EDITORIAL

Mortality Reduction with Low-Dose CT Screening for Lung Cancer

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Since the publication of the first mortality results from the National Lung Screening Trial (NLST), which showed a 20% reduction in lung-cancer mortality with low-dose computed tomographic (CT) screening,[1] the intervention has been adopted as policy in the United States, and there has been considerable discussion of the possibilities for its adoption in Europe.[2,3] Policy decisions are still awaited in many countries, despite the unequivocal nature of the original NLST results.[1] This is likely to be partly due to doubts fostered by the early publication of inconclusive results of a number of smaller trials in Europe.[4,5]

These doubts should be laid to rest by the results of the Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) reported in this issue of the *Journal* by de Koning et al.[6] In this trial, arguably the only adequately powered trial other than the NLST, 15,792 participants (84% male) were randomly assigned to periodic low-dose CT screening or no screening. At 10 years of follow-up, lung-cancer mortality was lower in the screening group that in the control group, both among men (lower by 24%) and among women (lower by 33%). The researchers estimate that approximately 60 deaths from lung cancer were prevented as a result of four offered rounds of screening in 7900 participants.

These results bear out the NLST finding that low-dose CT screening reduces lung-cancer mortality. Four further observations may be made. First, the intervals between the four screenings were 1 year, 2 years, and 2.5 years, as compared with strict 1-year intervals in the NLST. This suggests that a 2-year interval between screenings would be safe and effective, as has been speculated in the past.[3] Moreover, Figure 1B in the article by de Koning et al. suggests that the trajectories of lung-cancer mortality in the two trial groups became parallel at 8 years after randomization, approximately 2.5 years after the final screening in the trial. The NLST results suggest the same phenomenon occurring approximately 3.5 years after the final trial screening.[7] These findings imply that the protection afforded by a screening lasts between 2.5 and 3.5 years. A review of all the trials should further clarify this issue. The U.K. Lung Cancer Screening Trial, in which a single screening was offered to the participants in the screening group, may yield information of relevance here.[8]

Second, the inclusion of a small sample of women, seemingly as an afterthought, yielded the interesting suggestion of a greater relative benefit in women than in men. This too has been observed in the NLST and in another trial.[9,10] Further examination of this question is needed in the results of the other European trials to ascertain whether this is a general phenomenon and, more importantly, why it occurs.

Third, the NELSON results suggest overdiagnosis of approximately 10% at worst and considerably smaller numbers of overdiagnoses than of lives saved. Although there is no room for complacency in this regard (there is no "good" way to receive a diagnosis of lung cancer), the balance of overdiagnosis and mortality reduction is likely to be acceptable.

Fourth, an important observation relates to the numbers of screened participants undergoing further investigation. Results in the past have

indicated that approximately 20% of participants screened then undergo at least one additional scan to check for tumor growth or regression. In the NELSON trial, this level of additional testing was observed only at the first screening, with percentages of 1.9 to 6.7% at subsequent screenings and an average over all four screenings of less than 10%.

A previous article by the NELSON investigators provided an insight into the use of nodule volume and the doubling time of the nodule volume to identify highly suspicious malignant nodules.[11] Recently, the NELSON investigators evaluated both diameter and volume measurement to estimate lung-nodule size as an imaging biomarker for nodule management; this provided evidence that using mean or maximum axial diameter to assess nodule volume led to a substantial overestimation of nodule volume.[12] The approach to nodule-volume management described by de Koning et al. resulted in a substantial number of early-stage cancers identified at the time of diagnosis and avoided false positives from the overestimation incurred by management based on diameter.[6]

The lung-nodule management system used in the NELSON trial has been advocated in the European position statement on lung-cancer screening.[2] This will improve the acceptability of the intervention, because the rate of further investigation has been a major concern in lung-cancer screening.[2]

So what are the implications of the NELSON results? Most important, there can no longer be any doubt as to the efficacy of periodic low-dose CT screening in reducing mortality from lung cancer. The task for evaluation is now to estimate the cost-effectiveness of this screening. The latter, of course, does not have a single value and is country-specific. It will depend crucially on the interval between screenings and more crucially on the population targeted. Selecting high-risk persons with the use of validated models for predicting lung-cancer risk is considered essential.[2] In an era when most lung cancers in developed countries are diagnosed in ex-smokers, accurate estimation of individual risk becomes more important.

With the NELSON results, the efficacy of low-dose CT screening for lung cancer is confirmed. Our job is no longer to assess whether low-dose CT screening for lung cancer works: it does. Our job is to identify the target population in which it will be acceptable and cost-effective.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

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ABSTRACT

BACKGROUND

There are limited data from randomized trials regarding whether volume-based, low-dose computed tomographic (CT) screening can reduce lung-cancer mortality among male former and current smokers.

METHODS

A total of 13,195 men (primary analysis) and 2594 women (subgroup analyses) between the ages of 50 and 74 were randomly assigned to undergo CT screening at T0 (baseline), year 1, year 3, and year 5.5 or no screening. We obtained data on cancer diagnosis and the date and cause of death through linkages with national registries in the Netherlands and Belgium, and a review committee confirmed lung cancer as the cause of death when possible. A minimum follow-up of 10 years until December 31, 2015, was completed for all participants.

RESULTS

Among men, the average adherence to CT screening was 90.0%. On average, 9.2% of the screened participants underwent at least one additional CT scan (initially indeterminate). The overall referral rate for suspicious nodules was 2.1%. At 10 years of follow-up, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group; lung-cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively. The cumulative rate ratio for death from lung cancer at 10 years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; P=0.01) in the screening group as compared with the control group, similar to the values at years 8 and 9. Among women, the rate ratio was 0.67 (95% CI, 0.38 to 1.14) at 10 years of follow-up, with values of 0.41 to 0.52 in years 7 through 9.

CONCLUSIONS

In this trial involving high-risk persons, lung-cancer mortality was significantly lower among those who underwent volume CT screening than among those who underwent no screening. There were low rates of follow-up procedures for results suggestive of lung cancer. (Funded by the Netherlands Organization of Health Research and Development and others; NELSON Netherlands Trial Register number, NL580.)

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Lung cancer is the leading cause of death from cancer worldwide (18.4% of all cancer deaths) and causes more deaths than breast, colorectal, and cervical cancers combined — cancers for which population-based screening programs exist.[1] Only 15% of patients with lung cancer are still alive 5 years after diagnosis, because approximately 70% of patients have advanced disease at the time of diagnosis.[2] Although smoking prevalence is decreasing in Western countries, 17 to 28% of adults currently still smoke, and smoking initiation remains substantial in youths.[3] Lung cancer and other tobacco-related diseases are expected to remain important health problems worldwide for decades.[2,4]

The U.S.-based National Lung Screening Trial (NLST) showed that a strategy of three annual computed tomographic (CT) screenings resulted in 20.0% lower mortality from lung cancer than screening with the use of chest radiography among 53,454 participants at high risk for lung cancer after a median follow-up of 6.5 years, and the trial recently confirmed that mortality at a median follow-up of 5.5 and 6.0 years was as much as 19% lower with CT screening as with chest radiography.[5,6] The U.S. Preventive Services Task Force requested an independent review and a modeling study,[7,8] which resulted in the recommendation to annually screen persons 55 to 80 years of age with a smoking history of 30 or more pack-years, who currently smoke or quit smoking within the past 15 years. No other trial of lung-cancer screening has yet reported benefits with respect to mortality.[9]

The Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]), a population-based, randomized, controlled trial initiated in 2000, aimed to show a reduction in lung-cancer mortality of 25% or more with volume-based, low-dose CT lung-cancer screening in high-risk male participants at 10 years of follow-up. Here, we report lung-cancer incidence, mortality, and the performance of the four screening rounds in the NELSON trial among male participants (main analysis) and female participants (subgroup analyses).

Methods

Trial Oversight

The trial was approved by the Dutch Minister of Health and the medical ethics committee at each participating site.[10] Conceptualization of the trial, funding acquisition, data collection and curation, analysis of the primary outcome, the writing of the first draft of the manuscript, and revision of the manuscript based on review comments were performed by Erasmus MC and University Medical Center Groningen (UMCG). CT screening and follow-up were performed by the four screening sites (UMCG, University Medical Center Utrecht, Spaarne Gasthuis, and University Hospital Leuven). An independent cause-of-death committee defined the cause of death for some of the deceased participants (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Data on work-up, cancer diagnosis and stage, treatment, vital status, and cause of death were obtained through linkages with the Dutch Center for Genealogic and Heraldic Studies, Statistics Netherlands, and the Dutch Cancer Registry. Primary outcome data were kept confidential until unblinding. None of the funders had any role in the trial design, the collection or analysis of the data, or the writing of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org). No one who is not an author contributed to the writing of the manuscript.

Power Calculation and Eligibility Criteria

An overview of the previously published power calculation and trial design is available in the Supplementary Appendix.[11-13] The preferred risk-based selection scenario (scenario D[11]) required 17,300 to 27,900 participants (current or former smokers [those who had quit ≤10 years ago] who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years) to show a lung-cancer mortality that was lower by 20 to 25% in the screening group than in the control group at 10 years of follow-up, given the following conditions: one-sided testing, based on experience with the European Randomized Study of Screening for Prostate Cancer (two-sided testing was used for the final analyses); 90% power; 95% adherence in the screening group; 5% contamination (i.e., lung-cancer screening) in the control group; and an expected lung-cancer mortality of 3.4 per 1000 person-years without screening at 10 years of follow-up.[11] Exclusion criteria were patient report of moderate or severe

health problems and an inability to climb two flights of stairs; a body weight of more than 140 kg; current or past renal cancer, melanoma, or breast cancer; a diagnosis of lung cancer or treatment related to lung cancer within the past 5 years; or a chest CT scan within the past year.[11,12] A current smoker was defined as a person who had smoked cigarettes during the last 2 weeks.

The trial focused on men (see the Supplementary Appendix).[11] At the time of initiation (2000 through 2004), only a small number of women were eligible, because smoking was much less prevalent and much less intensive among women than among men. Because of the importance of the inclusion of women, a sample of high-risk women was approached for participation.

RECRUITMENT

On the basis of population registries, 606,409 persons 50 to 74 years of age who lived in four selected regions in the Netherlands and Belgium were approached with a general questionnaire and brief information about the trial in 2003 (first recruitment) or 2005 (second recruitment) (see the Supplementary Appendix, including Fig. S2).[14] A total of 30,959 respondents of the 150,920 who returned questionnaires were eligible. Eligible persons were invited to participate; 15,822 persons (51.1%), who provided written informed consent, underwent the initial randomization (in a 1:1 ratio) from December 2003 through July 2006 (median randomization date, November 2004) (Fig. S7).[11,13,14] After linkage with Statistics Netherlands and the Dutch Center for Genealogic and Heraldic Studies, 30 participants had died after providing informed consent and before the randomization date, which resulted in 15,792 formal participants (13,195 men, 2594 women, and 3 participants with unknown sex) (Table S1).

SCREENING ROUNDS AND NODULE-MANAGEMENT PROTOCOL

The screening rounds and the nodule-management protocol have been described previously (summarized in Fig. S8).[13,15-19] In short, from January 2004 through December 2012, participants in the screening group were invited to undergo four rounds of low-dose CT screening for lung cancer that were performed in the four CT screening sites with intervals of 1, 2, and 2.5 years.

For CT screening, low-dose 16-multidetector or, in later rounds, 64-multidetector CT systems were used to acquire isotropic volume data, without administration of contrast medium. Apart from local readings, all images were analyzed centrally at UMCG with the use of semiautomated software (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). The analysis included the semiautomated segmentation of nodules and determination of the nodule volume.[20] If the software was not able to segment a nodule accurately, the volume was corrected manually by the radiologist.[21] Depending on the volume and volume-doubling time, a screening could be negative, indeterminate, or positive (Fig. S8). Participants in the control group underwent no screening.

FOLLOW-UP DATA

Follow-up data were retrieved from national linkages at approximately 5, 7, and 10 to 11 years of complete follow-up. A total of 18 persons (13 men and 5 women) could not be linked, because a digital consent form could not be retrieved. Population data were available regarding randomization date, sex, date of lung-cancer diagnosis, and date and cause of death for all deceased Belgian persons up to December 2013 and September 2018 through linkages in January 2016 and October 2018, respectively.

CAUSE-OF-DEATH REVIEW

The primary outcome of the NELSON trial was lung cancer–specific mortality. A clinical expert committee was formed to assign the cause of death by an evaluation process using a flow chart and predetermined criteria.[22] A total of 296 completed and blinded medical files of 426 deceased Dutch male patients with lung cancer (69.5%) were reviewed and compared with official death certificates (cutoff, 10 years of follow-up or December 31, 2015). The overall concordance among members of the expert committee was 86.1%. The sensitivity and specificity of the official death certificate were 92.6% and 98.8%, respectively.[23] Death from lung cancer was considered valid only if the expert committee had concluded that lung cancer was the cause of death. The international mortality advisory committee deemed possible biases to be relatively small and agreed on further use of official statistics for the primary outcome, if lung cancer as

the cause of death was recorded in the national registry for vital statistics.

STATISTICAL ANALYSIS

The primary analysis of the trial consisted of a comparison of lung-cancer mortality between the screening group and the control group (main analysis, men; subanalyses, women), according to the intention-to-screen principle. Specifically, the rate ratio for death from lung cancer was compared between the two groups; the rate ratio was derived as the ratio of event rates, under the assumption of a Poisson distribution for the number of events (two-sided test). Secondary analyses compared all-cause mortality and the incidence of first recorded diagnosis of lung cancer between the two groups. The date of censoring of data for first recorded lung cancer, death from lung cancer, and death from any cause was December 31, 2015, or 10 years of follow-up since randomization (whichever came first). Event rates were defined as the ratio of the number of events to the person-years at risk for the event. For the incidence of first recorded lung cancer, person-years were measured from the time of randomization to the date of diagnosis of lung cancer, death, or censoring of data (whichever came first); for mortality, person-years were measured from the time of randomization to the date of death or censoring of data (whichever came first). Previously published definitions are summarized in the Supplementary Appendix.[13,15,16]

Continuous variables are presented as means and standard deviations (normal distribution) or as medians, interquartile ranges, and ranges (skewed distribution). Differences in distributions of baseline characteristics of participants in the screening group and participants in the control group were analyzed with the use of Pearson's chi-square test for nominal or categorical variables and the Mann–Whitney test for ordinal or continuous variables with a nonnormal distribution. Analyses were performed with the use of Stata software, R statistical packages, and SPSS software, version 25. Exact methods were used to calculate confidence intervals for the rate ratios. P values were calculated with the use of two-sided exact tests; a P value of less than 0.05 was considered to indicate statistical significance. No corrections for multiple comparisons were included. Missing data for the primary outcome were negligible owing to the linkages with the national registries (>98% coverage).

RESULTS

BASELINE CHARACTERISTICS OF MALE PARTICIPANTS

A total of 13,195 male participants were randomly assigned to either the screening group (6583 men) or the control group (6612 men). Baseline characteristics did not differ significantly between the two groups, except for duration of smoking (Table 1). At randomization, the median age of the male participants was 58 years in each group (interquartile range, 55 to 63 in the screening group and 54 to 63 in the control group), with a median smoking history of 38.0 pack-years (interquartile range, 29.7 to 49.5) in each group. Overall, 44.9% of the male participants were former smokers.

SCREENING RESULTS IN MALE PARTICIPANTS

In total, 22,600 CT scans were performed, and screening uptake was on average 90.0% (95% confidence interval [CI], 76.9 to 95.8) (Table 2). In 9.2% of the scans (2069 of 22,600), an indeterminate screening test required a repeat CT scan to calculate volume-doubling time before the final screening-test outcome could be defined. At baseline, the percentage of indeterminate tests was highest (19.7%), after which it decreased to between 1.9% and 6.7% at year 1 through year 5.5. In follow-up rounds, 55% of new nodules resolved.[24] Finally, 467 of 22,600 CT scans (2.1%) were test-positive and required further workup by the pulmonologist, leading to 203 screening-detected lung cancers. The overall positive predictive value of a positive screening test was 43.5%. This means that 264 of 22,600 screened participants over all rounds (1.2%) had a false positive test. No adverse events were reported. After a positive screening test, the national guidelines for treatment of lung cancer were applied by the local hospitals.

LUNG CANCER IN MALE PARTICIPANTS

Figure 1A shows the cumulative incidence of lung cancer according to follow-up period and trial group. (Results for lung cancer of stage III or higher are provided in Fig. S5.) At 10-year follow-up, the cumulative incidence of lung cancer was 5.58 cases per 1000 person-years (341 lung cancers with a known date of diagnosis)

Table 1. Baseline Characteristics of the Male Participants at Randomization.*

Characteristic	Screening Group (N=6583)	Control Group (N=6612)
Age		
Median (IQR) — yr	58 (55–63)	58 (54–63)
Range — yr	46–76	34–89
Distribution — no./total no. (%)†		
<50 yr	3/6560 (<0.1)	6/6571 (0.1)
50–54 yr	1611/6560 (24.6)	1694/6571 (25.8)
55–59 yr	2226/6560 (33.9)	2231/6571 (34.0)
60–64 yr	1554/6560 (23.7)	1475/6571 (22.4)
65–69 yr	797/6560 (12.1)	781/6571 (11.9)
70–74 yr	329/6560 (5.0)	337/6571 (5.1)
≥75 yr	40/6560 (0.6)	47/6571 (0.7)
Pack-yr of smoking‡		
Median (IQR)	38.0 (29.7–49.5)	38.0 (29.7–49.5)
Range	0.4–159.5	1.3–156.0
Cigarettes smoked per day — no./total no. (%)		
≤10	20/6565 (0.3)	18/6596 (0.3)
11–15	1470/6565 (22.4)	1437/6596 (21.8)
16–20	1859/6565 (28.3)	1859/6596 (28.2)
21–25	1732/6565 (26.4)	1779/6596 (27.0)
26–30	669/6565 (10.2)	723/6596 (11.0)
31–40	454/6565 (6.9)	437/6596 (6.6)
>40	361/6565 (5.5)	343/6596 (5.2)
Duration of smoking — no./total no. (%)		
≤25 yr	25/6563 (0.4)	21/6594 (0.3)
26–30 yr	657/6563 (10.0)	722/6594 (10.9)
31–35 yr	1652/6563 (25.2)	1700/6594 (25.8)
36–40 yr	2030/6563 (30.9)	2105/6594 (31.9)
41–45 yr	1451/6563 (22.1)	1317/6594 (20.0)
≥45 yr	748/6563 (11.4)	729/6594 (11.1)
Age at initiation of smoking — no./total no. (%)		
<15 yr	1153/6560 (17.6)	1141/6588 (17.3)
15–29 yr	5376/6560 (82.0)	5407/6588 (82.1)
≥30 yr	31/6560 (0.5)	40/6588 (0.6)
Smoking status — no./total no. (%)		
Current	3643/6566 (55.5)	3611/6595 (54.8)
Former	2923/6566 (44.5)	2984/6595 (45.2)
Years since cessation of smoking — no./total no. (%)		
<1	489/2908 (16.8)	493/2963 (16.6)
1–5	1316/2908 (45.3)	1334/2963 (45.0)
6–10	1054/2908 (36.2)	1096/2963 (37.0)
>10	49/2908 (1.7)	40/2963 (1.3)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† The trial was designed for persons 50 to 74 years of age. Some men who were younger or older than the birth cohort that was approached underwent randomization and were included in the analysis.
‡ Some men who had a lower smoking history than the inclusion criterion underwent randomization and were included in the analysis.

Table 2. Screening-Test Results in Each Screening Round for Male Participants in the Screening Group.

Screening	Screening Uptake		Indeterminate Test	Positive Test	Detection of Lung Cancer	Positive Predictive Value
	Men Eligible for Screening	Men Undergoing Randomization				
	number/total number (percent)					*percent*
Round 1	6309/6583 (95.8)	6309/6583 (95.8)	1241/6309 (19.7)	147/6309 (2.3)	56/6309 (0.9)	38.1
Round 2	6086/6459 (94.2)	6086/6583 (92.5)	357/6086 (5.9)	95/6086 (1.6)	45/6086 (0.7)	47.4
Round 3	5768/6285 (91.8)	5768/6583 (87.6)	385/5768 (6.7)	136/5768 (2.4)	65/5758 (1.1)	47.8
Round 4	4437/5771 (76.9)	4437/6583 (67.4)	86/4437 (1.9)	89/4437 (2.0)	37/4437 (0.8)	41.6
Total	22,600/25,098 (90.0)	22,600/26,332 (85.8)	2069/22,600 (9.2)	467/22,600 (2.1)	203/22,600 (0.9)	43.5

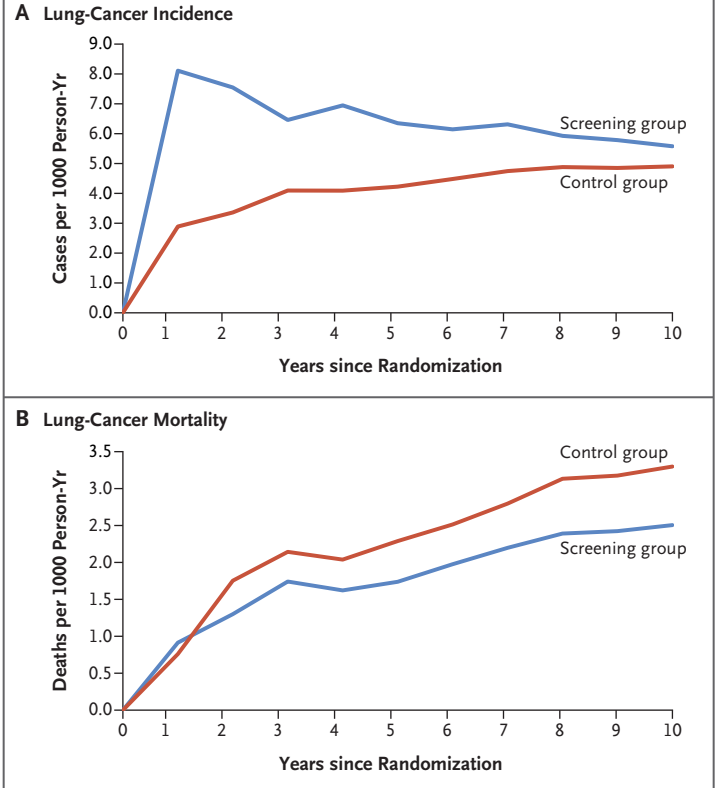

Figure 1. Lung-Cancer Incidence and Lung-Cancer Mortality among Male Participants.

Panel A shows the cumulative lung-cancer incidence (per 1000 person-years) according to follow-up year since randomization. Panel B shows the cumulative lung-cancer mortality (per 1000 person-years) according to follow-up year since randomization. Cause of death (with known date of lung-cancer diagnosis) was defined by the cause-of-death committee, if available, or by vital-statistics registries.

among male participants in the screening group and 4.91 cases per 1000 person-years (304 lung cancers with a known date of diagnosis) among those in the control group (rate ratio, 1.14; 95% CI, 0.97 to 1.33). A total of 59.0% (203 of 344) of all lung cancers in the screening group were detected on screening (Table 3), and 12.8% (44 of 344) were interval cancers. Screening-detected lung cancers were substantially more often diagnosed in stage IA or IB (58.6%), whereas only 14.2% (screening group) and 13.5% (control group) of the participants with non–screening-detected lung cancers received a diagnosis in stage IA or IB. Stage IV cancer was diagnosed in almost half the participants with non–screening-detected lung cancers (51.8% in the screening group and 45.7% in the control group), whereas only 9.4% of the screening-detected lung cancers were diagnosed in stage IV. Most (screening-detected) lung cancers were adenocarcinomas (52.0% in the screening group and 43.8% in the control group).

MORTALITY

At 10 years of follow-up, 156 men with a known date of lung-cancer diagnosis in the screening group and 206 in the control group had died from lung cancer (2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively), which resulted in a cumulative rate ratio for death from lung cancer of 0.76 (95% CI, 0.61 to 0.94; P=0.01). Similar rate ratios, which differed significantly between the two groups, were observed at years 8, 9, and 11 (Fig. 1 and

Table 3. Lung-Cancer Stage and Histologic Type of All First-Detected Lung Cancers in Male Participants at 10 Years of Follow-up or on December 31, 2015.*

Variable	Screening Group			Control Group
	Screening-Detected Lung Cancer (N=203)†	Non–Screening-Detected Lung Cancer (N=141)	Any Lung Cancer (N=344)	Any Lung Cancer (N=304)
	number of participants (percent)			
Stage				
IA	95 (46.8)	10 (7.1)	105 (30.5)	21 (6.9)
IB	24 (11.8)	10 (7.1)	34 (9.9)	20 (6.6)
IIA	8 (3.9)	4 (2.8)	12 (3.5)	13 (4.3)
IIB	11 (5.4)	6 (4.3)	17 (4.9)	17 (5.6)
IIIA	20 (9.9)	14 (9.9)	34 (9.9)	43 (14.1)
IIIB	13 (6.4)	14 (9.9)	27 (7.8)	34 (11.2)
IV	19 (9.4)	73 (51.8)	92 (26.7)	139 (45.7)
Unknown	13 (6.4)	10 (7.1)	23 (6.7)	17 (5.6)
Histologic type‡				
Adenocarcinoma	123 (60.6)	56 (39.7)	179 (52.0)	133 (43.8)
Squamous-cell carcinoma	39 (19.2)	38 (27.0)	77 (22.4)	94 (30.9)
Small-cell carcinoma	13 (6.4)	27 (19.1)	40 (11.6)	46 (15.1)
NSCLC	8 (3.9)	8 (5.7)	16 (4.7)	13 (4.3)
Other	20 (9.9)	12 (8.5)	32 (9.3)	18 (5.9)

* Percentages may not total 100 because of rounding. NSCLC indicates non–small-cell lung carcinoma.
† Data on three screening-detected lung cancers were not available in the national cancer registry (date of diagnosis unknown).
‡ Cases of lung cancer were classified into five main histologic types: adenocarcinoma, squamous-cell carcinoma, small-cell carcinoma, non–small-cell carcinoma, and other (*International Classification of Diseases for Oncology*, third edition).[25] The exact classification in subgroups is presented in Table S12.

Table S3). Table 4 shows the causes of death in the two groups. All-cause mortality at 10 years of follow-up was 13.93 deaths per 1000 person-years among male participants in the screening group and 13.76 deaths per 1000 person-years among those in the control group (rate ratio, 1.01; 95% CI, 0.92 to 1.11).

Analyses of data from the small subsample of women (with a known date of lung-cancer diagnosis) showed a rate ratio for death from lung cancer of 0.67 (95% CI, 0.38 to 1.14) at 10 years of follow-up. The rate ratio was 0.46 (95% CI, 0.21 to 0.96) at 7 years, 0.41 (95% CI, 0.19 to 0.84) at 8 years, and 0.52 (95% CI, 0.28 to 0.94) at 9 years.

SENSITIVITY ANALYSES

At the 11-year follow-up (up to December 2016), the rate ratio for death from lung cancer among male participants was 0.78 (95% CI, 0.63 to 0.95). After 10 years of follow-up, the subgroup of men 50 to 54 years of age — not included in the NLST — had a rate ratio of 0.85 (95% CI, 0.48 to 1.50). The subgroup of men 65 to 69 years of age had the lowest rate ratio of any age group, at 0.59 (95% CI, 0.35 to 0.98) (Table S2).

Approximately 50% of the participants in the NELSON trial met the eligibility criteria of the NLST. Among NLST-eligible men, the rate ratio at 10 years of follow-up was 0.82 (95% CI, 0.64 to 1.05). If all deaths from lung cancer, with no restriction regarding known date of diagnosis, were included, the rate ratio would be 0.76 (95% CI, 0.62 to 0.94) among all men in the NELSON trial and 0.81 (95% CI, 0.63 to 1.04) among NLST-eligible men.

Table 4. Cause of Death of Deceased Male Participants at 10 Years of Follow-up or until the Data-Cutoff Date of December 31, 2015.*

Variable	Screening Group (N=868)	Control Group (N=860)	Total (N=1728)	Rate Ratio (95% CI)
		number (percent)		
Cause of death — no. (%)				
Lung cancer	160 (18.4)	210 (24.4)	370 (21.4)	0.76 (0.62–0.94)
No lung cancer after cause-of-death review, no other specification	6 (0.7)	11 (1.3)	17 (1.0)	0.55 (0.17–1.61)
Other neoplasm	318 (36.6)	289 (33.6)	607 (35.1)	1.10 (0.94–1.30)
Cardiovascular disease	189 (21.8)	181 (21.0)	370 (21.4)	1.05 (0.85–1.29)
Respiratory disease	42 (4.8)	43 (5.0)	85 (4.9)	0.98 (0.62–1.53)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	37 (4.3)	20 (2.3)	57 (3.3)	1.86 (1.05–3.37)
Diseases of the digestive system	30 (3.5)	21 (2.4)	51 (3.0)	1.43 (0.79–2.63)
External causes of illness and death	24 (2.8)	19 (2.2)	43 (2.5)	1.27 (0.67–2.45)
Endocrine, nutritional, and metabolic diseases	21 (2.4)	9 (1.0)	30 (1.7)	2.34 (1.03–5.80)
Diseases of the nervous system	9 (1.0)	19 (2.2)	28 (1.6)	0.48 (0.19–1.10)
Other cause of death	26 (3.0)	28 (3.3)	54 (3.1)	0.93 (0.52–1.65)
Unknown	6 (0.7)	10 (1.2)	16 (0.9)	0.60 (0.18–1.83)
Total person-yr at risk	62,298	62,484	124,782	
All-cause mortality — deaths per 1000 person-yr	13.93	13.76	13.85	1.01 (0.92–1.11)

* Percentages may not total 100 because of rounding.

DISCUSSION

In the NELSON trial, volume CT lung-cancer screening of high-risk former and current smokers, with the introduction of growth-rate assessment as an imaging biomarker for indeterminate tests, resulted in low referral rates for additional assessments and substantially lower lung-cancer mortality (in both sexes) than no screening, despite screening intervals that increased over time. Adherence to CT screening was very high; at least 87.6% of the male participants underwent three screenings. In line with the mortality outcomes, volume CT screening in the NELSON trial has led to a substantial shift to lower-stage cancers at the time of diagnosis as well as to more frequent eligibility for curative treatment (mainly surgical).[26] Because only modest differences were found between participants and eligible nonrespondents,[14] we expect the results to be highly generalizable.

In the small subsample of women, the effects of screening on lung-cancer mortality were consistently more favorable. Post hoc analyses from the NLST also showed weak evidence of a differential effect size according to sex and histologic type.[27] In addition, the recently reported rate ratio for death from lung cancer among participants in the low-dose CT group as compared with those in the chest-radiography group in the NLST was 0.95 (95% CI, 0.83 to 1.10) among men and 0.80 (95% CI, 0.66 to 0.96) among women (dilution-adjusted analysis).[6] Recently, the German Lung Cancer Screening Intervention Trial showed a significant benefit with respect to lung-cancer mortality in the small subgroup of women who were invited to undergo screening (hazard ratio, 0.31; 95% CI, 0.10 to 0.96).[28] These outcome data are also consistent with differences between the sexes in the screening-detectable preclinical period (i.e., the period in which the lung cancer is detectable through CT screening but has not yet clinically manifested itself through symptoms).[29] Ad hoc analyses of data from male participants in the NELSON trial who met the eligibility criteria of the NLST

(although not powered and with overlapping confidence intervals) suggest more favorable effects on lung-cancer mortality than in the NLST, despite lower referral rates for suspicious lesions. Important differences were seen in screening results at baseline in the NELSON trial (volume-based nodule-management protocol) as compared with the NLST (diameter-based nodule-management protocol): the percentage of patients with a positive test was 2.1% in the NELSON trial and 24% in the NLST, and the positive predictive value was 43.5% and 3.8%, respectively.[5]

At baseline, participants in the screening group reported a longer duration of smoking than those in the control group but the same number of pack-years. Furthermore, smoking behavior was similar (intention-to-treat analyses) in the two groups after 2 years of follow-up.[30] Bias in screening effect in favor of the screening group is therefore not expected. The NELSON trial was not powered to show a possible favorable difference in all-cause mortality (expected within the range of 2.5%), because it would have required unrealistic sample sizes.[31] Comparisons of other causes of death showed no meaningful differences between the screening group and the control group.

Concerns have been raised about the potential for overdiagnosis in lung-cancer screening. Excess-incidence analysis of data from the NLST estimated an upper boundary of overdiagnosis risk of 18.5%.[32] In the NELSON trial, an excess of 40 cases (344 vs. 304) was found among the male participants in the screening group 10 years after randomization (4.5 years after the final screening round), which suggests an excess-incidence overdiagnosis rate of 19.7% (bootstrapped 95% CI, −5.2 to 41.6) for screening-detected cases. However, extending the follow-up to 11 years after randomization (5.5 years after the final screening round) reduced the number of excess cases to 18, yielding an excess-incidence overdiagnosis rate of 8.9% (bootstrapped 95% CI, −18.2 to 32.4) for screening-detected cases. This is in line with modeling analyses suggesting that the lead time of CT screening can be as long as 9 to 12 years for some cancers, which indicates that appropriate estimation of the level of overdiagnosis in the NELSON trial requires additional years of follow-up.[33] Because of this, an overdiagnosis rate of 8.9% for screening-detected cases may be considered as the upper limit of overdiagnosis in the NELSON trial. The clinical management strategy in the NELSON trial was highly restrictive with respect to invasive diagnosis and treatment of persistent subsolid nodules.

The high adherence to CT screening may reflect a high level of conscientiousness among trial participants. In the future, improvement in screening selection (personalized risk-based approach) will probably result in a more favorable trade-off between harms and benefits of CT lung-cancer screening.[4,9,34-38]

The NELSON trial showed that volume CT lung-cancer screening, with low rates of follow-up procedures for test results suggestive of lung cancer, resulted in substantially lower lung-cancer mortality than no screening among high-risk persons. Volume CT screening enabled a significant reduction of harms (e.g., false positive tests and unnecessary workup procedures), without jeopardizing favorable outcomes. Trial data suggest greater benefits in women than in men, but in a subgroup with a relatively low number of women. More research is required in women, as well as in other subgroups.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. DOI: 10.1056/NEJMoa1911793

Manuscript:

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Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

SUPPLEMENTARY APPENDIX I-III

This supplement contains the following items:

Research Team, (Medical Ethical) Approval, Supplementary Tables/Figures, and References

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APPENDIX II: (Medical Ethical) Approval NELSON trial

Medical Ethical Approval

The Netherlands

The NELSON-trial is a randomized controlled population-based screening trial and according to the Dutch Population Screening Act, approval is required by the Minister of Health, Welfare and Sports before randomization.[74]

In August 2000, a license in accordance with the population screening act was requested. The initial study protocol of three screenings was submitted and reviewed by the Dutch Health Council. The process of fair hearing, in which the protocol was also optimized based on the feedback, took almost three years. Under the condition of a survey on information acceptability, a positive advice was given. This survey amongst 195 individuals succeeded in October 2003. On 19th December 2003, the definitive study protocol and information leaflets were formally approved by the Minister of Health, including an extension to the regions Groningen and Haarlem. The Dutch committee did not want to speculate on the lung cancer mortality reduction, but the formally suggested stopping rule was a statistically significant 20% lung cancer mortality reduction in the intervention arm.

In 2009, extension of the trial was approved for a 4th screening round, up to July 1st 2012, with its aim to study the effect of the screening interval. All prerequisites on quality assurance were later met in the trial.

The local medical ethical committees (University Medical Center Groningen, University Medical Center Utrecht, Kennemer Gasthuis/Spaarne Gasthuis) gave their approval for conducting the trial in their medical centers.

Belgium

In Belgium, the trial was approved by the Medical Ethical Committee of Leuven University Hospital.

Process of Approval

The supervision/auditing is delegated to the Health Care Inspectorate, according to the Population Screening Act, Article 10.[74] In 2011, the Health Care Inspectorate visited the NELSON research team and concluded that the NELSON study met all quality requirements as imposed by the Inspectorate. After the visit of the Health Care Inspectorate, the trial was also overseen by the Deans of the three Dutch University Medical Centers of Rotterdam, Groningen and Utrecht, and interim reports were further submitted to the scientific boards of The Netherlands Organization for Health Research and Development and Dutch Cancer Society in 2012, 2014 and 2018.

Independent Mortality Advisory Committee

In 2016, an external Mortality Advisory Committee (MAC), comprising of four members (C.D. Berg, S. Moss, P.E. Postmus and J.D.F. Habbema), was asked to advice on the mortality analyses and its consequences. No interim testing had been performed before, given expected insufficient power. The MAC agreed to use the outcomes of the Cause of Death-reviews, if possible, but to use official statistics in more recent years, given high concordance of the national death certificates, also per arm.[77]

On 13rd March 2018, it was decided to unblind the arms, given sufficient follow-up and confidence in the official death statistics registries for the primary outcome measure.

On 31st July 2018, it was decided to present the results at the World Conference on Lung Cancer.[80] The MAC agreed with the afore mentioned power calculations and timing of a minimum of 10 years of complete follow-up, but also advised us to consider the Hanley methods, which emphasizes time and screening history specific reductions (originally not considered in our power calculations).[78] Based on the natural history of lung cancer (modelling), the expected maximum reductions by time were estimated, assuming a screen effect as seen in NLST, and the observed CT-scans and screening intervals. These analyses showed that the maximum effect was expected to levelling off after year 9 (which is consistent with the natural history[79]). Subsequently, 9, and 8 (and 11) complete follow-up discussion analyses were performed too. Another analysis was performed for females separately, with data up to December 16th 2016, analyses per 5-year age group, and for enrolled participants, who would have been eligible for NLST.

Abstract "Comprehensibility study"

May 14th 2004

(Whole report in Dutch)

Objective: The Dutch-Belgian lung cancer screening trial (NELSON) is a recently started randomized multi-center study to evaluate whether lung cancer screening with low dose spiral computer tomography can reduce lung cancer mortality with 25% in high risk subjects. Solely based on the NELSON information pamphlet, people are asked to decide whether they want to participate in the trial (informed consent). Therefore, approval of the Ministry of Health of the Netherlands was only obtained when the information material was proven to be sufficiently comprehensible. We present the design and start of the NELSON trial and the result of the evaluation of the comprehensibility of the information pamphlet (IP).

Methods: 106,850 people responded on a health questionnaire, which had been sent to 362,500 men aged 50-74 years (384,649 per regular mail and 13,851 by internet). From the internet responders, a random sample of 195 high-risk men, heterogeneous in terms of age and education was taken. They received the NELSON-IP and an invitation for a telephone interview.

Results: All of the 67 responders who were interviewed within two weeks after invitation, said to understand the information. The majority was aware of the aim of the trial, i.e. early detection of lung cancer (93%), and a lung cancer mortality reduction (54%). 87% knew that they would be randomized and 96% was aware that there is no screening in the control group. Most questions asked by participants were related to the moment when spiral CT scans will be performed and the site.

Conclusion: All main aspects of the NELSON-IP, on which informed consent is based, were well understood. Open-semi structured interviewing by phone is accurate to identify information needs in an IP. After adaptation of the NELSON-IP and approval of the Minister of Health of the Netherlands, NELSON has started. Presently, the first screenings are being performed.

Letter of Approval Screening Round 1-3

Ministry of Health, Welfare and Sport

To the Executive Board of the University Medical Center Rotterdam
Dr. Molewaterplein 40
3015 GD Rotterdam
Attn. Dr R.J. van Klaveren, Pulmonologist/Oncologist

Our reference	For information contact	Direct line	The Hague
GZB/GZ 2.159.288	J.R. Storm	070-340 7488	6 MARCH 2001
Subject		Enclosure(s)	Your letter

Licence under the Population Screening Act (WBO)

Dear Sirs,

You have applied for a license under the Population Screening Act [*Wet op Bevolkingsonderzoek, WBO*] for a randomized medical study of the importance of lung cancer screening with low-dose spiral CT scans in the Rotterdam and Utrecht regions. I submitted the application to the Health Council of the Netherlands on 2 August 2000 for review against the statutory criteria. The Council issued a recommendation on 12 October. The Director of Health Policy sent the recommendation to you on 6 December 2000.

The Council is of the opinion that the above population screening also qualifies as medical research, and that a license is required as the study focuses on cancer and uses ionizing radiation. It is the Council's view that your proposal meets the requirements of scientific validity. The Council feels that the study also complies with the statutory regulations, provided that experience shows that the information leaflets, the declaration of consent and reports on the results are easy to understand. The Council has decided that the benefits of your proposal outweigh the risks, provided that the proposed professional development and quality control (pages 23 and 24) are indeed carried out. Moreover, the Council feels that the criterion of the interest of public health has been met for the purpose of granting a license. The Council has recommended that a license with applicable regulations should be granted.

I deem the above review convincing. I am prepared to grant you a license upon receipt of the results of a test among the target group to determine whether the information material is easy to understand. Apart from the above, I would like to receive a brief report on the progress of the proposed professional development and quality control in due course.

Yours sincerely,

The Minister of Health,
Welfare and Sport

Dr E. Borst-Eilers

PO Box 20350
2500 EJ THE HAGUE
Telephone (070) 340 79 11
Fax (070) 340 78 34

Visiting address:
Parnassusplein 5
2511 VX THE HAGUE

Please only send correspondence to the postal address stating the date and reference of this letter

Website: www.minvws.nl

Letter of Approval 4th Screening Round

Ministry of Health,
Welfare and Sport

> Return address PO Box 20350 2500 EJ The Hague

Erasmus MC
PO Box 5201
3008 AE Rotterdam
Attn Dr R.J. van Klaveren (room GS-15)

Date 16 July 2009
Subject Extension of license for NELSON under the Population Screening Act

Department of Public Health

Visiting address:
Parnassusplein 5
2511 VX The Hague
T 070 340 79 11
F 070 340 78 34
www.minvws.nl

For information contact
A. Rendering
a.renderlng@minvws.nl
T 070 340 5112

Our reference
PG/OGZ-2944152

Enclosures

Your letter
3 July 2009

Please only send correspondence to the return address stating the date and reference of this letter

Dear Mr Van Klaveren,

On 6 March 2001, the Erasmus MC in Rotterdam was granted a conditional license to carry out lung cancer screening by means of a CT scan, also known as the NELSON study. This took place on the basis of a recommendation issued by the Health Council of the Netherlands on 22 November 2000, reference 2000/04WBO. The license was extended on 19 December 2003. The target group for the project are smokers and former smokers aged between 50 and 75.

On 3 July 2009 you applied to extend the license for lung cancer screening for a fourth screening round with additional research topics. I hereby grant the Erasmus MC permission to continue the above screening, as well as permission to conduct additional research supplementary to the license issued under the Population Screening Act [Wet op het bevolkingsonderzoek, WBO] on 19 December 2003. This concerns the fourth round of screening and additional research into the optimum number of screening rounds and the optimum screening interval. The validity period of the license will therefore be extended until 1 July 2012. The extension will have retroactive effect up to and including 1 January 2007.

Any party affected may lodge an objection against a decision under Article 7:1 of the General Administrative Law Act. This can be carried out by submitting a notice of objection to the Ministry of Health, Welfare and Sport, At the Department of Legislation and Legal Affairs, PO Box 20350, 2500 EJ The Hague. The time limit for filing a notice of objection is six weeks. This six-week period starts with effect from the day after the date stated on the decision.

Pursuant to Article 10 of the Population Screening Act, responsibility for monitoring compliance with the regulations lies with the Public Health Supervisory Service.
I will send a copy of the license to the Health Care Inspectorate and the Health Council of the Netherlands.

Yours sincerely,
The Minister of Health, Welfare and Sport, on his behalf, the Director of Public Health
Dr D. Ruwaard

Trial registration

The NELSON trial has been registered at www.trialregister.nl (registration number: NTR636) in June 2006 (after acceptance of the power calculations[46]).

Health condition(s) or problem(s) studied: lung cancer

Inclusion criteria

1) Born between 1928 and 1956;
2) 2a. Smoked > 15 cigarettes/day during > 25 years or;
3) 2b. Smoked > 10 cigarettes/day during > 30 years;
4) Current or former smokers who quit smoking =< 10 years ago.

Exclusion criteria

Subjects

1) With a moderate or bad self-reported health who were unable to climb two flights of stairs;
2) With a body weight >= 140 kilogram;
3) With current or past renal cancer, melanoma or breast cancer;
4) With lung cancer diagnosed less than 5 years ago or 5 years or more ago but still under treatment;
5) Who had a chest CT examination less than one year before they filled in the first NELSON questionnaire.

Primary Endpoints

- Lung cancer mortality (reduction)

Secondary Outcome Measures

- Lung cancer incidence (stage specific; time interval; screen-detected vs interval cancers e.g.) and survival
- Detection rates for first (prevalence) and subsequent (incidence) screening, as well as stage distribution.
- Sensitivity, specificity and positive predictive value
- Quality of life
- Quality adjusted life years
- Cost-effectiveness

http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=636

To come to an optimum risk-based selection from the general population, taking into account the available resources and screening capacity, the influence of selection criteria on the expected lung cancer mortality in the enrolled population and the power to detect a significant reduction in lung cancer mortality through screening at 10-year of follow-up , the trial focusses mainly on men.

There has been debate about the appropriateness of evaluating the lung cancer mortality impact of screening at a single time-point.[78,81] Due to the variation in screening effectiveness on mortality over time, maximum screening effectiveness can only be detected within a

certain timeframe. By modelling, we had estimated maximum reductions to be expected around 8-9 years (Figure S3). Our analyses indicate the cumulative mortality reduction at different time-points (8, 9 and 10 years of follow-up, respectively) is stable in men.

APPENDIX III: Supplementary Figures and Tables

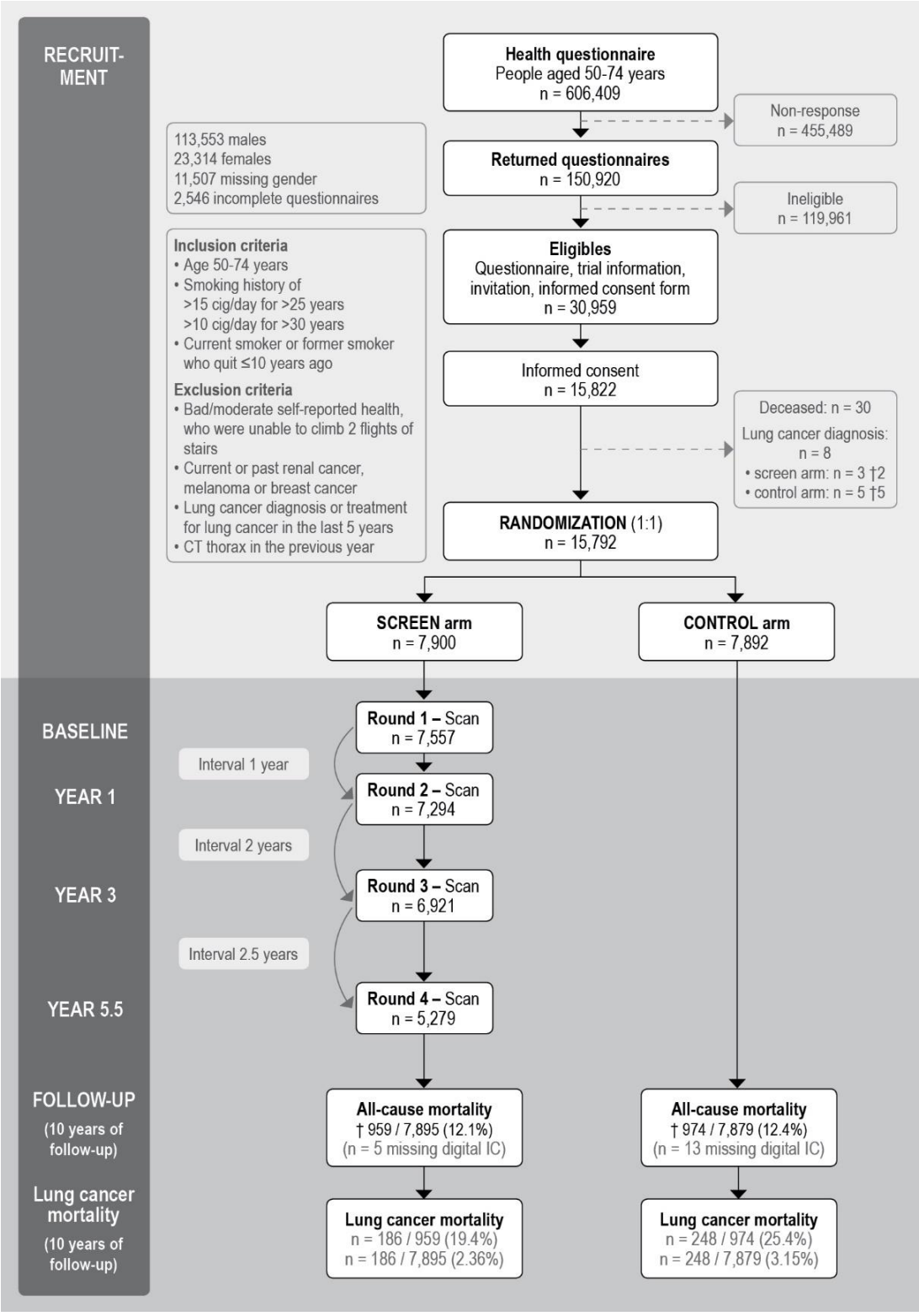


Figure S1: Consort flowchart NELSON trial (men and women).

personal data (name, address and date of birth) were destroyed after recruitment.

* lung cancer mortality indicates all lung cancer deaths with and without known lung cancer incidence data.

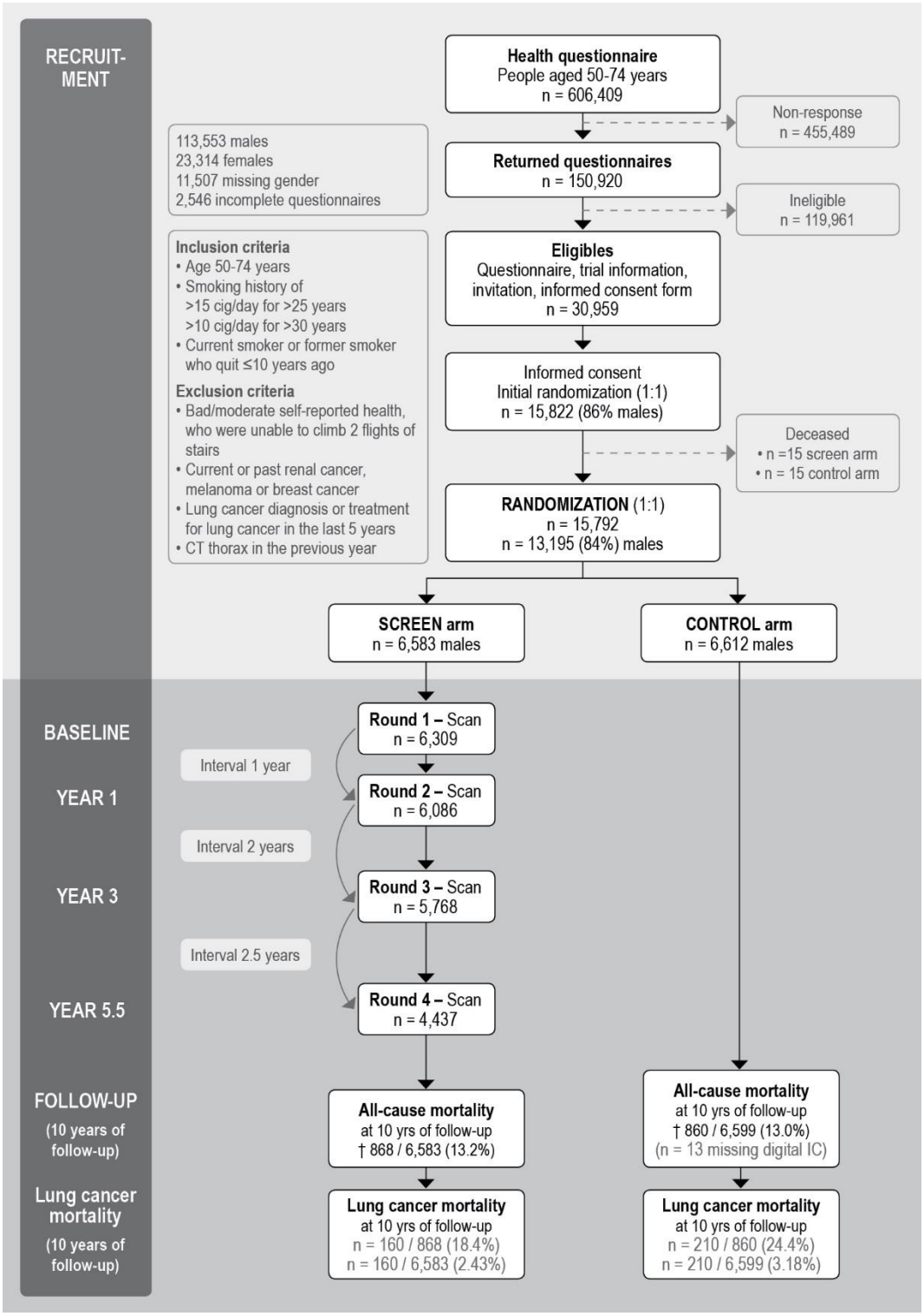


Figure S2. CONSORT diagram of male participants in the Dutch-Belgian Lung cancer Screening trial (NELSON)

personal data (name, address and date of birth) were destroyed after recruitment.

* lung cancer mortality indicates all lung cancer deaths with and without known lung cancer incidence data.

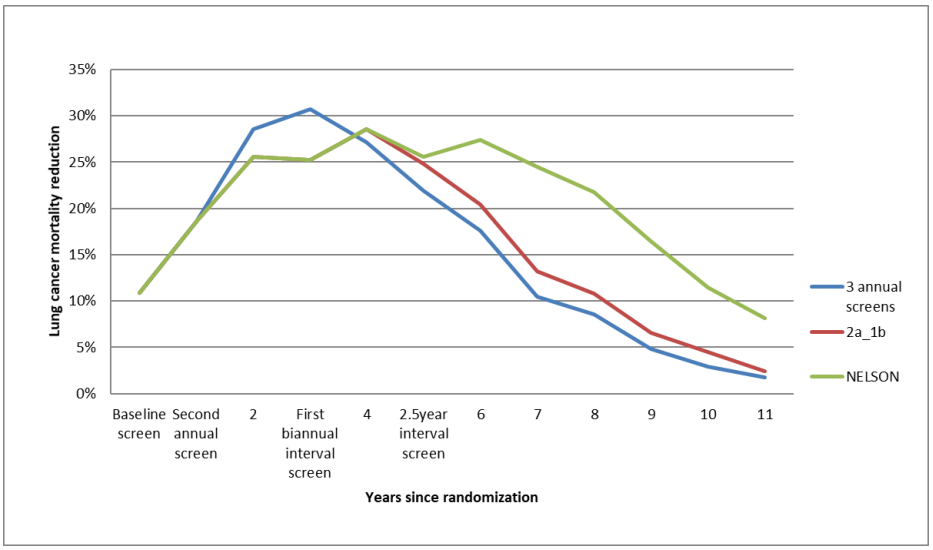
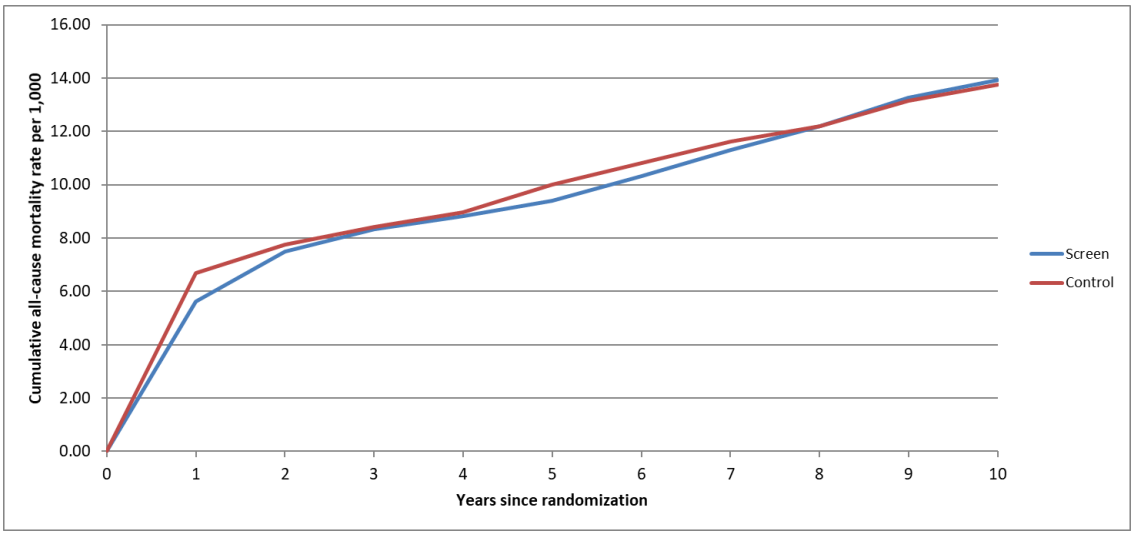


Figure S3. Potential lung cancer mortality reduction in NELSON male participants, based on lung cancer deaths in each year (incidence based mortality) reported after Mortality Advisory Committee-discussion, but before the cohort analyses.

"2a_1b" indicates three screening rounds with an annual interval between baseline screening round and screening round 2 and 1 biennial screening interval between screening round 2 and 3.



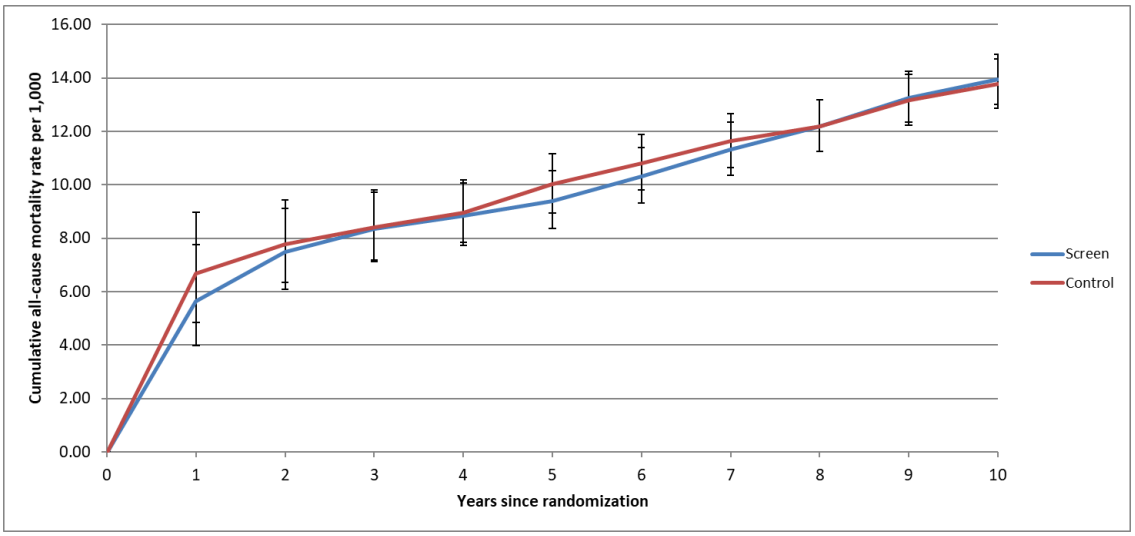


Figure S4a-b. The cumulative all-cause mortality rate (per 1,000) per year since randomization, comparing the NELSON screen and control arm (a; upper figure) without Confidence Intervals and (b; lower figure) with Confidence Intervals.

Table S1. Baseline characteristics of NELSON participants (men and women).

	All participants		**Screen group**		**Control group**	
	n	%	n	%	n	%
	15,792	100	7,900	50.0	7,892	50.0
gender						
males	13,195/15,789	83.6	6,583/7,900	83.3	6,612/7,889	83.8
females	2,594/15,789	16.4	1,317/7,900	16.7	1,277/7,889	16.2
age at randomization						
median (IQR)	58.0 (8.0)		58.0 (8.0)		58.0 (8.0)	
<50 years	14/15,727	<0.1	5/7,877	<0.1	9/7,850	0.1
50-54 years	4,167/15,727	26.5	2,045/7,877	26.0	2,122/7,850	27.0
55-59 years	5,333/15,727	33.9	2,683/7,877	34.1	2,650/7,850	33.8
60-64 years	3,543/15,727	22.5	1,796/7,877	22.8	1,747/7,850	22.3
65-69 years	1,808/15,727	11.5	918/7,877	11.7	890/7,850	11.3
70-74 years	768/15,727	4.9	384/7,877	4.9	384/7,850	4.9
≥75 years	94/15,727	0.6	46/7,877	0.6	48/7,850	0.6
smoked pack-years,						
median (IQR)	38 (19.8)		38 (19.8)		38 (19.8)	
Smoking intensity						
≤10 cig/day	38/15,755	0.2	20/7,881	0.3	18/7,874	0.2
11-15 cig/day	3,447/15,755	21.9	1,750/7,881	22.2	1,697/7,874	21.6
16-20 cig/day	4,415/15,755	28.0	2,212/7,881	28.1	2,203/7,874	28.0
21-25 cig/day	4,267/15,755	27.1	2,132/7,881	27.1	2,135/7,874	27.1
26-30 cig/day	1,693/15,755	10.7	808/7,881	10.3	885/7,874	11.2
31-40 cig/day	1,094/15,755	6.9	555/7,881	7.0	539/7,874	6.8
>40 cig/day	801/15,755	5.1	404/7,881	5.1	397/7,874	5.0
Smoking duration						
≤25 years	47/15,751	0.3	25/7,879	0.3	22/7,872	0.3
26-30 years	1,722/15,751	10.9	811/7,879	10.3	911/7,872	11.6
31-35 years	4,195/15,751	26.6	2,089/7,879	26.5	2,106/7,872	26.8
36-40 years	4,958/15,751	31.5	2,463/7,879	31.3	2,495/7,872	31.7
41-45 years	3,162/15,751	20.1	1,640/7,879	20.8	1,522/7,872	19.3
≥45 years	1,667/15,751	10.6	851/7,879	10.8	816/7,872	10.4
smoking status						
current smoker	8,748/15,749	55.5	4,415/7,880	56.0	4,333/7,869	55.1
former smoker	7,001/15,749	44.5	3,465/7,880	44.0	3,536/7,869	44.9

years since smoking cessation						
<1 years	1,165/6,963	16.7	581/3,450	16.8	584/3,513	16.6
1-5 years	3,216/6,963	46.2	1,601/3,450	46.4	1,615/3,513	46.0
6-10 years	2,492/6,963	35.8	1,219/3,450	35.3	1,273/3,513	36.2
>10 years	90/6,963	1.3	49/3,450	1.4	41/3,513	1.2

Table S2. Analyses amongst NELSON male participants by age group

	Screen arm lung cancer deaths	Screen arm person-years	Screen arm lung cancer mortality rate (per 1,000 person-years)	Control arm lung cancer deaths	Control arm person-years	Control arm lung cancer mortality rate (per 1,000 person-years)	Rate ratio (confidence intervals
50-54 at randomization	25	15,739	1.59	31	16,681	1.86	0.85 (0.48-1.50)
55-59 at randomization	35	21,376	1.64	50	21,543	2.32	0.71 (0.44-1.11)
60-64 at randomization	49	14,631	3.35	56	13,897	4.03	0.83 (0.55-1.24)
65-69 at randomization	26	7,270	3.58	43	7,107	6.05	0.59 (0.35-0.98)
70-74 at randomization	19	2,876	6.61	24	2,808	8.55	0.77 (0.40-1.47)

Table S3. Absolute numbers of lung cancer deaths, person-years and rate-ratio in screen and control arm of NELSON participants, by follow-up year, and amongst NLST-eligibles in NELSON participants.

	Men								Women						
	Screen arm lung cancer deaths	**Screen arm person-years**	**Screen arm lung cancer mortality rate (per 1,000 person-years)**	**Control arm lung cancer deaths**	**Control arm person-years**	**Control arm lung cancer mortality rate (per 1,000 person-years)**	**Rate ratio (95% confidence intervals)**		**Screen arm lung cancer deaths**	**Screen arm person-years**	**Screen arm lung cancer mortality rate (per 1,000 person-years)**	**Control arm lung cancer deaths**	**Control arm person-years**	**Control arm lung cancer mortality rate (per 1,000 person-years)**	**Rate ratio (95% confidence intervals)**
6-year follow-up	76	38,484	1.97	97	38,591	2.51	0.79 (0.57-1.07)		11	7,800	1.41	20	7,538	2.65	0.53 (0.23-1.16)
7-year follow-up	98	44,620	2.20	125	44,731	2.79	0.79 (0.60-1.03)		12	9,069	1.32	25	8,757	2.85	0.46 (0.21-0.96)
8-year follow-up	121	50,641	2.39	159	50,775	3.13	0.76 (0.60-0.97)		12	10,334	1.16	28	9,959	2.81	0.41 (0.19-0.84)
9-year follow-up	137	56,541	2.42	180	56,701	3.17	0.76 (0.61-0.96)		19	11,587	1.64	35	11,148	3.14	0.52 (0.28-0.94)
10-year follow-up	156	62,298	2.50	206	62,484	3.30	0.76 (0.61-0.94)		25	12,801	1.95	36	12,301	2.93	0.67 (0.38-1.14)
11-year follow-up	174	67,952	2.56	225	68,173	3.30	0.78 (0.63-0.95)		31	14,015	2.21	38	13,460	2.82	0.78 (0.47-1.29)

NLST-eligibles															
Men									Women						
	Screen arm lung cancer deaths	**Screen arm person-years**	**Screen arm lung cancer mortality rate (per 1,000 person-years)**	**Control arm lung cancer deaths**	**Control arm person-years**	**Control arm lung cancer mortality rate (per 1,000 person-years)**	**Rate ratio (95% confidence intervals)**		**Screen arm lung cancer deaths**	**Screen arm person-years**	**Screen arm lung cancer mortality rate (per 1,000 person-years)**	**Control arm lung cancer deaths**	**Control arm person-years**	**Control arm lung cancer mortality rate (per 1,000 person-years)**	**Rate ratio (95% confidence intervals)**
6-year follow-up	54	20,523	2.63	70	20,217	3.46	0.76 (0.52-1.10)		8	3,599	2.22	14	3,517	3.98	0.56 (0.20-1.43)
7-year follow-up	73	23,751	3.07	84	23,383	3.59	0.86 (0.62-1.18)		8	4,177	1.92	18	4,082	4.41	0.43 (0.16-1.05)
8-year follow-up	89	26,896	3.31	112	26,491	4.23	0.78 (0.59-1.04)		8	4,753	1.68	21	4,635	4.53	0.37 (0.14-0.87)
9-year follow-up	101	29,970	3.37	123	29,523	4.17	0.81 (0.62-1.06)		11	5,324	2.07	23	5,178	4.44	0.47 (0.20-0.99)
10-year follow-up	118	32,945	3.58	142	32,461	4.37	0.82 (0.64-1.05)		15	5,874	2.55	24	5,704	4.21	0.61 (0.30-1.21)
11-year follow-up	129	35,853	3.60	152	35,338	4.30	0.84 (0.66-1.06)		18	6,418	2.80	25	6,233	4.01	0.70 (0.36-1.33)

Note: only lung cancer deaths with known incidence date were included in these analyses.

NLST eligibles indicate those NELSON participants who fulfil the inclusion criteria of the National Lung Screening Trial: aged 55-74 years, who smoked 30 pack-years or more and, if quit smoking, no longer than 15 years ago.

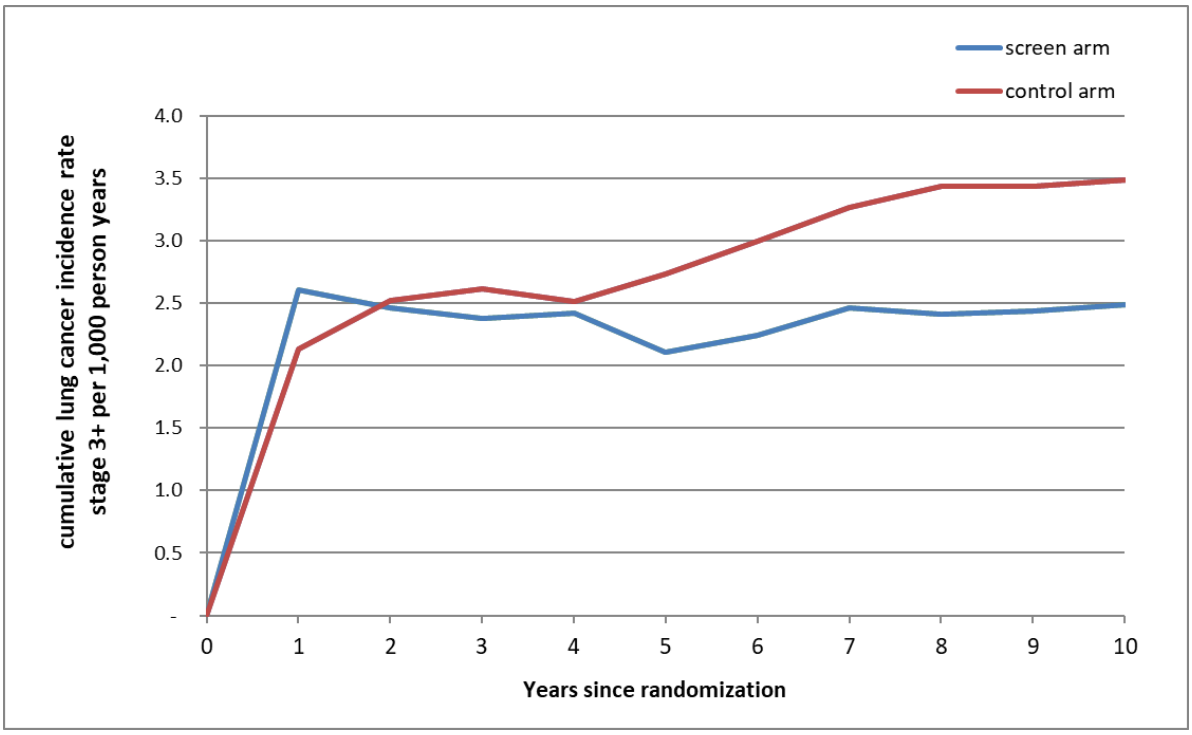
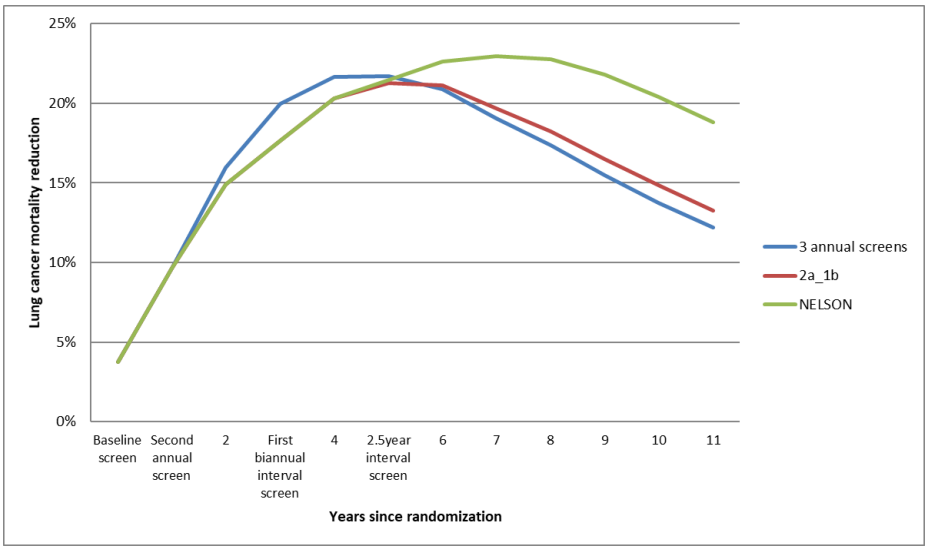


Figure S5. Cumulative lung cancer stage 3+ incidence rate (per 1,000 person-years) per follow-up year since randomization for screen and control arm in NELSON male participants



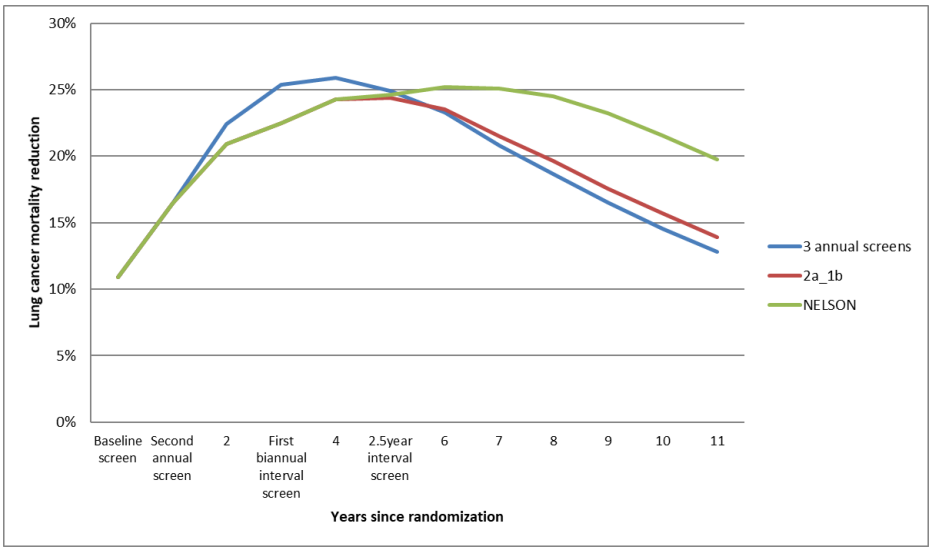


Figure S6a-b: Potential lung cancer mortality reduction, (a; upper figure) based on cumulative lung cancer deaths, normal mortality, in NELSON male participants and (b) based on cumulative lung cancer death, incidence based mortality in NELSON male participants.

"2a_1b" indicates three screening rounds with an annual interval between baseline screening round and screening round 2 and 1 biennial screening interval between screening round 2 and 3.

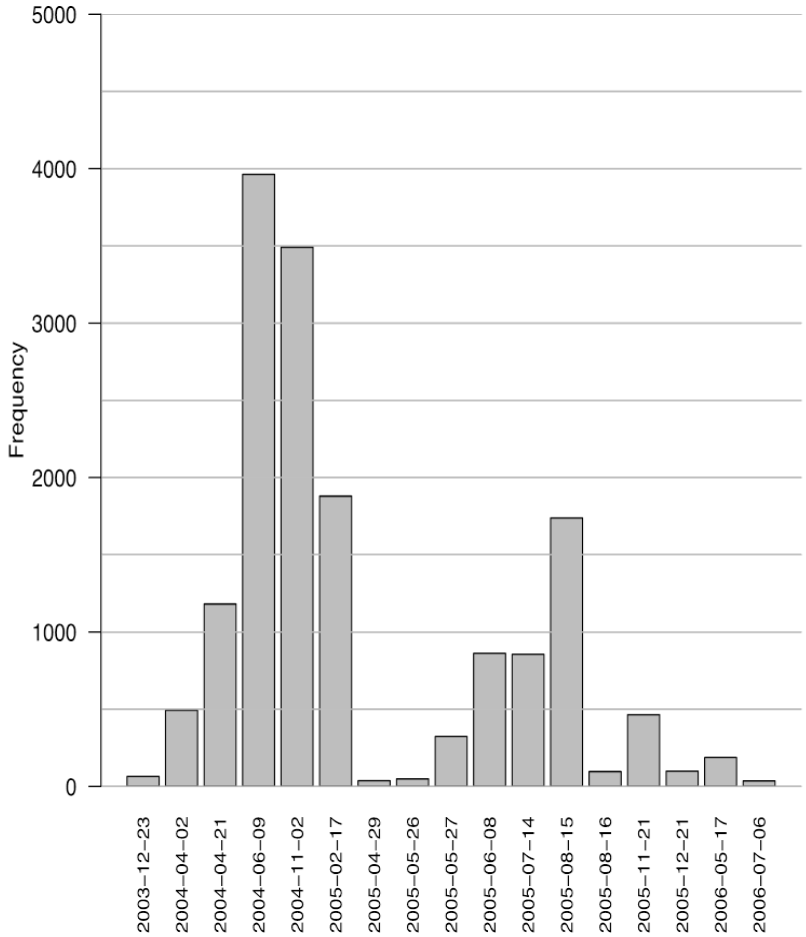


Figure S7: The number of randomized participants (men and women) at each randomization date, all centers combined.

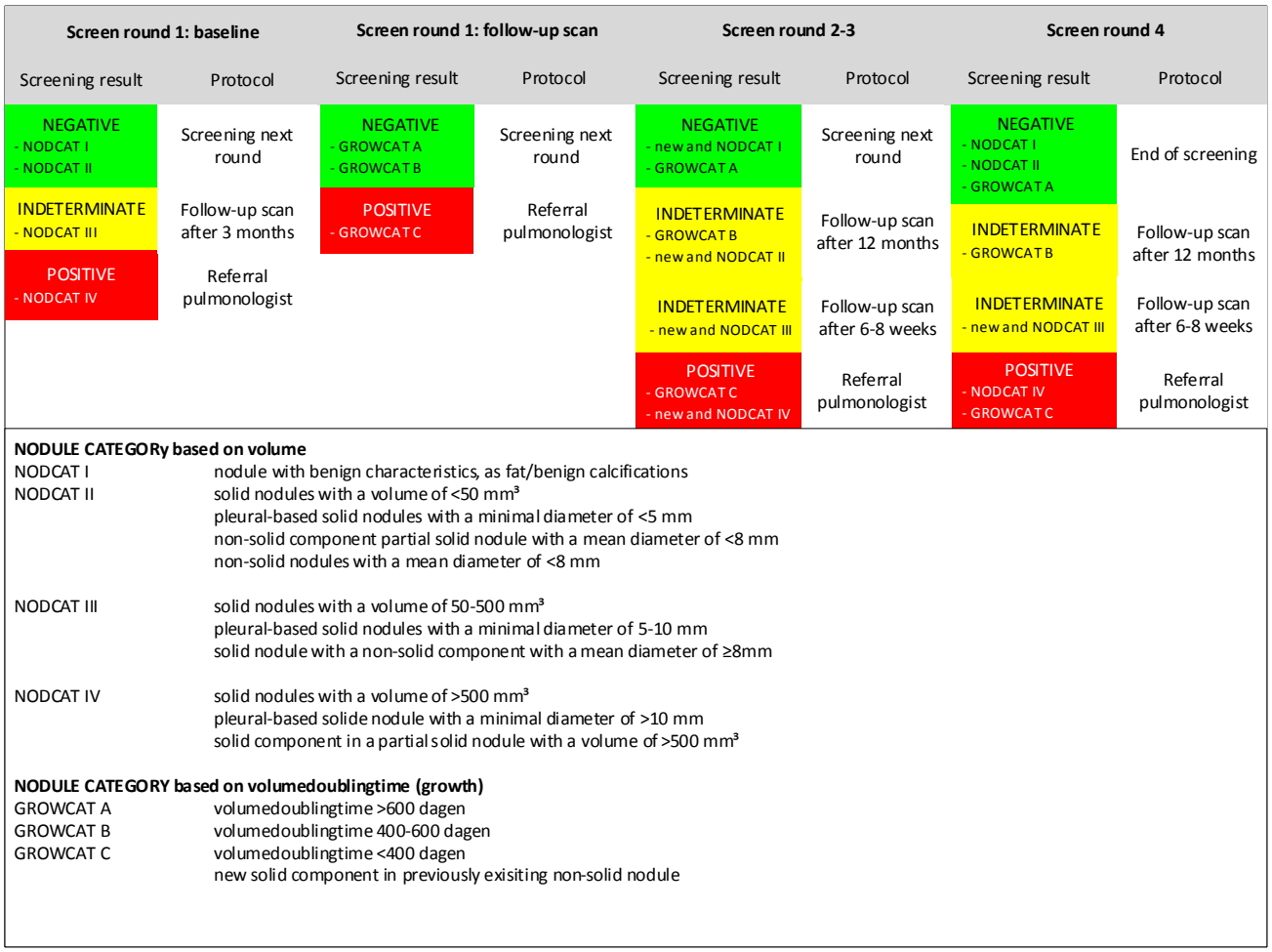


Figure S8: Nodule Management Protocol.[55]

Text box S1: Written message for NELSON participants with an indeterminate screening test result.

"We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 6-12 weeks.''

Table S4: Stage shift and change in first treatment by lung cancer screening.

A. Stage	Dutch CCC* 1996 N=7320	Prevalence screen Cornell 1998, n=27	Incidence screen Japan 1993-1998, n=36
Stage I	24%	86%	84%
Stage II	1%	4%	3%
Stage IIIA	16%	7%	6%
Stage IIIB	18%	4%	6%
Stage IV	41%	0%	3%
B. First Treatment			
Surgery	22%	93%	81%
Surgery + Radiotherapy	3.4%	0%	0%
Radiotherapy (RT)	29%	4%	6%
Chemotherapy	6%	0%	6%
Chemotherapy +RT	2%	4%	0%
Supportive Care	39%	0%	0%

* Comprehensive Cancer Center

Table S5: Health care effects of screening.

Positive effects of screening	**Negative effects of screening**
Increase in curative thoracotomies	Participation in the early detection trial
More curative radiotherapy	Increased follow-up (life years gained)
Decrease in pneumonectomies	Increased follow-up (lead time bias)
Decrease in chemo-radiotherapy	False-positive diagnosis
Decrease in palliative radiotherapy	Investigations of non-calcified nodules
Decrease in palliative chemotherapy	More thoracotomies (lobectomies)
Decrease in palliative and supportive care	More pre- and postoperative morbidity/mortality
Presumably a decrease in lung cancer mortality	

Table S6: Lung cancer mortality in the study population (50-74), rates per 100,000.

year of the study	1	2	3	4	5	6	7	8	9	10	**total**
men											
study rate	660.0	673.4	687.8	703.4	719.3	735.4	748.6	762.1	775.9	789.1	**639.8**
study numbers *	660	655	654	653	650	645	637	627	615	601	**6398**
Women											
study rate	205.4	207.5	209.6	211.6	213.6	215.6	216.9	218.2	219.5	220.5	**190.4**
study numbers *	205	203	201	197	194	191	186	181	175	169	**1904**

*: rounded numbers of lung cancer deaths in a population of 100,000 50-74 at entry

Table S7: Required number of participants aged 50-74 years at entry in control group

	Expected lung cancer mortality reduction			
	Men		Women	
	20%	25%	20%	25%
Pc=Ps=1, randomization 1:1	5,953	3,691	20,138	12,486
Pc=1, Ps=0.9, randomization 1:1	7,439	4,630	25,167	15,665
Pc=Ps=1, randomization 1:2	8,974 *	5,572 *	30,357 *	18,851 *
Pc=1, Ps=0.9, randomization 1:2	11,282 *	7,032 *	37,915 *	23,632 *

*: half of this number in screening group.

Table S8: Requested funding in the original study grant application (original study protocol).

	NZI-nrs.	year 1	Year 2	Year 3
1. Personnel	413, 422, 423	1.582.632	1.655.201	1.697.090
2. Equipment	4814, 485, 466	715.725	701.124	676.523
3. Procedures	COTG	0	0	0
4. Medical equipment	461, 462	1.632.250	168.250	196.250
Total Costs		3.930.607	2.524.574	2.569.862
5. Contributions from other sources		_ _ _	_ _ _	_ _ _
Balance		3.930.607	2.524.574	2.569.862

Table S9: Number of current and former smokers (n=73,022) of the first 106,931 male respondents on the first NELSON questionnaire, grouped by smoking history (age 50-75 years).[46]

Cigarettes per day	Smoking duration (years)	Number of respondents (n)						
		Duration of smoking cessation						
		current smokers	1 month to 5 years	6-10 years	11-15 years	16-20 years	>20 years	**Total[1]**
1-20	0-20	1,718	949	753	1,294	2,153	14,562	21,429 (29)
	21-30	1,865	1,176	1,299	1,74	1,42	3,246	10,746 (15)
	31-40	5,426	2,268	1,347	1,173	701	935	11,850 (16)
	41-50	3,683	1,26	599	383	145	183	6,253 (9)
	≥51	64	14	0	0	0	0	78 (0.1)
21-40	0-20	208	152	131	338	639	3,164	4,632 (6)
	21-30	572	469	643	957	707	1,384	4,732 (6)
	31-40	3,035	1,445	928	720	366	394	6,888 (9)
	41-50	1,978	809	329	239	84	77	3,516 (5)
	≥51	37	10	3	0	0	1	51 (0.1)
≥41	0-20	27	29	22	39	91	464	672 (1)
	21-30	61	67	93	131	120	259	731 (1)
	31-40	260	188	148	132	70	96	894 (1)
	41-50	236	126	91	51	20	18	542 (1)
	≥51	5	1	0	2	0	0	8 (0.01)
Total[1]		19,175 (26)	8,963 (12)	6,386 (9)	7,199 (10)	6,516 (9)	24,783 (34)	73,022 (100)

Note: Numbers also include respondents who later appeared to be ineligible for participation for reasons other than smoking history (exclusion criteria) (11%)

[1] Values in parentheses indicate % of ever smokers

Table S10: Estimated mortality rates (per 1,000 person-years) from lung cancer in current and former cigarette smokers by baseline amount and duration of smoking and duration of smoking cessation, men, calculated from the Cancer Prevention Study (CPS II and I), weighted by age categories of NELSON respondents.[46]

Cigarettes per day	**Smoking duration (years)**	**Duration of smoking cessation**					
		0-1 year (current smokers)	2-4 years	5-9 years	10-14 years	15-19 years	20-24 years
1-20	20-29	2.0	1.9	1.2	0.7	0.4	0.3
	30-39	1.8	1.7	1.1	0.6	0.4	0.3
	40-49	4.8	4.5	2.9	1.6	1.0	0.7
	≥50	9.5	9.1	5.8	3.2	2.0	1.4
21-40	20-29	1.6	1.5	1.0	0.5	0.3	0.2
	30-39	3.0	2.9	1.8	1.0	0.6	0.4
	40-49	6.3	6.0	3.8	2.1	1.3	0.9
	≥50	12.1	11.5	7.4	4.0	2.5	1.8
≥41	20-29	0.7	0.6	0.4	0.2	0.1	0.1
	30-39	4.2	4.0	2.6	1.4	0.9	0.6
	40-49	8.4	8.0	5.2	2.8	1.8	1.2
	≥50	15.3	14.6	9.4	5.1	3.2	2.3

Note: no data were available for smoking duration <20 years

Table S11: Estimated expected lung cancer mortality rates (per 1,000 person-years) without screening and sample sizes needed for various selections of the 106,931 respondents on the first NELSON questionnaire.[46]

Selection option	Selection scenario			Lung cancer mortality per 1,000 PY	$N_{eligibe}$[2]	Required sample size lung cancer mortality reduction after ten years			
	cigarettes per day	smoking duration (years)	duration of cessation (years)			20%	25%	30%	required participation rate (%)[1]
A	>15	>30	≤10	3.8	15,232	24,800	15,400	10,300	68
B	>15	>25	≤10	3.5	17,421	26,800	16,600	11,200	64
C	>15	>25	≤5	3.9	14,394	24,500	15,200	10.200	71
D	>15	>25	≤10	3.4	21,402	27,900	17,300	11,600	52
	>10	>30	≤10						
E	>15	>25	≤5	3.7	18,151	25,800	16,000	10,800	57
	>10	>30	≤5						
F	>15	>25	≤10	3.1	23,784	30,200	18,700	12,600	53
	>10	>30	≤15						
G	>15	>25	≤10	3.3	22,968	28,500	17,700	11,900	51
	>10	>30	≤10						
	>20	>20	≤10						

[1] one-size α = 0.05, 1:1 randomization: power = 80%[2]: 95% compliance screen group; 5% contamination; 10 years of follow-up after randomization. - Number of eligible subjects from the respondents on the first NELSON questionnaire. (Number also include respondents who appeared to be ineligible for participation for reason other than smoking history (exclusion criteria) (11%) - Required response among eligible subjects to show a lung cancer mortality difference between screen and control of 30% 10 years after randomization.

[2] 80% power turned out to be calculated as 90% power

Table S12. Histology categories according to the morphology codes according to the International Classification of Diseases for Oncology (3rd edition).[73]

	Histology				
	Adeno-carcinoma	Non-small cell lung cancer	Others	Small cell lung cancer	Squamous cell carcinoma
Morphology					
8000			X		
8010			X		
8012	X				
8013	X				
8020			X		
8022		X			
8033			X		
8041				X	
8042				X	
8044				X	
8045				X	
8046		X			
8070					X
8071					X
8072					X
8073					X
8083					X
8140	X				
8200	X				
8240			X		
8244			X		
8246			X		
8249			X		
8250	X				
8251	X				
8252	X				
8253	X				
8254	X				
8255	X				
8260	X				
8480	X				
8481	X				
8490	X				
8550	X				
8560	X				
8574	X				
9680			X		
9699			X		

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