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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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A Quick Take is available at NEJM.org

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 than 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

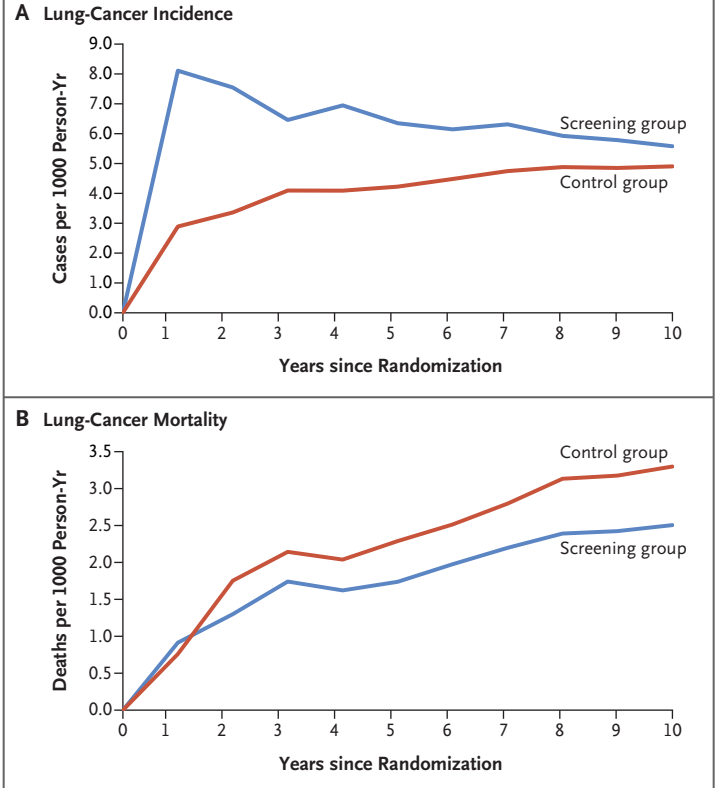

Figure 1. Lung-Cancer Incidence and Lung-Cancer Mortality among Male Participants.

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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APPENDIX

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