Washington University School of Medicine
Digital Commons@Becker

Open Access Publications

2013

Results of initial low-dose computed tomographic screening for lung cancer

Timothy R. Church
University of Minnesota School of Public Health

William C. Black
Darmouth-Hitchcock Medical Center

Denise R. Aberle
University of California - Los Angeles

Christine D. Berg
National Cancer Institute

Kathy L. Clingan
Westat, Rockville

See next page for additional authors

Follow this and additional works at: http://digitalcommons.wustl.edu/open_access_pubs

Authors

Timothy R. Church, William C. Black, Denise R. Aberle, Christine D. Berg, Kathy L. Clingan, Fenghai Duan, Richard M. Fagerstrom, Ilana F. Gareen, David S. Gierada, Gordon C. Jones, Irene Mahon, Pamela M. Marcus, JoRean D. Sicks, Amanda Jain, and Sarah Baum

ORIGINAL ARTICLE

Results of Initial Low-Dose Computed Tomographic Screening for Lung Cancer

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

Lung cancer is the largest contributor to mortality from cancer. The National Lung Screening Trial (NLST) showed that screening with low-dose helical computed tomography (CT) rather than with chest radiography reduced mortality from lung cancer. We describe the screening, diagnosis, and limited treatment results from the initial round of screening in the NLST to inform and improve lung-cancer–screening programs.

METHODS

At 33 U.S. centers, from August 2002 through April 2004, we enrolled asymptomatic participants, 55 to 74 years of age, with a history of at least 30 pack-years of smoking. The participants were randomly assigned to undergo annual screening, with the use of either low-dose CT or chest radiography, for 3 years. Nodules or other suspicious findings were classified as positive results. This article reports findings from the initial screening examination.

RESULTS

A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography); 26,309 participants (98.5%) and 26,035 (97.4%), respectively, underwent screening. A total of 7191 participants (27.3%) in the low-dose CT group and 2387 (9.2%) in the radiography group had a positive screening result; in the respective groups, 6369 participants (90.4%) and 2176 (92.7%) had at least one follow-up diagnostic procedure, including imaging in 5717 (81.1%) and 2010 (85.6%) and surgery in 297 (4.2%) and 121 (5.2%). Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants and stage IIB to IV in 120 vs. 112). Sensitivity and specificity were 93.8% and 73.4% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.

CONCLUSIONS

The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT and chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT. (Funded by the National Cancer Institute; NLST ClinicalTrials.gov number, NCT00047385.)

LUNG CANCER IS THE LARGEST SINGLE cause of deaths from cancer in the world[1-3] and is expected to account for more than 160,000 deaths in the United States during 2013.[4] Most patients with lung cancer have smoked cigarettes.[5] Of 94 million U.S. smokers, half are former smokers whose risk remains elevated decades after cessation.[6]

In the National Lung Screening Trial (NLST) of screening for lung cancer in older persons who were heavy smokers,[7] mortality from lung cancer was lower with the use of 3 years of annual screening with low-dose helical computed tomography (CT) than with the use of chest radiography.[8] In addition, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)[9] showed that among approximately 30,000 participants with baseline characteristics that were similar to those of the NLST participants, mortality from lung cancer did not differ significantly between participants undergoing screening by means of chest radiography and those receiving usual care,[10] confirming the results of previous randomized trials of screening with the use of chest radiography.[11-13]

The NLST, a joint effort of the Lung Screening Study (LSS) and the American College of Radiology Imaging Network (ACRIN), both funded by the National Cancer Institute (NCI), began randomly assigning participants in August 2002 to annual screening for 3 years with the use of either low-dose CT or chest radiography. Details of the study design[7] and the rationale for choosing chest radiography as the control procedure[14] have been published previously. A better understanding of the screening process, including the frequency and management of positive screening results, can inform the implementation of lung-cancer screening programs as well as efforts to improve them. Here, we describe the screening, diagnosis, and limited treatment results from the initial round of screening in the NLST.

METHODS

STUDY PARTICIPANTS AND STUDY CONDUCT

At 33 screening centers, we recruited asymptomatic men and women, 55 to 74 years of age, who had a history of at least 30 pack-years of cigarette smoking and who were either current smokers or had been smokers within the previous 15 years. Participants were randomly assigned to undergo annual screening for 3 years with the use of either low-dose CT or chest radiography. The study was approved by the institutional review board at each study center, and all participants provided written informed consent before undergoing randomization. Details of recruitment and randomization methods have been published previously.[7]

SCREENING EQUIPMENT AND PROCEDURES

Low-dose CT was performed on multidetector helical CT scanners of four or more channels. Single-view posteroanterior chest radiographs were obtained with the use of conventional film or digital radiographic systems. Technical standards and acquisition variables for both low-dose CT and chest radiographic screening have been published previously.[7,15-17]

IMAGE INTERPRETATION

Results were recorded on forms developed for the study. The screening image was classified as diagnostic, limited but diagnostic, or nondiagnostic, with the reasons documented.

For low-dose CT, all noncalcified nodules with long-axis diameters of 4 mm or greater in the axial plane were considered to be positive for potential lung cancer. For all positive nodules, the anatomical location (lobe), longest axial, perpendicular diameters, margin characteristics, attenuation, and representative slice number were recorded.

For chest radiography, the results were read on original film or digital image. All noncalcified nodules and masses were considered to be potentially positive for lung cancer, and for all positive nodules, the anatomical location, longest perpendicular diameters, and margin characteristics were recorded.

The interpreting radiologist judged whether the screening results were positive on the basis of findings such as noncalcified hilar or mediastinal adenopathy, atelectasis, and pleural disease. Available historical images were reviewed, and all results and recommendations were recorded. Screening results were classified as positive, negative with clinically significant abnormalities, negative with minor abnormalities, or negative with no abnormality. Participants without diagnostic results were considered to be unscreened. Although the NLST had guidelines for the follow-up of positive screening results, radiologists could make diagnostic recommen-

dations as they saw fit. Screening results were reported to the participant and the participant's designated health care provider, by mail, within 4 weeks.

FOLLOW-UP OF STUDY PARTICIPANTS

All participants were mailed annual questionnaires (for the LSS participants) or semiannual questionnaires (for the ACRIN participants) ascertaining vital status and interim cancer diagnoses. Among participants with positive screening results or with a diagnosis of lung cancer, all related diagnostic procedures, complications (not reported here), and results were abstracted by certified medical-record abstractors.

For cases of diagnosed lung cancer, the histologic type and grade, tumor stage,[18] and initial treatment were documented. To augment the ascertainment of deaths from questionnaires, the National Death Index was also searched through December 31, 2007. Determination of the cause of death led to the discovery of some previously unreported cases of lung cancer, which were also abstracted.

Here, we describe the results of the first round of screening and diagnostic evaluations that were initiated on the basis of positive findings at the screening visit, as well as all cancers diagnosed and treatments initiated at any time after randomization until the second screening, if applicable, or until 1 year after the first screening. A diagnostic evaluation consisted of a series of diagnostic procedures with no more than 12 months between consecutive procedures, including the first screening.

STATISTICAL ANALYSIS

We compared the two screening groups with respect to adherence of the participants to the testing protocol, image quality, types of diagnostic procedures, and results (positive or negative screening result, ultimate diagnosis, and initial treatment information). The results were stratified according to group and, in some cases, age, sex, race, educational level, and smoking history. All tabulations were performed with the use of SAS/STAT software, version 9.1 of the SAS System for Unix or version 9.2 for PC (SAS Institute).

Each screening result was judged to be positive or negative, and a strict algorithm was used to ascertain whether lung cancer was present at the time of screening (see details in the Supple-

mentary Appendix, available with the full text of this article at NEJM.org). Confidence intervals were calculated by means of bootstrapping.[19]

RESULTS

RECRUITMENT AND RANDOMIZATION

From August 2002 through April 2004, a total of 53,454 participants were enrolled at 33 sites across the United States; 26,722 were randomly assigned to low-dose CT and 26,732 to chest radiography. Figure 1 shows the follow-up of participants during the trial.[20] A total of 8 participants had lung cancer and 7 died before the first scheduled screening. Of the remaining 53,439 participants, 26,715 were in the low-dose CT group and 26,724 were in the radiography group.

SCREENING

The first scheduled screening examination was performed in 98.0% of the participants (52,344 of 53,439) — specifically, in 98.5% of the participants in the low-dose CT group (26,309 of 26,715) and in 97.4% of those in the chest radiography group (26,035 of 26,724) (Table 1). Compliance did not differ significantly according to sex, age, race or ethnic group, smoking status, or educational level (Table 1, and Table 1 in the Supplementary Appendix). Four participants undergoing low-dose CT and 13 participants undergoing chest radiography had nondiagnostic results, none of whom received a diagnosis of lung cancer during the follow-up period. The proportion of participants with positive screening results was higher in the low-dose CT group (7191 of 26,309 participants [27.3%]) than in the radiography group (2387 of 26,035 [9.2%]). Rates of positivity increased slightly with older age and a larger number of pack-years of smoking in both screening groups.

The proportion of all screened participants who had negative screening results but potentially clinically significant, noncancerous abnormalities was higher in the low-dose CT group (2695 of 26,309 [10.2%]) than in the radiography group (785 of 26,035 [3.0%]).

SCREENING ACCURACY

During the baseline follow-up period, lung cancer was diagnosed in 292 of the 26,309 participants (1.1%) who underwent low-dose CT screening versus 190 of the 26,035 participants (0.7%)
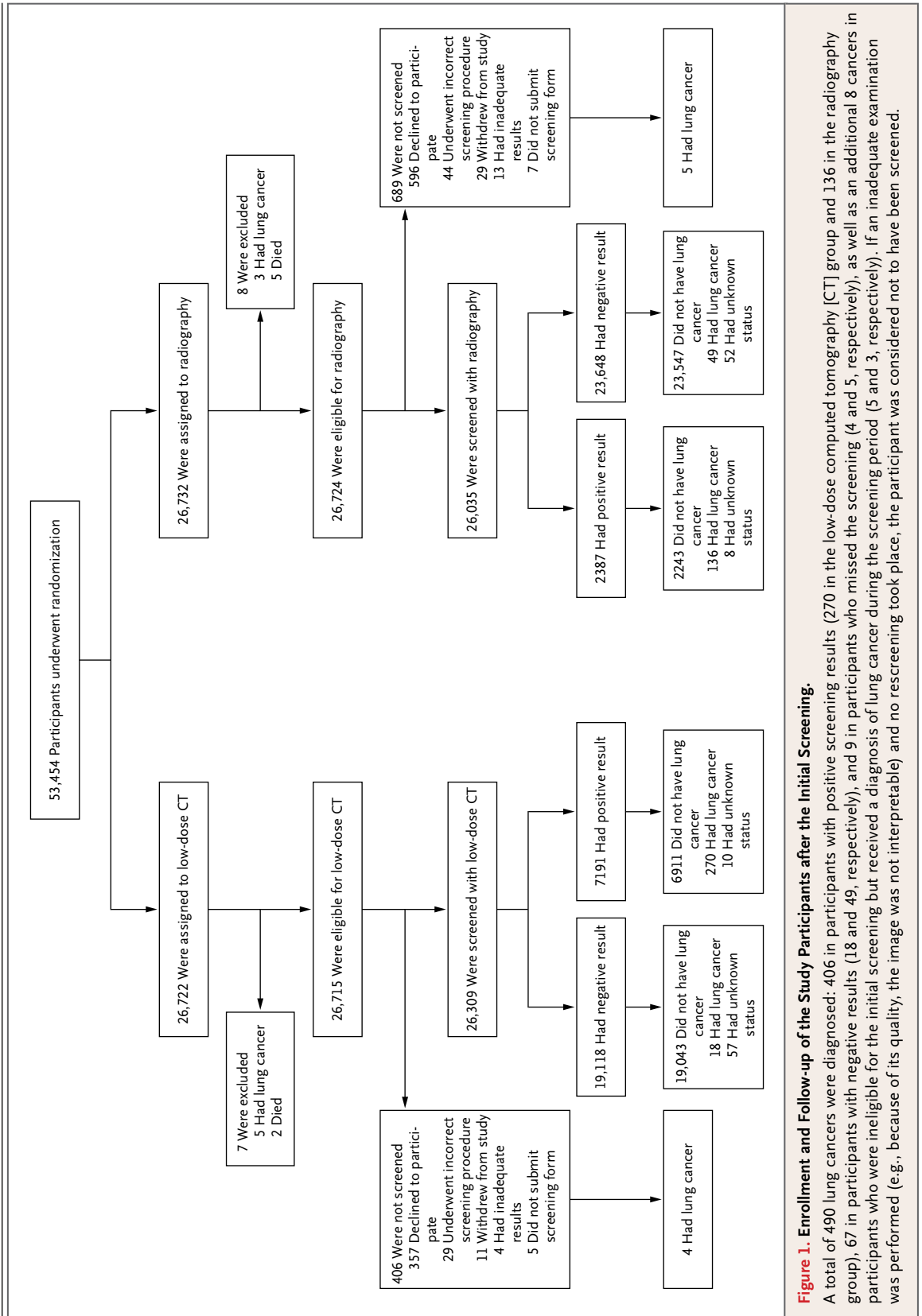
Figure 1. Enrollment and Follow-up of the Study Participants after the Initial Screening.

A total of 490 lung cancers were diagnosed: 406 in participants with positive screening results (270 in the low-dose computed tomography [CT] group and 136 in the radiography group), 67 in participants with negative results (18 and 49, respectively), and 9 in participants who missed the screening (4 and 5, respectively), as well as an additional 8 cancers in participants who were ineligible for the initial screening but received a diagnosis of lung cancer during the screening period (5 and 3, respectively). If an inadequate examination was performed (e.g., because of its quality, the image was not interpretable) and no rescreening took place, the participant was considered not to have been screened.

Table 1. Baseline Characteristics of the Study Participants, According to Study Group.*

Characteristic	Low-Dose CT			Chest Radiography		
	Randomized	Screened	Positive Result	Randomized	Screened	Positive Result
			number (percent)			
All participants	26,715	26,309 (98.5)	7191 (27.3)	26,724	26,035 (97.4)	2387 (9.2)
Sex						
Male	15,765	15,539 (98.6)	4194 (27.0)	15,758	15,400 (97.7)	1504 (9.8)
Female	10,950	10,770 (98.4)	2997 (27.8)	10,966	10,635 (97.0)	883 (8.3)
Age						
≤54 yr	2	2 (100)	1 (50.0)	4	4 (100)	0
55–59 yr	11,436	11,245 (98.3)	2730 (24.3)	11,417	11,103 (97.2)	870 (7.8)
60–64 yr	8,168	8,059 (98.7)	2217 (27.5)	8,196	7,975 (97.3)	747 (9.4)
65–69 yr	4,755	4,689 (98.6)	1456 (31.1)	4,760	4,661 (97.9)	480 (10.3)
70–74 yr	2,353	2,313 (98.3)	787 (34.0)	2,344	2,289 (97.7)	289 (12.6)
≥75 yr	1	1 (100)	0	3	3 (100)	1 (33.3)
Smoking status†						
Former smoker						
0 to <30 pack-yr	4	4 (100)	0	11	11 (100)	0
30 to <35 pack-yr	1,824	1,798 (98.6)	433 (24.1)	1,905	1,859 (97.6)	140 (7.5)
35 to <40 pack-yr	2,043	2,010 (98.4)	518 (25.8)	1,966	1,926 (98.0)	172 (8.9)
40 to <45 pack-yr	1,813	1,802 (99.4)	491 (27.2)	1,761	1,728 (98.1)	162 (9.4)
45 to <50 pack-yr	1,423	1,407 (98.9)	394 (28.0)	1,354	1,325 (97.9)	122 (9.2)
≥50 pack-yr	6,749	6,645 (98.5)	1791 (27.0)	6,832	6,666 (97.6)	608 (9.1)
Total	13,856	13,666 (98.6)	3627 (26.5)	13,829	13,515 (97.7)	1204 (8.9)
Current smoker						
0 to <30 pack-yr	2	2 (100)	0	4	4 (100)	1 (25.0)
30 to <35 pack-yr	1,099	1,081 (98.4)	251 (23.2)	1,152	1,117 (97.0)	93 (8.3)
35 to <40 pack-yr	1,859	1,834 (98.7)	453 (24.7)	1,869	1,820 (97.4)	131 (7.2)
40 to <45 pack-yr	2,394	2,353 (98.3)	646 (27.5)	2,304	2,232 (96.9)	200 (9.0)
45 to <50 pack-yr	1,549	1,523 (98.3)	444 (29.2)	1,585	1,534 (96.8)	172 (11.2)
≥50 pack-yr	5,956	5,850 (98.2)	1770 (30.3)	5,981	5,813 (97.2)	586 (10.1)
Total	12,859	12,643 (98.3)	3564 (28.2)	12,895	12,520 (97.1)	1183 (9.4)

* Participants 54 years of age or younger and those 75 years of age or older at enrollment were ineligible for the study, as were those with less than 30 pack-years of smoking, but data for them were included in the intention-to-treat analysis.
† Former smokers were participants who reported having quit tobacco use; current smokers were participants who reported that they were currently using tobacco.

who underwent radiographic screening (Fig. 1); 2 cases of lung cancer in each group were first reported in the National Death Index. In the low-dose CT group, 270 (92.5%) of the participants with lung cancer had a positive screening result (a true positive result), 18 (6.2%) had a negative screening result (a false negative result), and 4 (1.4%) missed the screening visit. In the radiog-raphy group, 136 (71.6%) of the participants with lung cancer had a positive screening result (a true positive result), 49 (25.8%) had a negative screening result (a false negative result), and 5 (2.6%) missed the screening visit. The sensitivity and specificity were 93.8% (270 of 288; 95% confidence interval [CI], 90.6 to 96.3) and 73.4% (19,043 of 25,954; 95% CI, 72.8 to 73.9), respec-

tively, for low-dose CT and 73.5% (136 of 185; 95% CI, 67.2 to 79.8) and 91.3% (23,547 of 25,790; 95% CI, 91.0 to 91.6), respectively, for chest radiography.

In the low-dose CT group, the positive predictive value for any positive finding that led to a biopsy procedure was 52.9% (265 of 501; 95% CI, 48.4 to 57.4), but the positive predictive value for positive screening results overall was only 3.8% (270 of 7181; 95% CI, 3.3 to 4.2) (Table 2). The positive predictive value for pulmonary nodules 4 mm or more in the longest diameter was 3.8% (267 of 7010; 95% CI, 3.4 to 4.3); the value increased from 0.5% to 41.3% as the diameter of the nodule increased from 4 to 6 mm to more than 30 mm. The positive predictive value for noncalcified hilar or mediastinal adenopathy was 18.5% (51 of 276; 95% CI, 14.1 to 23.4). Overall, with low-dose CT, the negative predictive value was 99.9% (19,043 of 19,061; 95% CI, 99.86 to 99.94).

In the radiography group, the positive predictive value was 70.2% (132 of 188; 95% CI, 64.0 to 76.8) for a positive screening result that led to a biopsy procedure but only 5.7% (136 of 2379; 95% CI, 4.8 to 6.6) for positive screening results overall (Table 2). The positive predictive value for pulmonary nodules was 5.8% (123 of 2105; 95% CI, 4.9 to 6.9); the value increased from 1.0% to 39.3% as the diameter of the nodule increased from 4 to 6 mm to more than 30 mm. The positive predictive value for noncalcified hilar or mediastinal adenopathy was 9.3% (8 of 86; 95% CI, 3.8 to 15.8). Overall the negative predictive value was 99.8% (23,547 of 23,596; 95% CI, 99.7 to 99.8).

The positive predictive values for atelectasis and consolidation could not be reliably estimated because, unlike pulmonary nodules 4 mm or greater in the longest diameter, these findings were not always considered to be positive and, even when reported on a positive screening result, they often coexisted with pulmonary nodules and so may not have determined a positive screening test.

DIAGNOSTIC FOLLOW-UP PROCEDURES

Of the 9578 participants with positive screening results, 9397 (98.1%) had completely documented diagnostic follow-up. At least one diagnostic procedure was performed in 6369 of 7049 participants (90.4%) in the low-dose CT group and

in 2176 of 2438 participants (92.7%) in the radiography group (Table 3). A total of 5717 participants (81.1%) and 2010 (85.6%) participants in the two groups, respectively, underwent at least one follow-up imaging procedure, with chest CT performed in 5153 (73.1%) and 1546 (65.8%) and 18F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) performed in 728 (10.3%) and 179 (7.6%); 155 (2.2%) and 83 (3.5%) underwent at least one percutaneous cytologic or biopsy procedure; 306 (4.3%) and 107 (4.6%) underwent at least one bronchoscopy (with or without transbronchial biopsy); and 297 (4.2%) and 121 (5.2%) underwent at least one diagnostic surgical procedure. In the low-dose CT group, thoracoscopy was performed in 44 participants with true positive results and in 38 participants with false positive results. In the radiography group, thoracoscopy was performed in 14 participants and 8 participants with true positive results and false positive results, respectively.

Because some of the imaging procedures were performed more than once in the same participant, a comparison of the total numbers of procedures in the two groups may best reflect the diagnostic burden. In the low-dose CT group, a total of 10,313 imaging procedures were performed, including 7288 chest CT examinations, as compared with 3657 imaging procedures in the radiography group, including 2158 chest CT examinations.

Procedure records were collected routinely only for participants with a positive screening result. However, participants with a negative screening result may also have undergone diagnostic procedures prompted by the screening result; thus, the data shown in Table 3 underrepresent the total number of procedures prompted by the screening examination.

STAGE, HISTOLOGIC FEATURES, AND TREATMENT OF LUNG CANCER

There were 292 cases of diagnosed lung cancer in the low-dose CT group and 190 in the radiography group, with the difference nearly completely accounted for by the higher incidence of stage IA cancer in the low-dose CT group (132 cases, vs. 46 in the radiography group). Table 4 shows the characteristics of the diagnosed lung cancers. There was no significant difference in the total number of lung cancers in stages IIB through IV between the low-dose CT group and the radiog-

Table 2. Frequency and Positive Predictive Value of Positive Screening Results, According to Study Group.*

Finding at Initial Screening	Low-Dose CT						Chest Radiography					
	Confirmed Lung Cancer			Total	PPV	PPV Range	Confirmed Lung Cancer			Total	PPV	PPV Range
	yes	no	unknown				yes	no	unknown			
					percent						*percent*	
Patients												
Positive screening	270	6911	10	7191	3.8	3.3–4.2	136	2243	8	2387	5.7	4.8–6.6
With subsequent biopsy	265 (98.1)	236 (3.4)	0	501 (7.0)	52.9	48.4–57.4	132 (97.1)	56 (2.5)	0	188 (7.9)	70.2	64.0–76.8
With noncalcified nodule or mass	267 (98.9)	6765 (97.9)	9 (90.0)	7041 (97.9)	3.8	3.3–4.2	123 (90.4)	1982 (88.4)	7 (87.5)	2112 (88.5)	5.8	4.9–6.9
Size of nodule or mass†												
<4 mm	0	1 (<1)	0	1 (<1)	0.0	0.0–0.0	1 (0.7)	40 (1.8)	1 (12.5)	42 (1.8)	2.4	0.0–7.9
≥4 mm	267 (98.9)	6743 (97.6)	9 (90.0)	7019 (97.6)	3.8	3.4–4.3	115 (84.6)	1807 (80.6)	6 (75.0)	1928 (80.8)	6.0	4.9–7.1
4–6 mm	18 (6.7)	3642 (52.7)	8 (80.0)	3668 (51.0)	0.5	0.3–0.7	5 (3.7)	491 (21.9)	2 (25.0)	498 (20.9)	1.0	0.2–2.0
7–10 mm	35 (13.0)	2079 (30.1)	1 (10.0)	2115 (29.4)	1.7	1.1–2.2	12 (8.8)	692 (30.9)	2 (25.0)	706 (29.6)	1.7	0.8–2.9
11–20 mm	111 (41.1)	821 (11.9)	0	932 (13.0)	11.9	9.8–13.9	38 (27.9)	481 (21.4)	2 (25.0)	521 (21.8)	7.3	5.1–9.7
21–30 mm	58 (21.5)	137 (2.0)	0	195 (2.7)	29.7	23.7–36.4	27 (19.9)	92 (4.1)	0	119 (5.0)	22.7	15.2–30.4
>30 mm	45 (16.7)	64 (0.9)	0	109 (1.5)	41.3	32.1–51.0	33 (24.3)	51 (2.3)	0	84 (3.5)	39.3	28.6–50.6
Unknown	0	21 (0.3)	0	21 (0.3)	0.0	0.0–0.0	7 (5.1)	135 (6.0)	0	142 (5.9)	4.9	1.8–8.7
Other findings												
Atelectasis, segmental or more extensive‡	3 (1.1)	69 (1.0)	0	72 (1.0)	4.2	0.0–9.0	4 (2.9)	24 (1.1)	0	28 (1.2)	14.3	3.4–29.5
Noncalcified hilar or mediastinal adenopathy or mass	51 (18.9)	225 (3.3)	1 (10.0)	277 (3.9)	18.5	14.1–23.4	8 (5.9)	78 (3.5)	0	86 (3.6)	9.3	3.8–15.8
Consolidation‡	7 (2.6)	80 (1.2)	0	87 (1.2)	8.0	2.6–14.4	3 (2.2)	41 (1.8)	1 (12.5)	45 (1.9)	6.8	0.0–14.4
Pleural thickening or effusion	16 (5.9)	439 (6.4)	1 (10.0)	456 (6.3)	3.5	1.9–5.3	10 (7.4)	161 (7.2)	1 (12.5)	172 (7.2)	5.8	2.5–9.4

* Data are number (percent) unless otherwise indicated. The patients with confirmed lung cancer do not include 76 participants in whom lung cancer was diagnosed during the initial-screening year: 9 who did not undergo the initial screening and 67 who had negative screening results. The positive predictive value (PPV) is defined as the proportion of patients with confirmed lung cancer among those with a positive result on screening whose lung-cancer status was known.

† Nodule size refers to the diameter of the largest nodule recorded on the screening examination.

‡ Because these conditions were not always considered positive, the PPV could not be reliably estimated.

Table 3. Diagnostic Follow-up of Positive Screening Results among the 9397 Patients with Data, According to Study Group and Lung-Cancer Status.*

Follow-up	Low-Dose CT			Chest Radiography		
	Confirmed Lung Cancer†		Total (N=7049)	Confirmed Lung Cancer†		Total (N=2348)
	yes (N=270)	no (N=6779)		yes (N=136)	no (N=2212)	
	number (percent)					
Any diagnostic follow-up	270 (100)	6099 (90.0)	6369 (90.4)	136 (100)	2040 (92.2)	2176 (92.7)
Clinical evaluation	248 (91.9)	4841 (71.4)	5089 (72.2)	117 (86.0)	1297 (58.6)	1414 (60.2)
Imaging studies	258 (95.6)	5459 (80.5)	5717 (81.1)	136 (100)	1874 (84.7)	2010 (85.6)
Chest radiography	112 (41.5)	1172 (17.3)	1284 (18.2)	63 (46.3)	804 (36.3)	867 (36.9)
Chest CT	181 (67.0)	4972 (73.3)	5153 (73.1)	131 (96.3)	1415 (64.0)	1546 (65.8)
FDG-PET or FDG-PET and CT	171 (63.3)	557 (8.2)	728 (10.3)	90 (66.2)	89 (4.0)	179 (7.6)
Percutaneous cytologic analysis or biopsy	98 (36.3)	57 (0.8)	155 (2.2)	66 (48.5)	17 (0.8)	83 (3.5)
Transthoracic	77 (28.5)	43 (0.6)	120 (1.7)	54 (39.7)	13 (0.6)	67 (2.9)
Extrathoracic	23 (8.5)	16 (0.2)	39 (0.6)	16 (11.8)	4 (0.2)	20 (0.9)
Bronchoscopy	158 (58.5)	148 (2.2)	306 (4.3)	76 (55.9)	31 (1.4)	107 (4.6)
With neither biopsy nor cytologic analysis	84 (31.1)	42 (0.6)	126 (1.8)	34 (25.0)	11 (0.5)	45 (1.9)
With biopsy or cytologic analysis	86 (31.9)	108 (1.6)	194 (2.8)	51 (37.5)	23 (1.0)	74 (3.2)
Surgical procedure	207 (76.7)	90 (1.3)	297 (4.2)	96 (70.6)	25 (1.1)	121 (5.2)
Mediastinoscopy or mediastinotomy	48 (17.8)	12 (0.2)	60 (0.9)	22 (16.2)	0	22 (0.9)
Thoracoscopy	44 (16.3)	38 (0.6)	82 (1.2)	14 (10.3)	8 (0.4)	22 (0.9)
Thoracotomy	156 (57.8)	41 (0.6)	197 (2.8)	78 (57.4)	18 (0.8)	96 (4.1)
Other procedure	46 (17.0)	122 (1.8)	168 (2.4)	17 (12.5)	38 (1.7)	55 (2.3)

* Numbers refer to the number of participants with a positive screening result who underwent any diagnostic procedure at least once. Not included are participants with a positive screening result for whom information on diagnostic procedures was incomplete (142 in the low-dose CT group and 39 in the radiography group). Diagnostic procedures were defined as follows: clinical evaluation (evaluation during an outpatient visit — physical examination, pulmonary-function testing, sputum cytologic assessment, or comparison of screening results with historical images), chest CT (diagnostic, low-dose, or limited-anatomy chest CT, with or without concurrent CT examination of the abdomen, pelvis, head and neck, or brain), fluorodeoxyglucose–positron-emission tomography (FDG-PET) CT (F-18 or fusion), extrathoracic percutaneous cytology or biopsy (extrathoracic lymph-node biopsy or percutaneous biopsy of liver, adrenal, or other extrathoracic tissue), thoracoscopy (with or without biopsy), or other procedures (other cytologic or biopsy procedures, procedures coded as "unknown," and procedures other than those listed by name on data-collection forms).
† The participants with confirmed lung cancer do not include the 8 participants who were ineligible for the initial screening because of a prior lung-cancer diagnosis and 76 participants who received a diagnosis of lung cancer during the initial-screening year (9 who did not undergo screening and 67 with a negative screening result). "No" denotes lung cancer that was not confirmed because of a negative diagnostic result or an unknown reference standard.

raphy group (120 vs. 112). There were many more bronchioloalveolar carcinomas and adenocarcinomas in the low-dose CT group than in the radiography group (38 vs. 8 and 123 vs. 71, respectively), but the frequencies of other histologic features were similar in the two groups. More patients with lung cancer were treated with some combination of surgery, chemotherapy, and ra-

diotherapy in the low-dose CT group than in the radiography group (277 vs. 181), but stage IA cancers that were treated only with surgery accounted for most of the difference (117 such cancers in the low-dose CT group vs. 40 in the radiography group) (Table 2 in the Supplementary Appendix). Only 10 patients in the low-dose CT group and 6 patients in the radiography group

Table 4. Stage and Histologic Features of Lung Cancers, According to Study Group and Screening Result.*

Stage or Finding	Low-Dose CT				Chest Radiography			
	Positive (N=270)	Negative (N=18)	None (N=4)	Total (N=292)	Positive (N=136)	Negative (N=49)	None (N=5)	Total (N=190)
	number/total number (percent)							
Stage								
IA	130/266 (48.9)	2/18 (11.1)	0	132/288 (45.8)	40/133 (30.1)	6/48 (12.5)	0	46/185 (24.9)
IB	25/266 (9.4)	1/18 (5.6)	0	26/288 (9.0)	22/133 (16.5)	2/48 (4.2)	0	24/185 (13.0)
IIA	7/266 (2.6)	2/18 (11.1)	1/4 (25.0)	10/288 (3.5)	3/133 (2.3)	0	0	3/185 (1.6)
IIB	11/266 (4.1)	1/18 (5.6)	0	12/288 (4.2)	8/133 (6.0)	2/48 (4.2)	0	10/185 (5.4)
IIIA	31/266 (11.7)	2/18 (11.1)	1/4 (25.0)	34/288 (11.8)	19/133 (14.3)	8/48 (16.7)	2/4 (50.0)	29/185 (15.7)
IIIB	21/266 (7.9)	7/18 (38.9)	2/4 (50.0)	30/288 (10.4)	15/133 (11.3)	12/48 (25.0)	0	27/185 (14.6)
IV	41/266 (15.4)	3/18 (16.7)	0	44/288 (15.3)	26/133 (19.5)	18/48 (37.5)	2/4 (50.0)	46/185 (24.9)
Unknown†	4/270 (1.5)	0	0	4/292 (1.4)	3/136 (2.2)	1/49 (2.0)	1/5 (20.0)	5/190 (2.6)
Histologic features								
Bronchioloalveolar carcinoma	38/268 (14.2)	0	0	38/290 (13.1)	8/136 (5.9)	0	0	8/189 (4.2)
Adenocarcinoma	118/268 (44.0)	4/18 (22.2)	1/4 (25.0)	123/290 (42.4)	53/136 (39.0)	15/48 (31.2)	3/5 (60.0)	71/189 (37.6)
Squamous-cell carcinoma	47/268 (17.5)	6/18 (33.3)	1/4 (25.0)	54/290 (18.6)	32/136 (23.5)	7/48 (14.6)	0	39/189 (20.6)
Large-cell carcinoma	14/268 (5.2)	3/18 (16.7)	0	17/290 (5.9)	8/136 (5.9)	5/48 (10.4)	0	13/189 (6.9)
Non–small-cell carcinoma, other classification‡	34/268 (12.7)	1/18 (5.6)	1/4 (25.0)	36/290 (12.4)	20/136 (14.7)	9/48 (18.8)	1/5 (20.0)	30/189 (15.9)
Small-cell carcinoma	15/268 (5.6)	4/18 (22.2)	1/4 (25.0)	20/290 (6.9)	15/136 (11.0)	11/48 (22.9)	1/5 (20.0)	27/189 (14.3)
Carcinoid	2/268 (0.7)	0	0	2/290 (0.7)	0	1/48 (2.1)	0	1/189 (0.5)
Unknown	2/270 (0.7)	0	0	2/292 (0.7)	0	1/49 (2.0)	0	1/190 (0.5)

* Cancer-stage classification is based on the sixth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.[21] The denominators for cancer stage and histologic features were the total number of cancers with a known stage and the total number of cancers with known histologic features, respectively. Negative screening results include findings that were classified as either minor or clinically significant abnormalities that were not suggestive of lung cancer.

† The 9 lung cancers of unknown stage included 2 carcinoids, 1 occult carcinoma, 2 with stage information that could not be classified, and 4 for which medical records were missing.

‡ The 66 lung cancers in this category included 8 adenosquamous carcinomas, 2 sarcomatoid carcinomas, 5 unclassified carcinomas, and 51 carcinomas coded only as "non–small-cell carcinoma."

received no treatment at all. However, for each cancer stage, the relative frequencies of treatment types did not differ significantly between the two screening groups (Table 1 in the Supplementary Appendix).

DISCUSSION

We report the prevalence of abnormalities in the NLST population at the onset of screening.[8] As expected, more positive screening results, more diagnostic procedures, more biopsies and other invasive procedures, and more lung cancers were seen in the low-dose CT group than in the radiography group during the first screening round. In addition, more early-stage lung cancers, but similar numbers of late-stage cancers, were diagnosed in the low-dose CT group.

Our findings for screening with the use of low-dose CT are similar to those in previous large studies of low-dose CT screening (Early Lung Cancer Action Project [ELCAP],[22] International Early Lung Cancer Action Program [I-ELCAP],[23] Mayo,[24] Milano,[25] Lung Screening Study Feasibility Phase,[26] Pittsburgh,[27] and NELSON [Current Controlled Trials number, ISRCTN63545820][28]). The ages and smoking histories of our participants were similar to those of participants in most of these studies. In addition, the sensitivity (93.8%), specificity (73.4%), rate of positive screening results (27.3%), and positive predictive value (3.8%) of low-dose CT were in the midrange of the corresponding values in the previous studies, as was the proportion of participants who underwent biopsy (1.9%).

Two additional findings suggest that screening by means of low-dose CT was well implemented in our study. The compliance rate of 98.5% was much higher than the 85% rate that was assumed for each screening round in our sample-size calculation, and only four of the low-dose CT scans were judged to be nondiagnostic.

The high rate of positive screening results (and the low positive predictive value) with low-dose CT resulted in the performance of many diagnostic procedures. Nonetheless, the number of follow-up chest CT scans per positive screening result in the low-dose CT group was modest — approximately 1 scan per positive screening result (i.e., 7288 CT scans performed per 7049 participants with a positive result of low-dose CT scanning). A recent cost-effectiveness analysis of lung-cancer screening[29] assumed, for the baseline case, that nodules 4 to 8 mm (presumably in the longest diameter) would be evaluated by means of serial CT at 3, 6, and 9 months, on the basis of the protocol for the Mayo study,[30] which started in 1999. Subsequent reports have recommended less frequent follow-up CT, as reflected in our trial, which should improve the cost-effectiveness of the procedure in the face of its high rate of positive results.

Some of our findings with respect to the initial low-dose CT screening are not fully consistent with those reported previously. The prevalence of lung cancer (1.1%) is at the low end of the reported range in prior large studies of participants with similar smoking histories (1.0 to 2.8%) but is close to the rate of 1.0% in the NELSON trial, the most recent study that is comparable to ours. This low rate may be due to some combination of the following factors: the healthy-volunteer effect (volunteers in trials are healthier than the general population), a younger population in our study than in the most recent studies, the high proportion of former smokers in our study, and the limitations of lung-cancer prediction estimates that are based on pack-years.[31] The proportion of all lung cancers classified as stage I (55%) was also low relative to the range reported in other studies (54 to 85%), but this may be partly due to exclusion of small-cell cancer in the other studies and the more frequent use of PET-CT to ascertain the cancer stage in our study. Adenocarcinoma was the most common histologic finding in both our study and previous studies. Bronchioloalveolar carcinoma occurred about twice as frequently in our study (with a rate of 13%) than in others, possibly because of higher spatial resolution of the screening procedure and more frequent reporting of this type of carcinoma. Bronchioloalveolar carcinoma is no longer reported in many centers, on the basis of recent recommendations,[32] and may soon be only of historical interest.

The results of chest radiography in our study were also similar to those in the comparable subgroup of participants in the PLCO radiography group.[10] In our radiography group and the PLCO radiography subgroup, 9.2% and 11.0% of participants, respectively, had positive screening results; 0.7% and 0.8% underwent biopsy; and 0.5% and 0.6% had lung cancer detected on screening; the sensitivity in the respective groups

was 74% and 77%, the specificity was 91% and 90%, and the positive predictive value was 5.7% and 5.5%. These similarities suggest that more important outcomes, including mortality from lung cancer, should also be similar.

Several limitations of our study deserve discussion. Our participants were similar to the general population of smokers in the United States except for a higher proportion of former smokers and a higher educational level, which may partly explain the lower prevalence of lung cancer in our study than in other studies. This suggests that caution should be used in generalizing other results of the initial round of screening in our study to the U.S. population of smokers. In addition, because the numbers of follow-up procedures were counted only in participants with positive screening results, they undoubtedly underestimate the frequency of diagnostic procedures performed because of a screening result (e.g., procedures performed to investigate potentially clinically significant abnormalities). Finally, because mortality was not reduced by screening with chest radiography among the PLCO participants who were comparable to our participants,[10] the anticipated comparison of the results of our first round of low-dose CT screening with no screening in the ongoing NELSON trial should be of great interest.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Vol. VIII. Lyon, France: International Agency for Research on Cancer, 2002.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30.
5. Malarcher AM, Schulman J, Epstein LA, et al. Methodological issues in estimating smoking-attributable mortality in the United States. Am J Epidemiol 2000; 152:573-84.
6. Cigarette smoking among adults and trends in smoking cessation — United States, 2008. MMWR Morb Mortal Wkly Rep 2009;58:1227-32.
7. Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. Radiology 2011; 258:243-53.
8. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
9. Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 2000;21:6 Suppl:251S-272S.
10. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-73.
11. Fontana RS. The Mayo Lung Project: a perspective. Cancer 2000;89:11 Suppl: 2352-5.
12. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer: results of the Memorial Sloan-Kettering study in New York. Chest 1984;86:44-53.
13. Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000;92:1308-16.
14. Church TR. Chest radiography as the comparison for spiral CT in the National Lung Screening Trial. Acad Radiol 2003; 10:713-5.
15. Cagnon CH, Cody DD, McNitt-Gray

MF, Seibert JA, Judy PF, Aberle DR. Description and implementation of a quality control program in an imaging-based clinical trial. Acad Radiol 2006;13:1431-41.

16. American College of Radiology. ACR standard for performance of pediatric and adult thoracic computed tomography (CT). In: Standards 2003-2004. Reston, VA: American College of Radiology, 2002: 115-9.

17. Gierada DS, Garg K, Nath H, Strollo DC, Fagerstrom RM, Ford MB. CT quality assurance in the lung screening study component of the National Lung Screening Trial: implications for multicenter imaging trials. AJR Am J Roentgenol 2009;193:419-424.

18. Sobin LH, Wittekind C. TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss, 2002.

19. Efron B, Tibshirani RJ. An introduction to the bootstrap (CRC monographs on statistics and applied probability). New York: Chapman & Hall, 1993.

20. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010; 152:726-32.

21. Greene FL, Page DL, Fleming ID, et al. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag, 2002.

22. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105.

23. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen O. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71. [Errata, N Engl J Med 2008;358:1875,359;877.]

24. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003;226: 756-61.

25. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003; 362:593-7.

26. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest x-ray screening for lung cancer. Lung Cancer 2005;47:9-15.

27. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med 2008;178:956-61.

28. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9.

29. McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. J Thorac Oncol 2011;6: 1841-8.

30. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002;165:508-13.

31. Peto J. That the effects of smoking should be measured in pack-years: misconceptions 4. Br J Cancer 2012;107:406-7.

32. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.

Copyright © 2013 Massachusetts Medical Society.