538-1546.

178. Schreuder A, Jacobs C, Gallardo-Estrella L, Prokop M, Schaefer-Prokop CM, Van Ginneken B. 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.

179. Tanner NT, Thomas NA, Ward R, Rojewski A, Gebregziabher M, Toll B et al. Association of cigarette type with lung cancer incidence and mortality: secondary analysis of the National Lung Screening Trial. JAMA Intern Med 21.10.2019 [Epub ahead of print].

180. Wang S, Chen A, Yang L, Cai L, Xie Y, Fujimoto J et al. Comprehensive analysis of lung cancer pathology images to discover tumor shape and boundary features that predict survival outcome. Sci Rep 2018; 8(1): 10393.

181. Warkentin MT, Tammemagi MC, Freedman MT, Ragard LR, Hocking WG, Kvale PA 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.

182. White CS, Dharaiya E, Dalal S, Chen R, Haramati LB. Vancouver Risk Calculator compared with ACR Lung-RADS in predicting malignancy: analysis of the National Lung Screening Trial. Radiology 2019; 291(1): 205-211.

183. Whittaker Brown SA, Padilla M, Mhango G, Powell C, Salvatore M, Henschke C et al. Interstitial lung abnormalities and lung cancer risk in the National Lung Screening Trial. Chest 2019; 156(6): 1195-1203.

184. Yong PC, Sigel K, De-Torres JP, Mhango G, Kale M, Kong CY et al. The effect of radiographic emphysema in assessing lung cancer risk. Thorax 2019; 74(9): 858-864.

185. National Cancer Institute. National Lung Screening Trial (NLST) screening (NLST): study details [online]. In: ClinicalTrials.gov. 20.05.2014 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00047385.

186. National Cancer Institute. National Lung Screening Trial (NLST) screening (NLST): study results [online]. In: ClinicalTrials.gov. 20.05.2014 [Accessed: 06.11.2019]. URL: https://ClinicalTrials.gov/ct2/show/results/NCT00047385.

187. Ali N, Lifford KJ, Carter B, McRonald F, Yadegarfar G, Baldwin DR 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.

188. Brain K, Carter B, Lifford KJ, Burke O, Devaraj A, Baldwin DR 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): 912-918.

189. Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A 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.

190. Dunn CE, Edwards A, Carter B, Field JK, Brain K, Lifford KJ. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. Patient Educ Couns 2017; 100(8): 1572-1579.

191. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T 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.

192. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE 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): 161-170.

193. Marcus MW, Duffy SW, Devaraj A, Green BA, Oudkerk M, Baldwin D et al. Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: the UKLS trial. Thorax 2019; 74(8): 761-767.

194. McRonald FE, Yadegarfar G, Baldwin DR, Devaraj A, Brain KE, Eisen T 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): 362-371.

195. Nair A, Gartland N, Barton B, Jones D, Clements L, Screaton NJ 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.

196. Nair A, Screaton NJ, Holemans JA, Jones D, Clements L, Barton B 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. Eur Radiol 2018; 28(1): 226-234.

197. Royal Liverpool & Broadgreen University Hospital Trust. UK Lung Cancer Screening Pilot Trial (UKLS) [online]. In: ISRCTN Registry. 19.10.2017 [Accessed: 06.11.2019]. URL: http://www.isrctn.com/ISRCTN78513845.

198. Garg K, Keith RL, Byers T, Kelly K, Kerzner AL, Lynch DA et al. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. Radiology 2002; 225(2): 506-510.

199. Blanchon T, Brechot JM, Grenier PA, Ferretti GR, Lemarie E, Milleron B 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): 50-58.

200. Husband JE. Proposals for lung cancer screening in the UK. Cancer Imaging 2001; 2: 6-16.

201. Gigerenzer G. Unstatistik des Monats: Lungenkrebs-Screening rettet Leben [online]. 28.02.2020 [Accessed: 05.03.2020]. URL: http://www.rwi-essen.de/unstatistik/100.

202. Manhire A, Charig M, Clelland C, Gleeson F, Miller R, Moss H et al. Guidelines for radiologically guided lung biopsy. Thorax 2003; 58(11): 920-936.

203. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Prostatakrebsscreening mittels PSA-Test: Vorbericht (vorläufige Nutzenbewertung); Auftrag S19-01 [online]. 20.12.2019 [Accessed: 18.02.2020]. URL: https://www.iqwig.de/download/S19-01_PSA-Screening_Vorbericht_V1-0.pdf.

204. Ten Haaf K, Bastani M, Cao P, Jeon J, Toumazis I, Han SS et al. A comparative modeling analysis of risk-based lung cancer screening strategies. J Natl Cancer Inst 30.09.2019 [Epub ahead of print].

205. Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA et al. Selection criteria for lung-cancer screening. N Engl J Med 2013; 368(8): 728-736.

206. Volk RJ, Mendoza TR, Hoover DS, Nishi SPE, Choi NJ, Bevers TB. Reliability of self-reported smoking history and its implications for lung cancer screening. Prev Med Rep 2020; 17: 101037.

207. 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.

208. Herth FJF, Reinmuth N, Wormanns D, Antoch G, Biederer J, Vogel-Claussen J 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. Pneumologie 2019; 73(10): 573-577.

209. American College of Radiology. Lung-RADS version 1.1: assessment categories [online]. [Accessed: 04.05.2020]. URL: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf?la=en.

210. Kauczor HU, Baird AM, Blum TG, Bonomo L, Bostantzoglou C, Burghuber O et al. ESR/ERS statement paper on lung cancer screening. Eur Radiol 12.02.2020 [Epub ahead of print].

211. Europäische Kommission. 4-IN THE LUNG RUN: towards INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening [online]. 02.04.2020 [Accessed: 18.08.2020]. URL: https://cordis.europa.eu/project/id/848294/de.

212. 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): 451-455.

213. Lefebvre C, Manheimer E, Glanville J. Searching for studies [online]. In: Higgings JPT, Green S (Ed). Cochrane handbook for systematic reviews of interventions: version 5.1.0. 03.2011 [Accessed: 05.09.2018]. URL: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm.

The full report (German version) is published under

https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentoese-verfahren/s-projekte/s19-02-lungenkrebsscreening-mittels-niedrigdosis-computertomografie.12379.html.

Appendix A – Search strategies

A.1 – Focused information retrieval for systematic reviews

The search lines for indication and intervention (in MEDLINE search lines 1 to 13) were taken from Snowsill 2018 [12] 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 [212] – 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

A.2 – Supplementary search for primary studies in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to June 11, 2020

The following filter was adopted:

- RCT: Lefebvre [213] – 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 filter was adopted:

- RCT: Wong [212] – 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/)
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).

A.3 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: 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/
- Type of search: Standard Search

Search strategy
lung cancer AND computed tomography OR lung cancer AND CT OR lung cancer AND LDCT