Screening for lung cancer with low dose CT scan in the Flemish general practice: a systematic review

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Abstract

Background: Lung cancer is a prevalent disease associated with significant morbidity and mortality so many research has already been done on lung cancer screening. The aim of this systematic review is to evaluate the effect of lung cancer screening by Low Dose CT (LDCT) on mortality and safety, followed by an extended evaluation, to provide an overview and see if lung cancer screening has a place in Flemish general practice.

Methods: This systematic review is performed according to the PRISMA guidelines, using the databases of MEDLINE, EMBASE and Cochrane Library. Only Randomised Controlled Trials comparing LDCT to radiography or no screening, in adults with smoking history or currently smoking, evaluating effect on mortality and safety, were included. Quality assessment was performed using the revised Cochrane risk of bias tool for randomised trials (RoB 2).

Results: After a systematic search, 8 Randomised Controlled Trials were included, all of high quality and low risk of bias. A significant effect on lung cancer mortality was found, averaging a risk reduction around 20% using LDCT. However, effect on all-cause mortality is rather limited, with most trials showing no significant reduction. Only a small number of trials report on safety, stating no important adverse effects arise from LDCT screening.

Discussion: Compared to other types of cancer screening, lung cancer screening raises a lot of questions and difficulties, with challenges in targeting the risk population, reducing false positives, avoiding overdiagnosis, all with impact on quality of life. It remains unclear how to deal with incidental findings, and how to implement smoking cessation guidance in a screening program. The cost-effectiveness and impact on primary care, and how they will support the general practitioners, will be an important issue. Further research concerning these topics is needed, before lung cancer screening can be organised.

Abstract (Nederlands)

Achtergrond: Longkanker is een prevalente ziekte die gepaard gaat met een aanzienlijke morbiditeit en mortaliteit, waardoor reeds veel onderzoek is gedaan naar longkankerscreening. Het doel van deze systematische review is om het effect van longkankerscreening met *Low Dose CT (LDCT)* op mortaliteit en veiligheid te evalueren, gevolgd door een bredere evaluatie om een overzicht te geven en te kijken of longkankerscreening een plaats heeft in de Vlaamse huisartsenpraktijk.

Methoden: Deze systematische review is uitgevoerd volgens de *PRISMA* richtlijnen, met behulp van de databases *MEDLINE*, *EMBASE* en *Cochrane Library*. Alleen gerandomiseerde onderzoeken met controlegroep waarin LDCT werd vergeleken met radiografie of geen screening, bij volwassenen met een rookverleden of die momenteel roken, en waarin het effect op mortaliteit en veiligheid werd geëvalueerd, werden geïncludeerd. De kwaliteit werd beoordeeld met behulp van de herziene *Cochrane risk of bias tool* voor gerandomiseerde onderzoeken (RoB 2).

Resultaten: Na een systematische zoekactie werden 8 gerandomiseerde onderzoeken geïncludeerd met een hoge kwaliteit en laag risico op bias. Er werd een significant effect op longkankersterfte gevonden, met een gemiddelde risicovermindering van ongeveer 20% bij gebruik van LDCT. Het effect op mortaliteit door alle oorzaken is echter vrij beperkt, waarbij de meeste trials geen significante reductie lieten zien. Slechts een klein aantal onderzoeken rapporteert over de veiligheid en stelt dat LDCT-screening geen belangrijke nadelige effecten heeft.

Discussie: Vergeleken met andere soorten screening roept longkankerscreening veel vragen en problemen op, met uitdagingen in het bereiken van de risicopopulatie, verminderen van fout-positieven, vermijden van overdiagnose, allemaal met een impact op de kwaliteit van leven. Het blijft onduidelijk hoe om te gaan met incidentele bevindingen en hoe rookstop begeleiding te implementeren in een screeningsprogramma. De kosteneffectiviteit en de impact op de eerstelijnszorg, en hoe de huisartsen hierin zullen worden ondersteund, zal een belangrijk punt van discussie worden. Verder onderzoek naar deze onderwerpen is nodig alvorens longkankerscreening kan worden georganiseerd.

Abbreviations

CI	Confidence Interval
cig	cigarettes
CXR	Chest X-Ray
GP	General Practitioner
HR	Hazard Ratio
KCE	Belgian Health Care Knowledge Centre
LC	Lung Cancer
LDCT	Low Dose Computed Tomography scan
LLPv2	Liverpool Lung Project risk model version 2
NNS	Number Needed to Screen
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Prostate-Specific Antigen
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RoB	Risk of Bias
RR	Relative Risk
RRR	Relative Risk Reduction
UK	United Kingdom
US	United States
y	years

Introduction

Lung cancer remains an important cause of morbidity and mortality in Flanders, despite increasing options for detection and treatment. In the most recent report of the Belgian Cancer Registry from 2021[1], lung cancer ranks second among the most common cancers in men and women in Belgium, after prostate and breast cancer. It has occupied this position among men for years, and has surpassed colon cancer among women for the first time. In 2021, 3347 Flemish men were diagnosed with lung cancer, with an average age of 71.5 years. In contrast, the disease was diagnosed in 1961 Flemish women, with an average age of 68.9 years. The five-year survival is only 23.7% and 31.6% respectively.

In Flanders, screening programs for colorectal cancer, cervical cancer and breast cancer have been in place for several years.[2] These three are also discussed in the *Domus Medica Gezondheidsgids*[3], with individual guidelines for each type of cancer. There is currently no population screening for prostate cancer, as screening is more debated. However, the Belgian Health Care Knowledge Centre (KCE) has developed a decision aid for this purpose in which shared decision making and informing the patient play a key role.[4]

Since the early 2000's, the possibility of screening for lung cancer has also been investigated. Numerous studies have been conducted worldwide on this subject, including some high-quality randomised controlled trials. One of these, the NELSON study[5], is a Dutch-Belgian collaboration in which the University Hospital of Leuven participated. However, there is currently no screening program for lung cancer in Belgium and by extension Europe. Pilot projects are already underway in many European countries. In the United States, a guideline from the US Preventive Services Task Force (USPSTF) was published in 2013, in which screening using low dose CT scan (LDCT) is recommended for patients at risk.[6] This guideline was recently revised in 2021.[7]

Screening has been taking place in the United States but not in Europe for several years now. Prevention and screening are an important part of the general practitioner's job and lung cancer screening would therefore mainly take place in the general practice. The aim of this systematic review is to determine the effect of screening using a low dose CT scan on lung cancer mortality, the safety and if there is a place for lung cancer screening in Flemish general practice.

Further, we also focus on additional considerations that need to be addressed before a screening program can be introduced and which may be an important reason why there is currently no organized lung cancer screening in many countries. Some examples are overdiagnosis and QoL, patient selection, smoking cessation guidance and cost-effectiveness.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[8]

Since this is a literature study, this type of research did not require approval from an authorized committee for medical ethics and was therefore automatically approved *(see Appendix 1)*.

Databases & Search Strategy

Literature was searched using the databases of MEDLINE (via Pubmed), EMBASE and Cochrane Library. Before conducting a systematic search, a search strategy was compiled based on three concepts: 'lung cancer', 'screening' and 'low dose CT scan'. For each of these concepts, we determined the according subject headings (Mesh terms for MEDLINE and Cochrane, Emtree terms for EMBASE) and their synonyms. These terms were than combined using 'AND' and 'OR', forming a final search string, adapted to the style of each database *(see Appendix 2).* No filters or date limits were applied. Last search in each database took place 31 October 2023.

The results of each database were centralised in Endnote, a citation and reference manager tool. Duplicates were detected by using this software, after which this list of duplicates was checked individually.

Selection process

Inclusion criteria were based on the following PICO (patient, intervention, comparison, outcomes).

P adults (18+), with or without smoking history
I screening with low dose CT scan
C no screening or radiography
O mortality (primary outcome), safety (secondary outcome)

Only Randomised Controlled Trials were included.

We excluded studies that (1) were non-randomised controlled trials, retrospective studies and systematic/narrative reviews, (2) had a language other than English and Dutch, (3) used different types of screening than low dose CT scan and (4) when full text was not available.

Screening of the identified literature was carried out by the main author and occurred in 2 rounds based on inclusion and exclusion criteria. First round screening was carried out by title and abstract followed by a second round of full text assessment.

Data extraction and analysis

Data was extracted from the included trials by the main author, using a predetermined data extraction form. These data include (1) author, (2) publication year, (3) location, (4) study design, (5) sample size, (6) inclusion criteria (screening population), (7) screening method/interval/follow-up period, (8) comparison and (9) outcomes.

A systematic narrative synthesis was conducted to give an overview of the data, the characteristics and the outcome measures of the included studies and to compare between the different studies.

Quality assessment

Quality assessment was performed using the revised Cochrane risk of bias tool for randomised trials (RoB 2).[9] This checklist was applied by the main author to each of the included trials, assessing the risk of bias. The results of this assessment were graphically presented using the risk of bias visualisation tool (robvis).

Results

Study selection and Characteristics

As described above, the search was conducted using the databases of MEDLINE, EMBASE and Cochrane Library. This resulted in the identification of 7,448 records, of which 5,149 eventually remained after removing duplicates using EndNote, individually verified by the author. After a first round screening based on title and abstract, 53 reports remained to be assessed for eligibility by full text reading. Eventually 8 records were included in this systematic review. This entire selection process is visualised in figure 1, including reasons of exclusion.

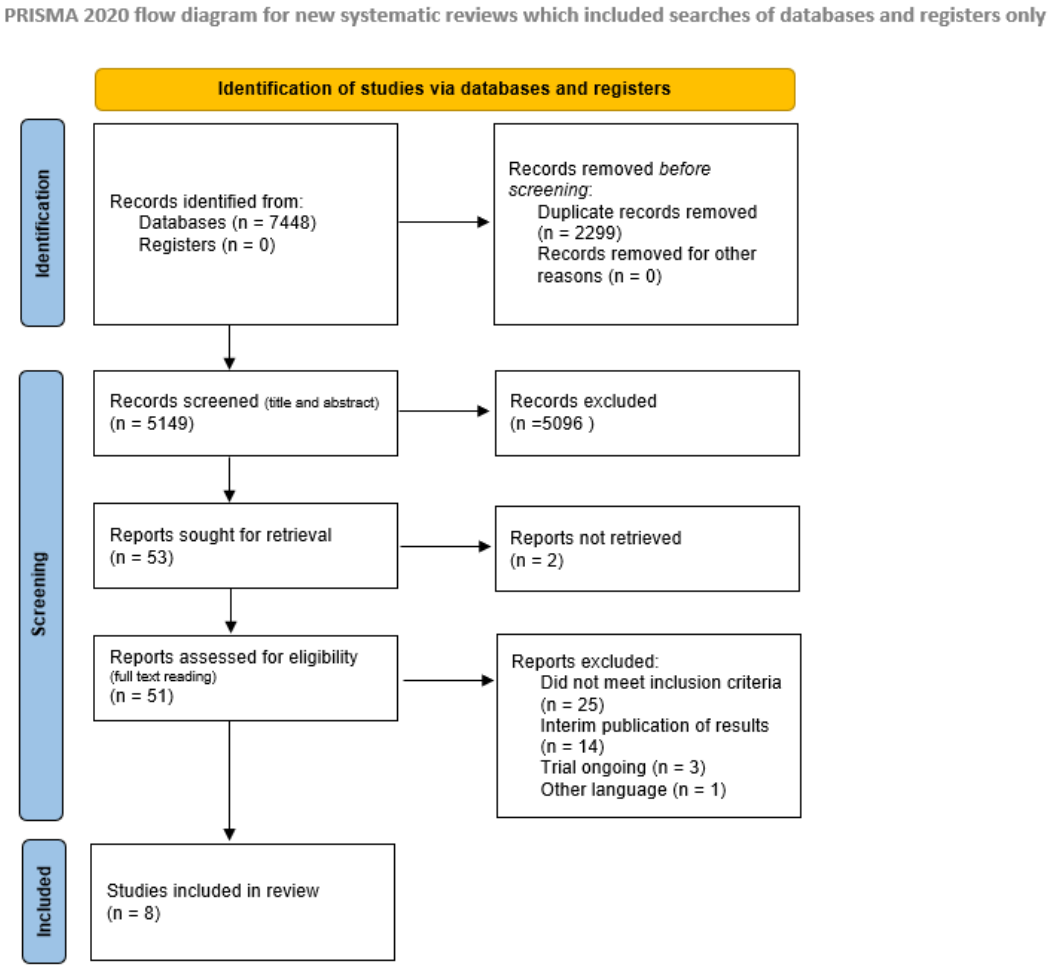


Figure 1: Detailed summary of the search strategy using the PRISMA Flowchart

A total of eight randomised controlled trials were included. The characteristics of these trials are presented in table 1. Two of these trials were conducted in the USA, while the other six took place in Europe. The most important difference between these, was the comparison group. The American trials compared between LDCT and Chest X-Ray, whereas the European trials compared with usual care without screening.

Table 1: Characteristics of included RCT

Author Publication Year Trial name	Location	Sample Size ▪ Intervention group ▪ Control group	Inclusion Criteria	Screening method Interval Median follow up period	Comparison	Outcomes	
						Lung Cancer Mortality	All-cause Mortality
Aberle DR et al. **2011** **NLST**[10]	USA	53,454 ▪ 26,722 ▪ 26,732	▪ 55-74y ▪ ≥30 pack years ▪ ≤15 years since quitting	LDCT 3 annual screenings 6.5y	CXR	RRR: **20.0%** (95% CI, 6.8-26.7; p = 0.004)	RRR: **6.7%** (95% CI, 1.2-13.6; p = 0.02)
Becker N et al. **2019** **LUSI**[11]	Germany	4,052 ▪ 2,029 ▪ 2,023	▪ 50-69y ▪ ≥15 cig/day for ≥25y OR ≥10 cig/day for ≥30y ▪ ≤10 years since quitting	LDCT 5 annual screenings 8.8y	No screening	HR: **0.74** (95% CI: 0.46-1.19; p = 0.21)	HR: **0.99** (95% CI: 0.79-1.25; p = 0.95)
de Koning HJ et al. **2020** **NELSON**[5]	Netherlands Belgium	15,792 Main analysis: men (13,195) ▪ 6,583 ▪ 6,612 Subanalysis: women (2,594) ▪ 1,317 ▪ 1,277	▪ 50-74y ▪ >15 cig/day for >25y OR >10 cig/day for >30y ▪ ≤10 years since quitting	LDCT 4 screenings (start/1y/3y/5.5y) 10y	No screening	Main analysis: men RR: **0.76** (95% CI, 0.61-0.94; p=0.01) Subanalysis women: RR: **0.67** (95% CI, 0.38-1.14)	RR: **1.01** (95% CI, 0.92-1.11) /
Field JK et al. **2016** **2021** **UKLS**[12,13]	UK	4,055 ▪ 2,028 ▪ 2,027	▪ 50-75y ▪ ≥4.5% five-year lung cancer risk (LLP_{v2} risk prediction model)	LDCT 1 screening 7.3y	No screening	RR: **0.65** (95% CI: 0.41-1.02; p=0.062)	RR: **0.91** (95% CI: 0.77-1.09; p=0.315)
Gohagan JK et al. **2005** **Doroudi M et al.** **2018** **LSS**[14,15]	USA	3,318 ▪ 1,660 ▪ 1,658	▪ 55-74y ▪ ≥30 pack years ▪ ≤10 years since quitting	LDCT 2 annual screenings 5.2y	CXR	RR: **1.24** (95% CI: 0.74-2.08)	RR: **1.20** (95% CI: 0.94-1.54)
Infante M et al. **2015** **DANTE**[16]	Italy	2,450 ▪ 1,264 ▪ 1,186	▪ Only males ▪ 60-74y ▪ ≥20 pack years ▪ ≤10 years since quitting	LDCT 5 annual screenings 8.35y	No screening	HR: **0.99** (95% CI: 0.688-1.433)	HR: **0.95** (95% CI: 0.769-1.165)
Paci E et al. **2017** **ITALUNG**[17]	Italy	3,206 ▪ 1,613 ▪ 1,593	▪ 55-69y ▪ ≥20 pack years ▪ ≤10 years since quitting	LDCT 4 annual screenings 9.3y	No screening	RR: **0.70** (95% CI: 0.47-1.03; p=0.07)	RR: **0.83** (95% CI: 0.67-1.03; p=0.08)
Wille MMW et al. **2015** **DLCST**[18]	Denmark	4,104 ▪ 2,052 ▪ 2,052	▪ 50-70y ▪ ≥20 pack years ▪ ≤10 years since quitting after the age of 50y	LDCT 5 annual screenings 10y	No screening	HR: **1.03** (95% CI: 0.66-1.60; p=0.888)	HR: **1.02** (95% CI: 0.82-1.27; p=0.867)

Table 1. Abbreviations: Lung Cancer (LC), Randomised Controlled Trial (RCT), years (y), cigarettes (cig), Low Dose CT (LDCT), Chest X-Ray (CXR), Relative Risk Reduction (RRR), Hazard Ratio (HR), Relative Risk (RR), Confidence Interval (CI)

Risk of Bias

Quality and risk of bias were assessed using the Cochrane RoB2 tool. Each of the included trials was screened for bias in 5 domains using predefined questions and flow charts for each domain. The results per domain of each study were centralised in an excel tool from the developer of the ROB2. The excel file with the full results can be found in supplement 1. Figure 2 is a schematic visualisation of these results using the robvis tool.

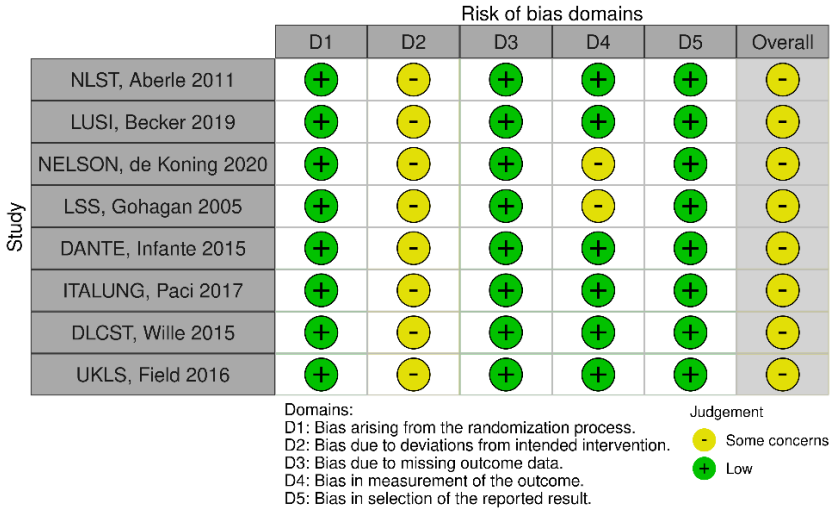


Figure 2: Visualisation of the results from ROB 2 using robvis tool.

Domain 1 (D1) evaluates the process of randomisation. Only RCTs were included in this review and all trials used an adequate method of randomisation. There were no significant differences in baseline characteristics between intervention groups. This resulted in a low risk of bias for all of the included trials.

Domain 2 (D2) checks for the risk of bias due to deviations from the intended intervention. Since the intervention is an act, namely a CT scan and the control group received either no scan or a CXR, participants and caregivers could not be blinded from their assigned group. This fact is inherent in the design of these trials and cannot be avoided. This has led to the judgment of 'some concerns' for all of these trials. The possible risk of bias that arises because of this design, is the possibility of participants from the control group receiving a LDCT on their own initiative or outside the trial. However, the likelihood that this eventually had an impact on the results is rather small. Most of the trials mention the amount of participants receiving a LDCT outside of the trial, which are mostly small. Saghir et. al[19] investigated this contamination in the DLCST, concluding that the amount of people receiving an off-study chest CT was higher in the control group, but relatively small and acceptable. The NELSON and DANTE trial did not provide information on these numbers.

Domain 3 (D3) looks at risk of bias due to missing outcome data. Adherence to screening was high in most of the trials, with participation rates around 90%. Only the ITALUNG trial reported a lower adherence to the screening protocol of 81%. However intention-to-treat analysis was used, so the risk of bias was assessed as low. Overall, no concerns were noted for the included trials regarding this domain.

Domain 4 (D4) focuses on the measurement of the outcomes. Collection of outcome data (lung cancer mortality) occurred mostly by acquiring death certificates from population registries. These were then reviewed and verified by a team who were blinded for the patient's allocation, through comparing with the patient's medical files or by contacting the treating clinic. Most of the trials used this method resulting in a low risk of bias. The NELSON trial started with using a clinical expert committee, yet this was abolished during the trial and official statistics from registries were used. The assessors were also unblinded during the trial. For these reasons, some concerns were withheld for the NELSON trial. Also the LSS trial did not use a review team, only using death certificates in an unblinded way, resulting in some concerns.

Domain 5 (D5) checks for risk of bias due to selective reporting. For all of the trials, this risk was esteemed low.

In conclusion, the quality of the included trials was high and no major risks of bias were found. Because of the results from the second domain (D2), inherent to the design of these trials, the overall judgement seems more negative, resulting in 'some concerns' for all of the trials.

Outcomes

Mortality

The first RCTs published on this topic took place in the United States. The Lung Screening Study (LSS)[14] was the first trial in this field and was a pilot study to assess the feasibility of a larger RCT. A total of 3,318 subjects were randomised to compare between LDCT and CXR. A higher positivity rate after imaging (25.8% vs 8.7%) was found, which resulted in a higher detection rate of lung cancers over the study period (40 vs 20). These results paved the way for a larger RCT. Doroudi et al.[15] performed long term follow up of the LSS trial to assess any difference in mortality rate. A non-significant higher rate of LC deaths (RR: 1.24; 95% CI: 0.74-2.08) and all-cause mortality (RR: 1.20; 95% CI: 0.94-1.54) was found in the LDCT group.

Following these results, the larger National Lung Screening Trial (NLST)[10] was conducted, using the same selection criteria and comparison (CXR) of the LSS. This is the largest RCT to date, enrolling 53,454 persons, who received 3 annual rounds of LDCT or CXR. Unlike the LSS trial, a significant reduction of 20.0% in LC mortality was reported between both groups (RRR: 20.0%; 95% CI: 6.8-26.7; p = 0.004). All-cause mortality was also lower, however the reduction was not as large (RRR: 6.7%; 95% CI: 1.2-13.6; p = 0.02).

In Europe, multiple smaller trials were conducted, evaluating the possibility of LDCT screening. Whereas the American trials compared with CXR, the European studies chose to compare with usual care and thus no screening. Most of these trials were smaller and not powered enough to detect a significant reduction in mortality, yet one of the objectives was to pool all these results and provide evidence for lung cancer screening in Europe.

Two of these trials reported a reduction in LC mortality, however not significant. The German Lung cancer Screening Intervention trial (LUSI)[11] included 4,052 participants of which the intervention group received 5 annual LDCT screening rounds. The hazard ratio for LC mortality was 0.74 (95% CI: 0.46-

1.19; p = 0.21), while all-cause mortality was almost the same (HR: 0.99; 95% CI: 0.79-1.25; p = 0.95). Secondary analysis showed a significant reduction in LC mortality among women (HR: 0.31; 95% CI: 0.10-0.96; p = 0.04). Results from the Italian ITALUNG trial[17] were greater than the German trial. After 4 annual screenings with LDCT and a slightly longer follow up period, a reduction of 30% in LC mortality (RR: 0.70; 95% CI: 0.47-1.03; p=0.07), and 17% in all-cause mortality (RR: 0.83; 95% CI: 0.67-1.03; p=0.08) was found. However, these results were also not significant. Despite the lack of significance, these results were larger than those in the NLST trial. One of the reasons is the longer follow-up period in the ITALUNG trial. They base this on the consistent temporal trend, showing no difference in mortality rate during the screening phase (4 years), whereas a significant reduction was observed in the post-screening period, especially evident from the sixth year.

The DANTE trial[16], another Italian trial, was slightly smaller with 2,450 participants and only males were included. No difference in LC mortality (HR: 0.993; 95% CI: 0.688-1.433) and all-cause mortality (HR: 0.947; 95% CI: 0.769-1.165) was found. The most important reasons for these findings appear to be the smaller sample size, and the fact that only males were included. The Danish Lung Cancer Screening Trial (DLCST)[18] also showed no reduction in LC mortality (HR: 1.03; 95% CI: 0.66-1.60; p=0.888) or all-cause mortality (HR: 1.02; 95% CI: 0.82-1.27; p=0.867). They attribute this result to their selection criteria of younger participants with a lesser smoking history and better lung function, compared to other trials. Performing a high risk subgroup analysis showed a nonsignificant difference in LC mortality, leading the authors to conclude that high-risk profiling is important.

The largest European trial is the Dutch-Belgian NELSON trial[5]. They included 13,195 men (primary analysis) and 2,594 women (subgroup analysis), receiving 4 rounds of LDCT. Unlike the previous trials, a significant reduction in LC mortality was found in the group of men alone (RR: 0.76; 95% CI, 0.61-0.94; p=0.01), even larger than the 20% reduction of the NLST. In line with the other trials, a larger reduction was found in the subgroup analysis of women (RR: 0.67; 95% CI, 0.38-1.14). No difference in all-cause mortality was found (RR: 1.01; 95% CI, 0.92-1.11).

The last RCT took place in the UK, namely the UK Lung Cancer Screening Trial (UKLS)[12,13]. They included 4,055 participants, of which the intervention group received only 1 screening of LDCT. Despite the small sample size and only one round of screening, a meaningful reduction in LC mortality was found, however not significant (RR: 0.65; 95% CI: 0.41-1.02; p=0.062). The ultimate goal of the UKLS was to pool their data and all the data of the previously discussed trials into a meta-analysis. This showed a significant relative reduction in LC mortality of 16% (RR: 0.84; 95% CI: 0.76-0.92). The all-cause mortality reduction was much smaller (RR: 0.97; 95% CI: 0.94-1.00). This led the authors to conclude that there is unequivocal support for LC screening in identified risk groups.

All of the trials use relative risk to evaluate the effect of lung cancer screening on mortality, which can be misleading and may lead to a possible overestimation of the effect. By example, the NLST gives a RRR of 6.7% on all-cause mortality. We used the number of all-cause deaths from the NLST to calculate the absolute risk reduction and Number Needed to Screen (NNS). There were 1,877 deaths over 144,103 person-years in the LDCT group and 2,000 deaths over 143,368 person-years in the control group. This gives an Absolute Risk Reduction (ARR) of 92 deaths/100,000 person-years, resulting in a NNS of 1,087. So based on these numbers, 1,087 people need to be screened to prevent one death from any cause.

Safety

Only two of the included trials reported numbers about safety and adverse events rising from LDCT and subsequent diagnostic procedures.

The NLST[10] reported low rates of complications after a diagnostic procedure for a positive screening test, with comparable rates between the LDCT group and CXR group (1.4% vs 1.6%). The amount of major complications after an invasive diagnostic procedure was 0.06% in participants with a positive screening test that did not result in diagnosis of LC and 11.2% in those who were diagnosed with LC. In the CXR group, the corresponding percentages were 0.02% and 8.2%. A total of 16 patients (10 of whom had LC) in the LDCT group died within 60 days after an invasive diagnostic procedure compared to 10 patients in the CXR group. However, it is uncertain if complications of these procedure were the cause of death. Based on these numbers, the authors conclude that death because of invasive procedures is a rare occurrence.

The ITALUNG[17] trial reports similar death rates between the LDCT group and control group 60 days after surgical treatment (1.2 vs 1.3 per 1000) and 60 days after invasive procedures (3.7 vs 3.8 per 1000). The adverse events in the LDCT group occurred sooner in time due to diagnostic anticipation. They also conclude that no important adverse effects arise from LDCT screening.

Discussion

Mortality

Overall, we can state that most trials show a decrease in lung cancer mortality, significant or not. The largest trials, NLST and NELSON, show a significant relative risk of 0.80 and 0.75 after screening with LDCT compared with no screening or screening with CXR. Most results from the smaller trials were not significant, where authors often attributed this to the smaller sample size. Results from a meta-analysis conducted by Field et. al (UKLS trial) are in line with these findings, indicating a significant relative risk of 0.84, using data of all the European trials and the NLST. Most of the trials show that lung cancers in the LDCT groups are detected in an earlier stage. This supports the hypothesis that as a result of screening, lung cancers are detected earlier, leading to better treatment options and thus a decrease in lung cancer mortality.

However, the results for all-cause mortality are less convincing. NLST reports a relative risk of 0.94, while the meta-analysis by Field et. al shows a relative risk of 0.97. These results may just be significant, but the decrease in mortality is rather limited. However, most of the trials show no difference in all-cause mortality, partially because of lack of power due to small sample sizes.

When considering if lung cancer screening can be implemented, all-cause mortality is more useful since it takes into account the possible benefits and harms of screening and its treatment. An example is that some side effects of screening and treatment can be harmful and be registered as another cause of death than lung cancer. It gives us a more accurate picture of whether screening can save lives.

Patient selection

A yet remarkable observation is the difference between men and women. In a post-hoc analysis of the NLST by Pinsky et al.[20] a difference in all-cause mortality was found between men (0.92) and women (0.73). The NELSON trial included only a small amount of women, but subgroup analysis also showed an increased RR in LC mortality. Also in the other smaller trials, a similar effect was found. Infante et. al included only males in the DANTE trial, where no difference in mortality was found, where the authors considered the lack of women as a possible reason for this. The hypothesis for this finding is the difference in histologic tumour subtypes. The difference between male and female participants was only investigated trough post-hoc analyses, so further research is needed to clarify this difference.

A key issue in LC screening is the selection of the patient population and their risk of developing lung cancer. For screening to be successful and cost-effective, patients at sufficiently high risk must be targeted. Most of the RCTs included their patients based on age and smoking history, with small differences between the RCTs. In the US, where a lung cancer screening program is in place[7], screening addresses adults between 50 and 80 with a 20 pack-year smoking history who currently smoke or have quit within the last 15 years. Of the included trials, only the UKLS trial chose another approach, using the LLPv2 risk prediction model. This model calculates the risk of developing lung cancer in the next 5 years using following variables: sex, age, smoking history, asbestos exposure and personal/family history of respiratory disease. The advantage of this method is that it does not exclude certain groups that also have an increased risk of lung cancer, and that a more personalised risk stratification can be made. However, since more data are needed, it could lead to certain groups being harder to reach in a national screening programme. These models need to be further investigated and compared.

Most of the RCTs included only a small number of women or even none, which can have an impact on mortality as described earlier. Furthermore all the RCTs took place in Europe or the US. However, when implementing a screening programme, we do so in a society with increasing diversity and where the proportion of women in the at-risk population is higher. More research needs to be done in these specific subgroups of patients.

Overdiagnosis & QoL

In any form of screening, we have to consider false positives and overdiagnosis. Particularly for lung cancer screening, there are also incidental findings that can be detected, as a CT scan examines more than just the lungs. The proportion of these phenomena and the psychological impact they have on patients and their quality of life need to be properly investigated before a national screening programme can be introduced.

Overdiagnosis is defined as a diagnosis of lung cancer, detected by screening, that would never have been diagnosed in the patient's lifetime had screening not taken place, because of the lack of symptoms or harm. Rates vary widely between studies, partly due to differences in definitions of overdiagnosis. Patz et al.[21] report a rate of 18.5% (95% CI, 5.4%-30.6%) in the NLST. NELSON and UKLS report lower rates of 8.9% (95% CI, -18.2-32.4) and 15% respectively. Brodersen et al.[22] performed a meta-analysis trying to estimate the degree of overdiagnosis compared with no screening. They state that overdiagnosis can be an important risk in lung cancer screening because slowly/nongrowing types of lung cancer exist, LDCT is a high-resolution imaging technology and eligible screening participants have a high risk of dying from causes other than lung cancer. Including results from 5 European RCT (DLCST, ITALUNG, LUSI, MILD and NELSON), they estimate an overdiagnosis rate of 38% (95% CI 14%–63%), however concluding that there remains an uncertainty due to the heterogeneity of all included trials, imprecision of the point estimate and large variation in the quality of the included trials.

Rates of false positive results also vary remarkably between studies, mainly due to the different way of defining. NLST spoke of a positive result for any nodule >4mm suspicious for lung cancer, including indeterminate scans. Hereby 24.2% of all scans over the 3 screening rounds were marked as positive, of which 96.4% were false positive after further investigation (new scan or invasive procedure). So 23.3% of all the scans were false positive. NELSON and UKLS did not include indeterminate scans when counting false positives, which just needed a follow-up scan and no further invasive diagnostic procedure, resulting in much lower rates of false positives. NELSON reported a false positive result in 1.2% of all participants over all screening rounds. However, 1.6% had a positive test result and 19.7% had an indeterminate scan at baseline of which eventually 95.5% tested negative for lung cancer.[23] UKLS reported a false positive rate of 3.6%. To reduce false positive rates and improve sensitivity/specificity, a good pulmonary nodule management guideline is needed.

Compared with other types of cancer screening, screening for lung cancer with LDCT has the possibility of detecting incidental findings. While we should be wary of potential risks and adverse effects, it also offers opportunities for health gains beyond lung cancer screening. The ITALUNG trial observed an unexpected significant decrease in cardiovascular mortality in the LDCT group, probably due to coronary artery calcification detected on LDCT, however further investigation is needed.[24] Tisi et al.[25] investigated the prevalence of pulmonary and extrapulmonary incidental findings in the SUMMIT study (a prospective observational cohort study to examine the performance of delivering a low-dose CT (LDCT) screening service to a high-risk population). They found incidental findings to be common and

the most frequent to be coronary artery calcification (64.2%) and emphysema (33.4%). More recently a European Respiratory Society (ERS) task force was formed to provide an expert consensus for the management of incidental findings.[26] They selected 9 topics to be most frequent and important: interstitial lung abnormalities, emphysema, bronchiectasis, consolidation, coronary calcification, aortic valve disease, mediastinal mass, mediastinal lymph nodes and thyroid abnormalities. For each of these incidental findings, they provide a statement on how to manage these findings, based on current guidelines /recommendations. When considering implementing screening with LDCT, these incidental findings need to be further investigated. They have the potential to yield additional health gains, but also have the potential consequence of overdiagnosis, additional pressure on healthcare and primary care and impact on cost-effectiveness. Further research on how this can benefit or harm the patient is needed and protocolised evidence-based approaches on how to manage these findings should be implemented.

Both overdiagnosis, false positives and incidental findings can have a major impact on quality of life. When considering implementation of a screening program, it is important to also take this impact into account and not only focus on hard endpoints like mortality. Quality of life and anxiety were evaluated in the NELSON[27] and NLST[28] trial using specific questionnaires. No significant differences in short-term or long-term negative effects on QoL were found. The UKLS trial reported short-term negative consequences to be modest and temporary, which did not persist at long-term follow-up. Wu et al.[29] conducted a systematic review on the psychological burden of lung cancer screening. They state that lung cancer screening might potentially be associated with short-term adverse psychological burden. However, these adverse effects diminish over time and no substantial long-term effects were observed. Evidence regarding this matter is very limited. Most of the evidence is retracted from trials examining the effect of lung cancer screening and may be biased. More research needs to be done to better estimate the real impact on QoL.

Smoking cessation guidance

One of the concerns with lung cancer screening is the so-called 'licence to smoke'. This is the fact that smokers come to see lung cancer screening as an extra protection against the adverse effects of smoking, which could lead to fewer people being inclined to quit smoking. Otherwise, lung cancer screening may also serve as a teachable moment, increasing the readiness and motivation to quit smoking, as recently established in a RCT by Williams et al.[30] In addition, lung cancer screening also raises some ethical questions. Unlike other forms of screening, the at-risk population consists of smokers/ex-smokers, so the disease develops as a result of patient behaviour. So the question arises to what extent should we as a society allocate money and resources to screen for lung cancer in this group of people instead of putting these resources into smoking cessation counselling.

Slatore et al.[31] conducted a systematic review evaluating the effect of lung cancer screening on smoking abstinence. They conclude that lung cancer screening by itself has no impact on abstinence rates. Brain et al.[32] found higher quitting rates in the UKLS trial of 11% at short term and 22% at longer term compared to a cessation rate of 4% in the general UK population. There were small differences between LDCT and control group (T1: 14% vs. 8%; T2: 24% vs. 21%). They conclude that participants with a negative result were not less likely to quit ('license to smoke') and found a positive scan result to be an additional stimulus for quitting.

Implementing smoking cessation counselling in a lung cancer screening programme has the potential to reduce mortality and provide additional health benefits. However, the question remains how great this additional benefit can be and in which manner we can implement this in a screening program. Iacarrino et al.[33] conducted a systematic review seeking to identify the optimal approach for delivering smoking cessation interventions for patients undergoing LDCT screening. They included several trials, using various ways of smoking cessation guidance, with different outcomes. Less intensive interventions (e.g. brochures, brief interventions) made no significant impact, while more intensive interventions (e.g. several counselling visits) appeared to be more effective. The NCI's (National Cancer Institute USA) Smoking Cessation at Lung Examination (SCALE) Collaboration includes eight randomised trials, each assessing evidence-based interventions among smokers undergoing lung cancer screening, of which results are awaited. In the UK, the NHS (National Health Service) are testing to implement a broader Targeted Lung Health Check (TLHC) in screening for lung cancer. One of the elements is a smoking cessation guidance, yet the most effective way to do so is still investigated. One RCT found that immediate, intensive telephone-based smoking cessation support with pharmacotherapy, delivered within a TLHC setting increased the 3-month quit rate. Further research concerning this topic needs to be done. Multiple trials, evaluating different ways of smoking cessation guidance are still ongoing. In addition, more research determining cost-effectiveness of these interventions needs to be done.

Cost-effectiveness

When implementing a nationwide screening program, an important analysis that needs to be made by the government is the cost-effectiveness. Multiple analysis were already made by different countries. Behr et al.[34] recently conducted a systematic review including 43 papers regarding full health economic evaluations of population screening with chest LDCT. They report that cost-effectiveness ratio ranged from US$ 10,000 to US$ 90,000/QALY for screening with LDCT compared to no screening. Most of the included analysis conclude LDCT screening to be cost-effective for current and former smokers aged 55–74 with a minimum of 30 pack-years of smoking history.

During the preparation of this master paper, the Belgian Health Care Knowledge Centre (KCE) published a health technology assessment (HTA) examining lung cancer screening in a high-risk population in Belgium.[35] They have made an economic model of the base case, presented in a 1000-person figure *(see Appendix 3)*. When screening 1000 high-risk individuals, they estimate 704 will have normal scans, 232 will need an extra scan but not have lung cancer (indeterminate result), 34 will need an invasive test but not have lung cancer (false-positive result) and 30 will be diagnosed with lung cancer. Of these 30 individuals, 3.3 lives will be saved thanks to screening and 6.1 would never have caused the person harm (overdiagnosis). These numbers are largely based on the same American and European trials as in this review, using the all-cause mortality rates, and the results are in line with our findings. This scenario results in an Incremental Cost-Effectiveness Ratio (ICER) of €18,530/QALY. Depending on several variables, they conclude that LDCT screening can be cost-effective if the policymaker’s willingness to pay ranges between €20 000 and €30 000 per QALY gained.

Strengths and Limitations

This systematic review tries to give an unbiased overview of the current evidence for lung cancer screening with LDCT. On the one hand, we seek to answer the most important question of whether there is a decrease in mortality, with a key focus on all-cause mortality. On the other hand, we also

provide an overview of important themes inextricably linked to screening in general, and specifically for lung cancer. One of the limitations is that a single author conducted the entire process of this review. All of the included RCTs report their results as relative risks. We made a calculation of the absolute risk reduction an number needed to screen for one RCT, based on this study's original data, yet were unable to do so for all of the included trials. We have to keep in mind that using relative risks can be misleading and may lead to a possible overestimation of the effect.

Conclusion

Lung cancer screening is a topic generating a significant amount of coverage and discussion. All over the world, countries are evaluating the implementation of a nationwide lung cancer screening program. Some high quality trials have shown a significant reduction in lung cancer mortality, averaging a risk reduction around 20%. However, the reduction of screening on all-cause mortality is limited, and surely this is a more important value measure when we want to introduce a screening programme.

Compared to other forms of cancer screening, lung cancer screening involves specific questions and concerns, some of which are already well studied, while others certainly require further research. Targeting the risk population is complex, as risk classification is mainly based on a behavioural characteristic, namely smoking behaviour. This calls for an individual approach to the risk group to be selected, for which risk prediction models can provide a solution. However, the information (e.g. smoking behaviour) is not available for every patient. In the US, where a screening programme has been in place for several years, they observed that the at-risk population is difficult to reach. Strategies to better reach this high-risk group needs to be further investigated. As with other forms of screening, lung cancer screening comes with potential harms, due to radiation, false positives, overdiagnosis and subsequent invasive examinations. This involves physical consequences, but especially the psychological consequences under the form of anxiety and impact on QoL should not be underestimated. In addition, we also have incidental findings through the use of a CT scan on which much more than lung cancer can be detected. On the other hand, these also offer an additional opportunity for health benefits, for example in terms of cardiovascular risk management. Concrete guidelines on how to deal with these incidental findings need to be further developed. Lung cancer screening seems to be cost-effective, however ethical questions arise. To what extent should society's resources be used to screen for disease as a result of patient behaviour? Implementing smoking cessation counselling may provide an answer to this, although the most effective way, impact on mortality and cost-effectiveness need further investigation.

All the above elements make lung cancer screening a complex operation. It therefore requires a highly individualised approach, where comprehensive patient information and shared decision play an important role. Patients should be thoroughly informed about the possible pros and cons of screening and guided in these to make an informed choice. Whereas the CT scan will be done in the hospital, the targeting of at-risk patients, informing and shared decision making will mainly be done in primary care and primarily by the GP. This potentially puts significant additional pressure on primary care. Knowledge about lung cancer screening and willingness of GPs to take on this task should be further explored.

Thus, before a nationwide lung cancer screening program can be introduced, many questions still need to be answered. Policymakers need to take these elements into account, weigh up the pros and cons and ultimately look at the total cost. An alternative to a nationwide screening programme is a decision aid like the one KCE has developed for PSA screening in prostate cancer.[4] This allows the GP to make an informed choice together with the patient. Of course, an important question remains how we would or would not finance this with government funding.

To conclude, lung cancer screening has the potential to add additional health benefit in a targeted risk population. However, compared to other types of screening, lots more questions arise and several topics need to be further investigated, before a nationwide screening program can be implemented. Sufficient patient information on pros and cons, with shared decision being paramount, and guidance on smoking cessation will be important elements. Here, it will also be very important to provide GP practices, where the bulk of screening would be organised, with sufficient guidance, tools and financial resources to support them.

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Competing interests

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Appendices

Appendix 1: Ethical approval

Screening naar longkanker met behulp van low dose CT scan in de Vlaamse huisartsenpraktijk: een systematische review

Dossiernr.:	MP028431
Masterproef:	Masterproef I HAIO, 2022-2025
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2023-2024
Korte omschrijving / abstract:	**Onderzoeksthema** Is er een plaats voor screening naar longkanker in de Vlaamse huisartsenpraktijk? **Achtergrond** Meer en meer stemmen gaan op om screening naar longkanker op te nemen in de preventieve geneeskunde. Naast de gekende preventieve onderzoeken, zou de huisarts hier ook een belangrijke rol in kunnen spelen, aangezien screening een belangrijke taak is in het takenpakket van de huisarts. Indien blijkt dat screening een nut heeft, zal de uiteindelijke screening uitgevoerd moeten worden binnen de huisartsenpraktijk. Zij zullen patiënten selecteren die behoren tot de risicopopulatie en motiveren om aan screening deel te nemen. Recent had ikzelf nog een casus van een dame met een gemetastaseerde longtumor die misschien wel eerder ontdekt had kunnen worden. De vraag is dus of er een plaats is voor screening naar longkanker, wat toch nog steeds 1 van de belangrijkste kankers is in de Belgische populatie. **Onderzoeksdoel** Graag zou ik via het maken van deze masterpaper een antwoord proberen te formuleren op volgende 2 vragen: 1. Is er een plaats voor screening naar longkanker? 2. Hoe zou dit georganiseerd kunnen worden in de Vlaamse huisartsenpraktijk? De eerst vraag is de kern van deze masterpaper. Door het maken van een systematic review probeer ik een overzicht te maken van de huidige evidentie rondom screening naar longkanker en of het wel een plaats heeft in ons screeningsprogramma. Aan de hand van de resultaten uit deze systematic review zou ik dan graag de denkoefening maken hoe we dit concreet zouden kunnen organiseren in de huisartsenpraktijk. (welke doelgroep screenen, hoe organiseren? Hoe frequent screenen?) Ik zou dit willen bespreken in de 'discussie' van mijn paper. Als tweede luik van de discussie zou ik graag de voor- en nadelen van screening ook bespreken.
Toegepaste technieken:	systematic review a.d.h.v. PRISMA guidelines
Gewenste taal van communicatie:	nl
Promotor:	Dr Nicolas Delvaux (u0099109)
Copromotor:	dr. Bernard Duvivier (u0143349)
Organisatie:	KU Leuven
Dienst:	Maatschappelijke Gezondheidszorg en Eerstelijnszorg, Campus Kulak Kortrijk
Discipline:	Masterproef
Extra groepsleden:	Louis Vandaele louis.vandaele@student.kuleuven.be r0625355

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef een zuivere literatuurstudie betreft en dat er op geen enkele wijze gebruik wordt gemaakt van proefdieren, proefpersonen of menselijk lichaamsmateriaal.

Dit type onderzoek vereist geen goedkeuring van een gemachtigde commissie voor medische ethiek.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij het akkoord om het onderzoek in het kader van de masterproef te starten. Deze mail dient als bewijs van goedkeuring mocht u uw onderzoek wensen te publiceren.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet deze goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier.

Appendix 2: Search strings

- **MEDLINE (via Pubmed):**

((("Respiratory Tract Neoplasms"[Mesh] OR "respiratory tract neoplasm*"[tiab] OR "neoplasm* of the respiratory tract"[tiab] OR "respiratory tract cancer*"[tiab] OR "cancer* of the respiratory tract"[tiab] OR "respiratory tract tumor*"[tiab] OR "respiratory tract tumour*"[tiab] OR "tumor* of the respiratory tract"[tiab] OR "tumour* of the respiratory tract"[tiab] OR "respiratory system neoplasm*"[tiab] OR "neoplasm* of the respiratory system"[tiab] OR "respiratory system cancer*"[tiab] OR "cancer* of the respiratory system"[tiab] OR "respiratory system tumor*"[tiab] OR "respiratory system tumour*"[tiab] OR "tumor* of the respiratory system"[tiab] OR "tumour* of the respiratory system"[tiab] OR "respiratory neoplasm*"[tiab] OR "respiratory cancer*"[tiab] OR "respiratory tumor*"[tiab] OR "respiratory tumour*"[tiab] OR "lung neoplasm*"[tiab] OR "neoplasm* of the lung"[tiab] OR "lung cancer*"[tiab] OR "cancer* of the lung"[tiab] OR "lung tumor*"[tiab] OR "lung tumour*"[tiab] OR "tumor* of the lung"[tiab] OR "tumour* of the lung"[tiab] OR "pulmonary neoplasm*"[tiab] OR "pulmonary cancer*"[tiab] OR "pulmonary tumor*"[tiab] OR "pulmonary tumour*"[tiab]) AND ("Early Detection of Cancer"[Mesh] OR "early detection"[tiab] OR "early diagnosis"[tiab] OR "screening"[tiab] OR "screening test"[tiab])) AND ("Tomography, X-Ray Computed"[Mesh] OR "computed tomography"[tiab] OR "CT"[tiab] OR "CT-scan"[tiab])) AND ("low dose"[tiab] OR "low-dose"[tiab] OR "ultra low dose"[tiab] OR "ultra-low-dose"[tiab] OR "LDCT"[tiab])

- **EMBASE:**

('respiratory tract cancer'/exp OR ‘respiratory tract cancer*’:ti,ab,kw OR ‘respiratory tract neoplasm*’:ti,ab,kw OR ‘neoplasm* of the respiratory tract’:ti,ab,kw OR ‘cancer* of the respiratory tract’:ti,ab,kw OR ‘respiratory tract tumor*’:ti,ab,kw OR ‘respiratory tract tumour*’:ti,ab,kw OR ‘tumor* of the respiratory tract’:ti,ab,kw OR ‘tumour* of the respiratory tract’:ti,ab,kw OR ‘respiratory system neoplasm*’:ti,ab,kw OR ‘neoplasm* of the respiratory system’:ti,ab,kw OR ‘respiratory system cancer*’:ti,ab,kw OR ‘cancer* of the respiratory system’:ti,ab,kw OR ‘respiratory system tumor*’:ti,ab,kw OR ‘respiratory system tumour*’:ti,ab,kw OR ‘tumor* of the respiratory system’:ti,ab,kw OR ‘tumour* of the respiratory system’:ti,ab,kw OR ‘respiratory neoplasm*’:ti,ab,kw OR ‘respiratory cancer*’:ti,ab,kw OR ‘respiratory tumor*’:ti,ab,kw OR ‘respiratory tumour*’:ti,ab,kw OR ‘lung neoplasm*’:ti,ab,kw OR ‘neoplasm* of the lung’:ti,ab,kw OR ‘lung cancer*’:ti,ab,kw OR ‘cancer* of the lung’:ti,ab,kw OR ‘lung tumor*’:ti,ab,kw OR ‘lung tumour*’:ti,ab,kw OR ‘tumor* of the lung’:ti,ab,kw OR ‘tumour* of the lung’:ti,ab,kw OR ‘pulmonary neoplasm*’:ti,ab,kw OR ‘pulmonary cancer*’:ti,ab,kw OR ‘pulmonary tumor*’:ti,ab,kw OR ‘pulmonary tumour*’:ti,ab,kw) AND ('cancer screening'/exp OR ‘cancer screening’:ti,ab,kw OR ‘early detection’:ti,ab,kw OR ‘early diagnosis’:ti,ab,kw OR ‘screening’:ti,ab,kw OR ‘screening test’:ti,ab,kw) AND ('computer assisted tomography'/exp OR ‘computer assisted tomography’:ti,ab,kw OR ‘computed tomography’:ti,ab,kw OR ‘CT’:ti,ab,kw OR ‘CT-scan’:ti,ab,kw) AND (‘low dose’:ti,ab,kw OR ‘low-dose’:ti,ab,kw OR ‘ultra low dose’:ti,ab,kw OR ‘ultra-low-dose’:ti,ab,kw OR ‘LDCT’:ti,ab,kw)

- **Cochrane Library:**

#1: [mh "Respiratory Tract Neoplasms"]

#2: ((“respiratory tract” NEXT neoplasm*) OR (neoplasm* NEXT “of the respiratory tract”) OR (“respiratory tract” NEXT cancer*) OR (cancer* NEXT “of the respiratory tract”) OR (“respiratory tract” NEXT tumor*) OR (“respiratory tract” NEXT tumour*) OR (tumor* NEXT “of the respiratory tract”) OR (tumour* NEXT “of the respiratory tract”) OR (“respiratory system” NEXT neoplasm*) OR (neoplasm* NEXT “of the respiratory system”) OR (“respiratory system” NEXT cancer*) OR (cancer* NEXT “of the respiratory system”) OR (“respiratory system NEXT tumor*) OR (“respiratory system NEXT tumour*) OR (tumor* NEXT “of the respiratory system”) OR (tumour* NEXT “of the respiratory system”) OR (“respiratory” NEXT neoplasm*) OR (“respiratory” NEXT cancer*) OR (“respiratory” NEXT tumor*) OR (“respiratory” NEXT tumour*) OR (“lung” NEXT neoplasm*) OR (neoplasm* NEXT “of the lung”) OR (“lung” NEXT cancer*) OR (cancer* NEXT “of the lung”) OR (“lung” NEXT tumor*) OR (“lung” NEXT tumour*) OR (tumor* NEXT “of the lung”) OR (tumour* NEXT “of the lung”) OR (“pulmonary” NEXT neoplasm*) OR (“pulmonary” NEXT cancer*) OR (“pulmonary” NEXT tumor*) OR (“pulmonary” NEXT tumour*)):ti,ab,kw

#3: [mh "Early Detection of Cancer"]

#4: (“early detection” OR “early diagnosis” OR “screening” OR “screening test”):ti,ab,kw

#5: [mh "Tomography, X-Ray Computed"]

#6: (“computed tomography” OR “CT” OR “CT-scan”):ti,ab,kw

#7: (“low dose” OR “low-dose” OR “ultra low dose” OR “ultra-low-dose” OR “LDCT”):ti,ab,kw

#8: #1 OR #2

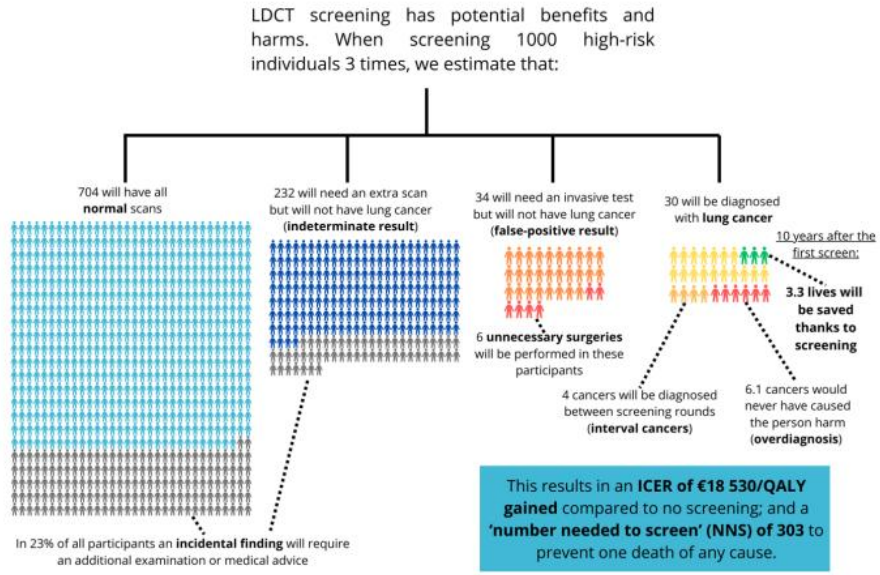
#9: #3 OR #4

#10: #5 OR #6

#11: #7 AND #8 AND #9 AND #10

Appendix 3: 1000-person figure of the KCE base case[35]

Figure 37 – 1000-person figure of the KCE base case



Abbreviations: LDCT = low dose CT scan; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; NNS = number needed to screen. Examples of invasive tests include a biopsy or a bronchoscopy. The information used to create mutually exclusive groups after three screening rounds is published in Horeweg et al.[234] Information about the number of surgeries for false positives is derived from van 't Westeinde et al.[71] Note: the 1000-person figure is also available for other scenarios of overdiagnosis (see further).