Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial

Nanda Horeweg[1,2], Carlijn M. van der Aalst[1], Rozemarijn Vliegenthart[3], Yingru Zhao[3], Xueqian Xie[3], Ernst Th. Scholten[4], Willem Mali[5], Erik Thunnissen[6], Carla Weenink[7], Harry J.M. Groen[8], Jan-Willem J. Lammers[9], Kristiaan Nackaerts[10], Joost van Rosmalen[1], Matthijs Oudkerk[3] and Harry J. de Koning[1]

Affiliations: [1]Dept of Public Health, Erasmus MC, Rotterdam, [2]Dept of Pulmonary Medicine, Erasmus MC, Rotterdam, [3]Dept of Radiology, University of Groningen, UMCG, Groningen, [4]Dept of Radiology, Kennemer Gasthuis, Haarlem, [5]Dept of Radiology, UMCU, Utrecht, [6]Dept of Pathology, VUMC, Amsterdam, [7]Dept of Pulmonary Medicine, Kennemer Gasthuis, Haarlem, [8]Dept of Pulmonary Medicine, UMCG, Groningen, and [9]Dept of Pulmonary Medicine, UMCU, Utrecht, The Netherlands. [10]Dept of Pulmonary Medicine, UZ Gasthuisberg, Leuven, Belgium.

Correspondence: N. Horeweg, Erasmus MC, University Medical Centre Rotterdam, Dept of Public Health/Pulmonary Medicine, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: n.horeweg@erasmusmc.nl

ABSTRACT Several medical associations recommended lung cancer screening by low-dose computed tomography scanning for high-risk groups. Counselling of the candidates on the potential harms and benefits and their lung cancer risk is a prerequisite for screening.

In the NELSON trial, screenings are considered positive for (part) solid lung nodules with a volume >500 mm^3 and for (part) solid or nonsolid nodules with a volume-doubling time <400 days. For this study, the performance of the NELSON strategy in three screening rounds was evaluated and risk calculations were made for a follow-up period of 5.5 years.

458 (6%) of the 7582 participants screened had a positive screen result and 200 (2.6%) were diagnosed with lung cancer. The positive screenings had a predictive value of 40.6% and only 1.2% of all scan results were false-positive. In a period of 5.5 years, the risk of screen-detected lung cancer strongly depends on the result of the first scan: 1.0% after a negative baseline result, 5.7% after an indeterminate baseline and 48.3% after a positive baseline.

The screening strategy yielded few positive and false-positive scans with a reasonable positive predictive value. The 5.5-year lung cancer risk calculations aid clinicians in counselling candidates for lung cancer screening with low-dose computed tomography.

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For editorial comments see page 1459.

This article has supplementary material available from www.erj.ersjournals.com

Received: Dec 06 2012 | Accepted after revision: June 14 2013 | First published online: July 11 2013

Clinical trial: The NELSON trial is registered at www.trialregister.nl (identifier number ISRCTN63545820).

Support statement: The NELSON trial is supported by: ''Zorg Onderzoek Nederland-Medische Wetenschappen'' (ZonMw) (grant number 120610015), ''KWF Kankerbestrijding'' (grant number EMCR 2007-3857) and ''Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen'' (RvvZ). Roche Diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of the volumentric measurements of lung nodules.

Conflict of interest: None declared.

Introduction

A number of prominent medical associations recently recommended screening for lung cancer in high-risk groups by low-dose computed tomography (LDCT) scanning [1–4]. The recommendation resulted from the efforts that have been made by many researchers over the past decade, especially by the National Lung Screening Trial (NLST) research team [5]. The latest systematic review on computed tomography (CT) screening for lung cancer concluded that there are still substantial uncertainties regarding how to translate the positive recommendation into clinical practice [6].

Most individuals eligible for screening will not develop lung cancer but are exposed to several potential harms: radiation exposure, psychological distress while awaiting results, and distress, morbidity and mortality in case of false-positive results [7, 8]. However, for individuals who actually will develop lung cancer, LDCT screening is often able to detect lung cancer at an early stage [5, 9, 10]. The NLST has demonstrated that LDCT screening reduces the risk of dying from lung cancer significantly [5]. Nevertheless, the early detection of lung cancer also leads to a prolonged disease course and will not be beneficial in persons who would otherwise never be diagnosed with lung cancer.

Therefore, to be able to counsel individuals adequately on the benefits and harms of LDCT-screening, clinicians should inform the candidates of their risk of true-positive and false-positive screen results [6]. In the NLST, for example, 24.2% of the subjects had a positive screening, but only 3.6% was diagnosed with lung cancer [5]. Furthermore, to be able to make an informed choice on future screenings, high-risk subjects should know how their probability of screen-detected lung cancer changes after their first screening.

In our trial, the Dutch–Belgian lung cancer screening trial (NELSON) solid lung nodules are assessed with three-dimensional measurements (volume). Screening results are considered positive for volumes >500 mm^3 (diameter $\sim$9.8 mm) or volume-doubling times (VDT) <400 days [9, 11]. This is considerably more stringent than the NLST policy to refer any nodule with a maximum diameter $\geqslant 4$ mm [11, 12]. The volumetry-based screening strategy of the Danish lung cancer screening trial (DLCST) was adopted from our trial and led to a positive screen result in 2.0% of the participants with 34.8% of these results being true-positive [10, 13].

In this study, we will evaluate the performance of the NELSON screening strategy in the first three screening rounds. We will calculate lung cancer detection rates and positive predictive values and compare our results with other LDCT screening trials. Furthermore, we will calculate the 5.5-year risk of false-positive screen results and screen-detected lung cancer stratified by the result of the first screening scan. This will provide valuable information for clinicians who are confronted with individuals who consider or have already undergone LDCT screening for lung cancer.

Methods

Details of the design and conduct of the NELSON trial have been reported elsewhere [11, 14]. Briefly, subjects aged 50–75 years, who had smoked either $\geqslant 15$ cigarettes per day for 25 years or $\geqslant 10$ cigarettes for 30 years and were still smoking or had quit <10 years ago met the inclusion criteria. Before inviting the eligible subjects, persons with a moderate or bad self-reported health, the inability to climb two flights of stairs, a body weight $\geqslant 140$ kg, current or past renal cancer, melanoma or breast cancer and lung cancer diagnosed <5 years ago or still under treatment were excluded [14].

Ultimately, 15 822 individuals were randomised (1:1) to screening (n=7915) with low-dose CT at baseline (first round), 1 year later (second round) and 3 years later (third round) or no screening (n=7909). The main purpose of the trial is to determine whether CT screening will have reduced mortality from lung cancer by at least 25% at 10 years of follow-up [14, 15].

For this study, all 7915 participants randomised to the screening arm were included. Complete data on interval cancers were not yet available and, consequently, no analyses of screening sensitivity were performed.

Equipment and execution of screening examinations

A detailed description of the equipment and the execution of the screening examinations have previously been published [11]. In short, in each of the four screening sites, 16-detector CT scanners were used in a low-dose setting, without the administration of intravenous contrast media [11]. Datasets were derived from images of the thorax with a slice thickness of 1 mm and a slice interval of 0.7-mm [11]. CT images were analysed using software for semi-automated volume measurements (LungCARE; Siemens AG, Erlangen, Germany) [16–18]. In cases where the software was not able to measure nodule volume (*e.g.* in pleural based or nonsolid nodules), the diameter of the nodule was measured manually by the radiologist.

DOI: 10.1183/09031936.00197712

Nodule management protocol

The management protocol of the NELSON trial has been published previously [9, 11, 19]. Briefly, screening could lead to three different outcomes: 1) a negative screen result (no other action than an invitation for the next screening round); 2) an indeterminate result (invitation for a follow-up scan); or 3) a positive result (referral to a pulmonologist for diagnostic work-up).

For newly detected solid nodules and the solid component of part-solid nodules, the volume determined the screening result as follows: <50 mm^3 was negative, 50–500 mm^3 was indeterminate and >500 mm^3 was positive.

For previously detected and nonsolid nodules, the percentage volume change was calculated: $<25\%$ was a negative result and $\geqslant 25\%$ led to the assessment of the VDT. The VDT in days was calculated using the following formula:

$$VDT=(\ln 2 \times \Delta t)/(\ln(V2/V1))$$

where V1 represents nodule volume on the first examination and V2 the volume the second examination and Δt the time between the examinations in days [11]. In case the software was not able to measure nodule volume, manually measured diameters were used to calculate VDT in days using the following formula:

$$VDT=(\ln 2 \times \Delta t)/(\ln((MaxDiamXY2 \times PerpDiamXY2 \times MaxDiamZ2)/ MaxDiamXY1 \times PerpDiamXY1 \times MaxDiamZ1))$$

where MaxDiamXY is the maximum diameter in the *x*/*y*-axis, PerpDiamXY the maximum diameter perpendicular to MaxDiamXY and MaxDiamZ is the maximum diameter in *z*-axis [11].

For nodules with VDTs of 400–600 days, the result was indeterminate; for VDTs of <400 days the result was positive. From the second round onwards, participants with a nodule with a VDT of 400–600 days were invited for a 12-month repeat scan [19]. Furthermore, the screening was also positive if a new solid component had emerged in a previously nonsolid nodule. The screening result was negative for all nodules with fat, benign calcification patterns or other benign abnormalities [11, 19].

Referral, diagnostic work-up and diagnoses

After a positive screening, participants were referred for diagnostic work-up *via* their general practitioner and received usual care according to national and international guidelines [4, 20–23]. All data were prospectively collected and histological specimens were reassessed by our chief pathologist (E. Thunnissen).

Definitions and statistics

Screen-detected lung cancers are the lung cancers that are diagnosed by the diagnostic work-up initiated for a positive screening. The lung cancer detection rate is the number of screen-detected lung cancers divided by the number of screened participants. A true-positive test result is a positive scan in a participant who actually has lung cancer. A false-positive test result is a positive scan, when lung cancer is not diagnosed.

The normality of the distribution of the continuous variables (age and pack-years) was evaluated by studying the Q-Q plots. As the variables were not normally distributed, the variables were described by the median and interquartile range. For analysing the difference between the continuous variables across the three screening rounds, the Kruskal–Wallis H test was used. For analysing the difference between the nominal variables (sex and smoking status) across the three screening rounds, the likelihood ratio-based Chi-squared test was used. To calculate 95% confidence intervals of proportions, bootstrapping was performed based on 1000 samples. For all analysis, $\alpha<0.05$ was considered significant and PASW Statistics, SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used.

Ethics and legal approval

The NELSON trial was approved by the Dutch Minister of Health and the ethics board at each participating centre. The NELSON trial is registered at www.trialregister.nl (number ISRCTN63545820). All participants gave written informed consent for participation and the evaluation of personal data from hospital charts and national registries.

Results

Evaluation of the NELSON screening strategy

7582 (95.8%) of the 7915 participants randomised to the screen-arm of the trial were actually screened. The participation rates remained high across the three screening rounds: 7557 (95.5%) in round one, 7295 (92.2%) in round two and 6922 (87.5%) in round three.

In three screening rounds, 24 354 CT scans were made. 21 773 (89.4%) of the scans were a regular ''round scans'' and 2581 (10.6%) were follow-up scans, performed to assess the VDT of indeterminately sized nodules. The scans detected a total of 31 683 nodules: 266 (0.8%) were part-solid and 298 (0.9%) nonsolid.

The screening result was negative in 87.2% of all scans (21 232 out of 24 354). The result was indeterminate in 10.8% (2629 out of 24 354) and positive in 2.0% (493/24 354) of the scans. In the first round, the proportion of indeterminate and positive scan results was relatively higher than in later rounds. A detailed overview of the scan results per screening round is presented in figures 1–3.

The 493 positive screen results led to the diagnosis of lung cancer in 200 participants. 14 (7.0%) of these 200 participants were referred for a part-solid nodule and eight participants (4.0%) for a nonsolid nodule. 40.6% (200 out of 493) of all positive screenings were ''true-positive'' (95% CI 36.1–45.2). The positive predictive value slightly increased across the three rounds, from 35.5% (95% CI 28.4–42.1) in round one to 42.0% in round two (95% CI 34.4–49.6) to 45.5% (95% CI 37.6–53.3) in round three.

The cumulative lung cancer detection rate of the three rounds was 200 (2.6%) out of 7582 (95% CI 2.3–3.0). This detection rate was relatively stable across the three screening rounds: 0.9% (75 of 6922, 95% CI 0.7–1.2%) in round one, 0.8% (55 of 7295, 95% CI 0.6–1.0) in round two and 1.1% (75 of 6922, 95% CI 0.8–1.3) in round three.

The 493 positive screen results did not lead to a lung cancer diagnosis in the remaining 293 cases. Hence, 59.4% (293 of 493, 95% CI 54.8–63.9) of the positive screen results were actually ''false-positive''. Overall, 1.2% (293 of 24 354) of the scans performed in three rounds of the NELSON trial had a false-positive result.

The ratio of the overall true-positive and false-positive results (the true-positive/false-positive ratio) was 0.69. The true-positive/false-positive ratio tended to improve over time, from 0.69 in round one to 0.72 in round two, and to 0.83 in round three.

To detect lung cancer in 200 participants, 7582 individuals underwent three rounds of screening. In the first screening round, 108 (7557/70) participants were screened to detect one lung cancer. In the second round

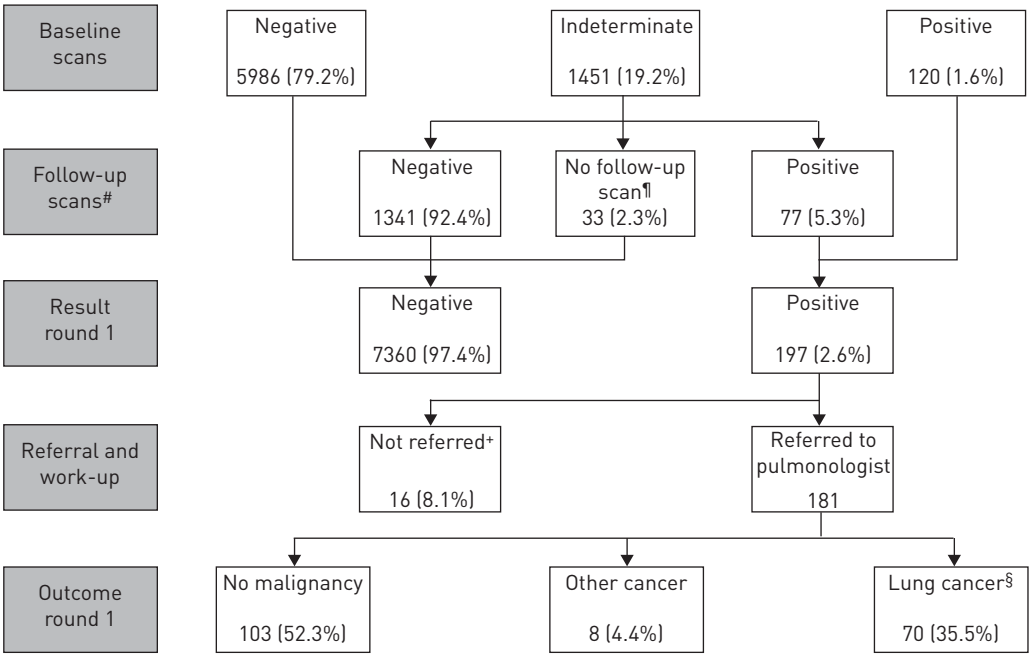

FIGURE 1 Results of the first round of screening (January 2004 to December 2006): 7915 participants were randomised to the screening arm of the trial and 7557 participants underwent screening; 25 (0.3%) participants missed screening in the first round but were screened in the second round and 333 (4.2%) participants did not respond to the invitation for screening. Please note that percentages for outcome are calculated using the total number of positive results as the denominator. #: after mean ± SD 99.6 ± 18.3 days. In 8.3% of the subjects with an indeterminate result, the nodule(s) had disappeared. ¶: reasons were administrative error (n=15), no show (n=13), refusal (n=3), and already receiving treatment from another specialist (n=2). +: reasons were decision by tumour board (n=10), administrative error (n=3), and already receiving treatment from another specialist (n=3). §: 67 (95.7%) out of 70 lung cancer diagnoses were confirmed by cytology or histology. Details concerning the basis of the diagnosis of the three other cases can be found in the online supplementary data.

DOI: 10.1183/09031936.00197712

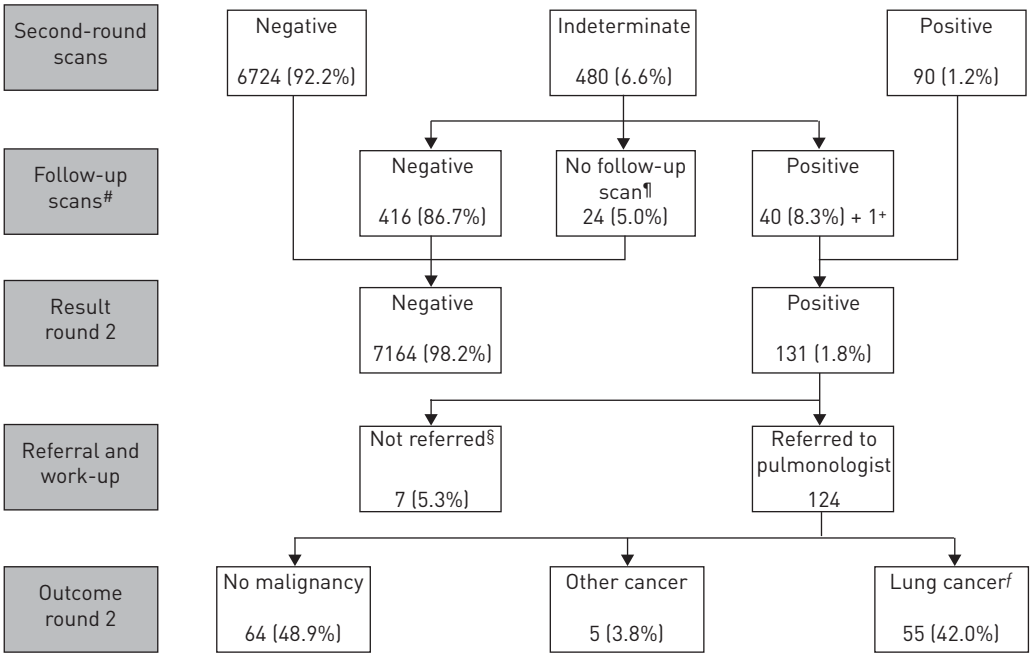

FIGURE 2 Results of the second round of screening (January 2005 to September 2008) involving 7295 participants. 287 participants did not undergo a second-round scan (7557 participants of the first round plus 25 participants who missed screening in round one, minus 7295) because of lung cancer (n=68; two subjects diagnosed with lung cancer did receive a second round scan because of an administrative error), death (n=27), participant declined (n=115), participant was either unattainable or repeatedly no show (n=47), paticipant was still in diagnostic work-up from round one (n=1), administrative error (n=1), and no screening performed in second round, but was screened in third round. Please note that percentages for outcome are calculated using the total number of positive results as the denominator. #: after mean±SD 76.5±35.4 days. In 15.5% of the subjects with an indeterminate result the nodule(s) had disappeared. ¶: reasons: administrative error (n=12), no show (n=6), already receiving treatment from another specialist (n=5) and death (n=1). +: one participant missed the second round scan (therefore only 7294 second-round scans were performed and only 480 scans were indeterminate), but this patient received a follow-up scan instead later on, which had a positive result. §: reasons: administrative error (n=2) and already receiving treatment from another specialist (n=5). f: 52 (94.5%) out of 55 lung cancer diagnoses were confirmed by cytology or histology. Details concerning the basis of the diagnosis of the three other cases can be found in the online supplementary data. Note that mortality data were available only for the Dutch participants until August 14, 2011.

133 (7295/55) and in the third round 92 (6922/75) subjects were screened for the detection of one lung cancer. Cumulatively, to detect one lung cancer 38 participants underwent three screening rounds.

False-positive screenings

6% (458 out of 7582) of the participants had at least one positive screening result. 31 subjects had two positive screening results and two subjects had three positive screens. As 200 individuals were diagnosed with lung cancer, this implies that the remaining 258 participants had one or more false-positive screening result (244 subjects had one, 12 subjects had two and two subjects had three false-positive results). However, even 15 participants who were diagnosed with lung cancer had a false-positive screening in an earlier round. Thus, 3.6% of all participants (273 out of 7582) had a false-positive screening result.

67 (24.5%) out of the 273 participants with one or more false-positive screen result underwent an invasive procedure in the diagnostic work-up. 61 (91.0%) of these invasive procedures were surgeries (three mediastinoscopies, one sternotomy, nine video-assisted thoracoscopies and 48 thoracotomies) and the remaining six procedures were transthoracic biopsies (more details are supplied in the online supplementary data). Hence, 0.9% (67 out of 7582) of all screened participants underwent an ''unnecessary'' invasive diagnostic procedure.

5.5-year risk calculations

In the online supplementary data, we present an overview of subsequent screening results and lung cancer diagnoses to visualise the longitudinal character of the 5.5-year risk calculations. 70.4% of the screened participants (5340 out of 7582) had exclusively negative screen results.

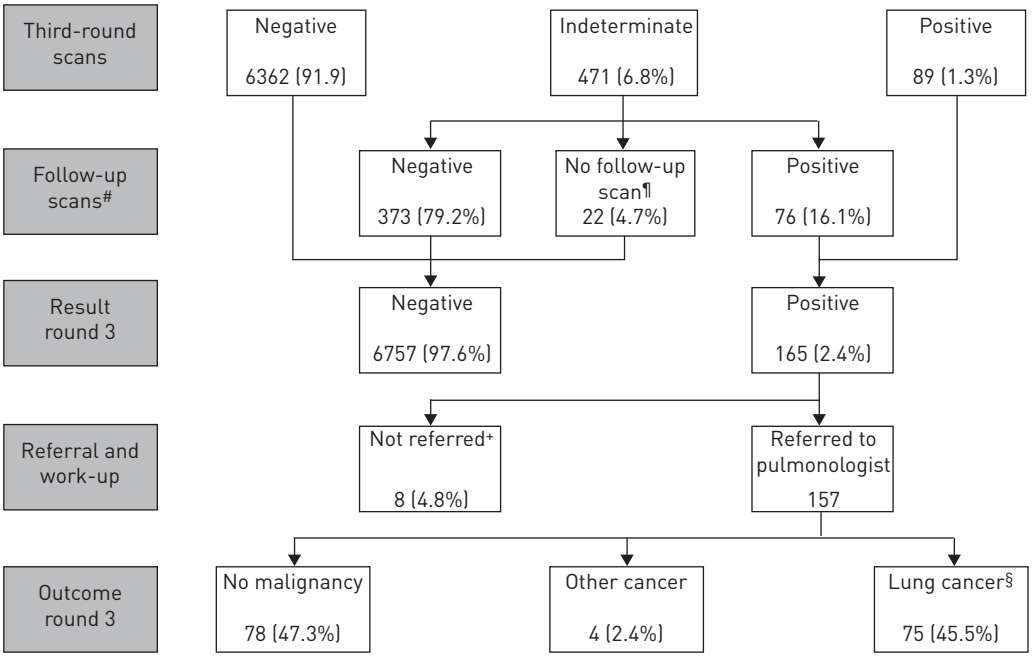

FIGURE 3 Results of the third round of screening (January 2007 to October 2010) involving 6922 paticipants. 400 participants were not screened in the third round (7294 participants of the second round plus 28 participants who missed screening in round two minus 6922) because of lung cancer (n=57), death (n=84), participant declined (n=155), participant unattainable or repeatedly no show (n=98), administrative error (n=3) and unknown (n=3). Please note that percentages for outcome are calculated using the total number of positive results as the denominator. #: follow-up scans were performed after mean±SD 60.3±61.9 days. In 13.6% of the subjects with an indeterminate result the nodule(s) had disappeared. ¶: reasons: administrative error (n=8), no show (n=6), refusal (n=3) and already receiving treatment from another specialist (n=5). +: reasons: decision tumour board (n=3), refusal (n=1) and already receiving treatment from another specialist (n=4). §: 68 (90.7%) out of 75 lung cancer diagnoses were confirmed by cytology or histology. Details concerning the basis of the diagnosis of the seven other cases can be found in the online data supplement. Note that mortality data were available only for the Dutch participants until August 14, 2011.

The individuals with a negative first screening had a probability of 86.5% to receive exclusively negative screening results in 5.5 years. Furthermore, their risk of a false-positive screen result in the following 5.5 years was 1.3% (80 out of 5986 participants) and their 5.5-year risk of lung cancer was only 1.0% (60 out of 5986 participants).

The participants with an indeterminate result from their first screening had a probability of 72.1% to have exclusively negative screening results in the 5.5 years after the first screening. Their risk of a false-positive follow-up scan in the first screen round was 4.3% (62 out of 1451). The risk of one or more false-positive scans in round two or three in this subgroup was 4.8% (70 out of 1451). To summarise, after an indeterminate baseline scan result, the risk of one or more false-positive scan results in 5.5 years was 8.8% (128 out of 1451). The risk of screen-detected lung cancer after an indeterminate baseline scan was 1.0% (15 out of 1451) in round one and 4.6% (67 out of 1451) in rounds two and three. Hence, the 5.5-year lung cancer risk after an indeterminate baseline scan result was 5.7% (82 out of 1451).

The participants with a positive first screen result had a probability of 30.0% (36 out of 120) to have only negative screening results in the following 5.5 years. Their risk of a false-positive screening was 54.2% (65 out of 120) in the first round and 4.2% (five out of 120) in the second or third round. Furthermore, their risk to be diagnosed with screen-detected lung cancer within 5.5 years was 48.3% (58 out of 120). This was 45.8% (55 out of 120) directly in round one and 2.5% (three out of 120) in rounds two and three. The three individuals with a lung cancer diagnosis in rounds two or three were, in retrospection, referred twice for the same suspicious nodule.

The risk calculations show that the result of the baseline scan divides the screened population in three subgroups with distinct risks of lung cancer. The characteristics of the screened participants and the three subgroups are presented in table 1. When comparing participants with a negative, indeterminate and a positive baseline scan result, a statistically significant increase in age and number of pack-years was observed. However, there was no significant difference in the proportion of females and current smokers (table 1).

DOI: 10.1183/09031936.00197712

TABLE 1 Participants' characteristics and comparison stratified by baseline scan result

Characteristics	All screened participants	Baseline scan result negative	Baseline scan result indeterminate	Baseline scan result positive	p-value
Participants	7582	5986	1451	120	
Females	1254 (16.5)	1016 (17.0)	210 (14.5)	22 (18.3)	0.06
Age years median (IQR)	58.0 (8)	57.0 (8)	59.0 (8)	63.0 (10)	<0.001
Current smoker	4215 (55.6)	3315 (55.4)	809 (55.8)	68 (56.7)	0.94
Pack-years median (IQR)	37.8 (19.8)	38.0 (19.8)	38.7 (19.8)	38.7 (24.0)	<0.001

Data are presented as n or n (%), unless otherwise stated. IQR: interquartile range.

Discussion

In this study, we evaluated the performance of the NELSON screening strategy in the first three screening rounds and we assessed the 5.5-year risk of false-positive screenings and screen-detected lung cancer.

If we compare the performance of the NELSON screening strategy with other LDCT screening trials we find notable differences. The percentage of positive scans in our trial (2.0%) was the same as in a Danish trial [10, 13], but substantially lower than in the NLST (24.2%) [5]. Also, the percentage of participants with one or more positive scan was 6.0% in our trial, which is low compared with the 39.1% in the NLST (the percentage in DLCST was not published) [5].

Despite the lower percentage positive screenings, our strategy detected 200 lung cancers in the three screening rounds. As a result, the cumulative lung cancer detection rate (2.6%) was a little higher than in the NLST (649 (2.4%) out of 26 309), but lower than in the DLCST (69 (3.4%) out of 2047) [5, 10]. The latter is probably due to the two additional screening rounds that have been completed in the DLCST.

The predictive value of a positive screen result was higher in the NELSON trial (40.6%) than in both the DLCST (34.8%) and the NLST (3.6%) [5, 10, 13]. Hence, the percentage of false-positive results was 59.4% in the NELSON trial, 65.2% in the DLCST and 96.4% in the NLST. The proportion of false-positive scans out of all scans is 1.2% in the NELSON trial, 1.3% in the DLCST and 23.3% in the NLST [5, 10, 13].

In the NELSON trial, we observed that the ratio between the true-positive and false-positive results improved over the rounds (0.69, 0.72 and 0.83 in rounds one, two and three, respectively). This is probably the result of the possibility in later rounds to compare current with previous images and to calculate VDTs. In the NLST, the true-positive/false-positive ratios were 0.039 in round one, 0.025 in round two and 0.055 in round three (figures in the DLCST were not published) [5]. The improvement in the third round probably results from the fact that only in the third round were stable nodules $\geqslant$4 mm in diameter not classified as positive.

Finally, the number needed to screen for the detection of one lung cancer was 92–133 per round in the NELSON trial, which is a little less than in the other trials (97–147 in the NLST and 116–180 in the DLCST) [5, 10].

In the three screening rounds, 3.6% of all participants had a false-positive screening result and this led to invasive diagnostic procedures in 0.9% of all participants. Although we are convinced of the need to reduce these numbers, we realise that these ''unnecessary'' invasive procedures cannot be eliminated because it is sometimes the only way to distinguish lung cancer from other malignancies or benign conditions.

In the second part of this study, we found that participants with a negative, indeterminate or positive baseline scan had very distinct risks of positive screening results and lung cancer. Hence, the risk of a false-positive screening result in the next 5.5 years was 1.3%, 8.8% and 54.2%, respectively, for the individuals with a negative, indeterminate or positive baseline scan. Moreover, the 5.5-year risk of screen-detected lung cancer was only 1.0% for the individuals with a negative baseline scan result, 5.7% for subjects with an indeterminate baseline result and 48.3% for those with a positive baseline. In other words, after the first screening, the individual's lung cancer risk has either decreased by 62% or increased by 219% or 1858%.

Analyses showed a significant increase in age and number of pack-years when comparing participants with a negative, indeterminate and positive baseline scan, which are all well known risk factors for developing lung cancer [24].

The presented results could aid clinicians when counselling high-risk subjects who are considering or have already undergone LDCT screening for lung cancer. This study has created the opportunity to personalise

counselling and enables the individual at risk to make an informed choice. Moreover, this is the first study that quantifies both the potential benefit of screening (early detection) and a potential harm of screening (false-positive screening results).

The main strengths of this trial are its design (a large, randomised controlled trial), the population-based recruitment and prospective data collection [14, 25]. Limitations of the current study are the lack of data on false-negative screenings, the control arm of the trial and lung cancer mortality. These analyses were not performed because the required data was not yet available [14].

Future research should focus on confirming the efficacy of LDCT screening for reducing lung cancer mortality. The planned lung cancer mortality analyses of the NELSON trial will be crucial in this part, as our trial is the only other trial (besides the NLST) that is sufficiently powered. Furthermore, efforts should be made to reduce false-positive screen results by optimising the cut-off criteria for nodule volume and VDT.

In conclusion, in this study, we evaluated the performance of the NELSON screening strategy in the first three screening rounds. We demonstrated that our strategy yields a low percentage of positive and false-positive scans with a reasonable positive predictive value. Furthermore, we used our experience with lung cancer screening to provide an overview of the 5.5-year risks of lung cancer and false-positive screenings, which aids clinicians in counselling individuals who are considering or have already undergone LDCT screening for lung cancer.

Acknowledgements

We thank our secretary M. Quak, our data manager R.M. Vernhout and our system controllers R. Faber and F.J.P. Santegoets (all at the Erasmus Medical Center, Rotterdam, the Netherlands) for their contributions and maintenance of the database.

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