DOI: 10.1093/jnci/djq434
Advance Access publication on November 22, 2010.

ARTICLE

Baseline Characteristics of Participants in the Randomized National Lung Screening Trial

The National Lung Screening Trial Research Team
Writing committee: Denise R. Aberle, Amanda M. Adams, Christine D. Berg, Jonathan D. Clapp, Kathy L. Clingan, Ilana F. Gareen, David A. Lynch, Pamela M. Marcus, Paul F. Pinsky

Manuscript received May 4, 2010; revised June 10, 2010; accepted October 1, 2010.

Correspondence to: David A. Lynch, MB, Division of Radiology, National Jewish Health, 1400 Jackson St, Denver, CO 80206 (e-mail: lynchd@njhealth.org)

Background The National Lung Screening Trial (NLST), a randomized study conducted at 33 US sites, is comparing lung cancer mortality among persons screened with reduced dose helical computerized tomography and among persons screened with chest radiograph. In this article, we present characteristics of the study population.

Methods Eligible participants were aged 55–74 years and were current or former smokers with a cigarette smoking history of at least 30 pack-years. Randomization was stratified by site, sex, and age. To assess representativeness of the study population, demographic characteristics of individuals from the general population who met NLST age and smoking history inclusion criteria were obtained from the Tobacco Use Supplement of the US Census Bureau Current Population Surveys.

Results The NLST enrolled 53 456 persons, with 26 733 randomly assigned to chest radiograph screening and 26 723 to computerized tomography screening. Characteristics of the participants were as follows: 31 533 (59%) were men, 39 234 (73%) were younger than 65 years, 25 779 (48%) were current smokers, and 16 839 (32%) had a college or higher degree. Median cigarette exposure was 48 pack-years. Among Tobacco Use Supplement respondents who met NLST age and smoking history criteria, 59% were men, 65% were younger than 65 years, and 57% were current smokers. Median cigarette exposure among this group was 47 pack-years, and 14% had a college degree or higher.

Conclusion The NLST cohort has a distribution of sex and pack-year history that is similar to the component of the general US population that meets the major NLST eligibility criteria; however, NLST participants are younger, better educated, and less likely to be current smokers.

J Natl Cancer Inst 2010;102:1771–1779

Lung cancer remains the leading cause of cancer-related death in both men and women in the United States (1). Because prognosis is related to stage, there has been long-standing interest in detecting lung cancer while the disease is still asymptomatic, in the hope that it will be more responsive to treatment. Several observational studies have shown that screening by reduced dose helical computed tomography can detect smaller sized and earlier stage lung cancers than can be detected by symptoms or by screening chest radiographs (2–9). However, it is not known whether the increased detection of apparently early-stage lung cancers by computerized tomography screening ultimately results in decreased lung cancer–specific mortality. To answer this critical question, the National Lung Screening Trial (NLST) was launched on September 18, 2002. The NLST, a randomized controlled trial designed to determine whether screening with computerized tomography could reduce lung cancer mortality relative to single-view chest radiograph screening, is a multi-institutional trial funded by the US National Cancer Institute (NCI). It is conducted through a collaboration of the NCI Division of Cancer Prevention, which administers the component of NLST known as the Lung Screening Study through a contract mechanism, and the NCI Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, which funds the component administered by the American College of Radiology Imaging Network (ACRIN) through a grant mechanism.

The NLST used a 1:1 ratio to randomly assign individuals to receive either three annual computerized tomography or three annual chest radiograph screens, with follow-up for outcomes for at least 5 years after randomization. Entry criteria, as described previously in detail (10), required subjects to be aged between 55 and 74 years and to have a minimum of 30 pack-years of cigarette smoking history at the time of random assignment. Former smokers were required to have quit within 15 years of random assignment. Current smokers were defined as those who still smoked cigarettes regularly. Recruitment was conducted by 33 medical institutions across the United States, with the goal of enrolling a sample representative of the US population at high risk of lung cancer death. Accrual was completed in April 2004, and participants currently are being followed to evaluate clinical outcomes, including vital status and cause of death. The primary

CONTEXT AND CAVEATS

Prior knowledge

The National Lung Screening Trial (NLST) is comparing lung cancer mortality among persons who were randomly assigned to screening with reduced dose helical computerized tomography or with chest x-ray.

Study design

Baseline demographic characteristics of individuals from the NLST were compared with those from the general population who met NLST age and smoking history inclusion criteria who were selected from the Tobacco Use Supplement of the US Census Bureau Current Population Surveys. Eligible participants were aged 55–74 years and were current or former smokers with a cigarette smoking history of at least 30 pack-years.

Contribution

Characteristics of the NLST participants were compared with those of a group representing the general population. In both populations, 59% were men. NLST participants were younger than those from the general population, fewer were current smokers, and more than twice as many had a college degree or higher.

Implications

The proportion of men and pack-year history were similar between NLST participants and the groups from the general US population that met the major NLST eligibility criteria. There were differences between the two groups on age, education, and smoking status.

Limitations

Data on personal, family, and occupational history were self-reported and collected with a self-administered questionnaire.

From the Editors

endpoint of the NLST is lung cancer–specific mortality, and the trial has 90% power to detect a 20% mortality reduction in the computerized tomography arm relative to the chest radiograph arm. Conclusive results for the primary endpoint are expected by mid-2011. The purpose of this article was to provide a detailed description of demographic, medical, and other characteristics of the NLST study population at the time of randomization.

Participants and Methods

The study was performed after approval by an institutional review board at each institution. Written informed consent was obtained from each subject.

Recruitment Strategies

Thirty-three medical institutions participated in the NLST (Clinicaltrials.gov, NCT 00047385) and were widely dispersed throughout the United States (Figure 1 and Table 1). Participants were recruited by use of techniques that included targeted mailings, local radio and newspaper advertisements, outreach including health fairs and presentations to unions and community groups, NCI and institutional Web sites, Internet-based advertising that listed toll-free numbers for the NCI's Cancer Information Service, and public service television and radio announcements. Local chapters of the American Cancer Society provided recruitment support to many sites.

Minority Recruitment Strategies

Targeted minority recruitment plans were implemented at specific sites on the basis of regional demographic data and site-specific strategies and included advertising at minority-focused conferences and events; direct mailings to minority communities; advertisements in local minority newspapers and on radio stations; use of minority "ambassadors" in community settings; dissemination of information on NLST by minority health-care providers; translation of trial-related materials into Spanish, Chinese dialects, and Farsi; and provision of minority press kits to more than 70 media outlets. These efforts were assisted through collaboration with the NCI Cancer Information Service Partnership Program, the American Public Health Association's Black Caucus of Health Workers, the NCI Spirit of Eagles Program, and the American Cancer Society.

Enrollment and Randomization of Participants

Study eligibility, including smoking history, was assessed through use of an eligibility screener, which was administered by telephone or in-person by trained interviewers. The eligibility screener was designed to allow for the computation of number of pack-years of cigarettes smoked and determination of whether subjects smoked within the past 15 years. Randomization occurred after data coordinating centers confirmed that eligibility criteria had been met for a given individual; participants were then assigned to either the computerized tomography arm or chest radiograph arm in a 1:1 ratio, stratifying by site, sex, and 5-year age group. Stratified randomization was accomplished by use of a block size of six or eight, with block size chosen at random. At the time of the enrollment, participants filled out a questionnaire that contained questions on personal history of selected diseases, including respiratory diseases, cardiovascular diseases, stroke, and diabetes; family history of lung cancer; occupational history (jobs and industries either previously demonstrated or thought to be associated with increased risk of lung disease or lung cancer); weight and height; and demographic factors such as education and marital status. Compliance with questionnaire completion was 99.6% (53 267 of the 53 456 participants) and was similar in both study arms.

Comparison Between the NLST Population and the General Population at Risk for Lung Cancer

To assess whether the NLST population was representative of the overall US population that was likely to be eligible for the trial, we used the Census Department's Tobacco Use Supplement of the Continuing Population Survey for 2002–2004, the years corresponding to the period of NLST enrollment (11). The Tobacco Use Supplement contains questions about respondents' past and present cigarette smoking, captures demographic information and other behavioral data, and contains information on a scientifically selected, nationally representative sample of approximately 240 000 individuals. Using the responses to Tobacco Use Supplement questions, we identified the subset of respondents who were aged 55–74 years, had smoking history of at least 30 pack-years, and were either current smokers or former smokers who had quit within the past 15 years. For this subset of 9090 individuals, we

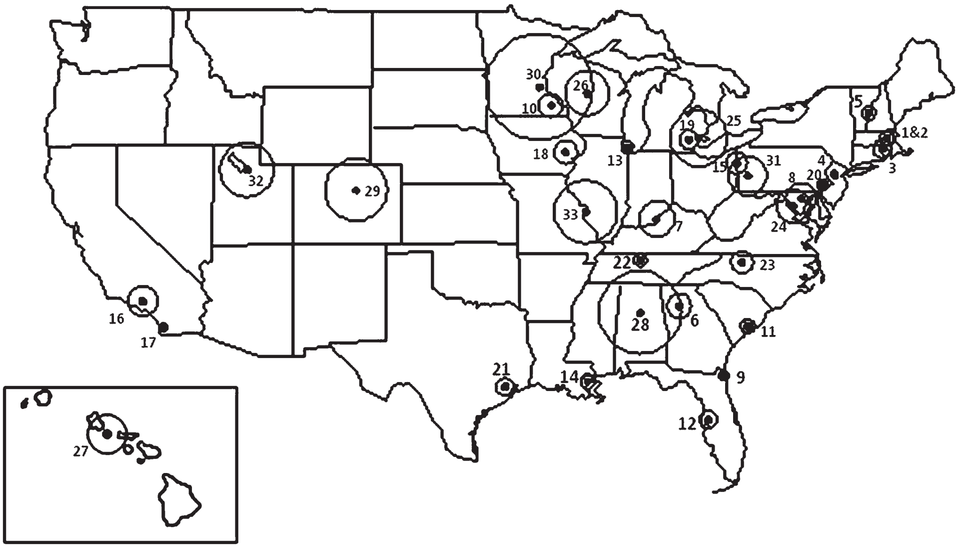

Figure 1. Map of the United States showing National Lung Screening Trial screening centers. The size of the bubble surrounding each site indicates the relative number of participants enrolled at the site. The number adjacent to each site corresponds to the number assigned to the site in Table 1.

evaluated the distribution of age, sex, race, Hispanic ethnicity, marital status, and education, as well as smoking status (current vs former) and pack-years of cigarettes smoked. We compared distributions of participants identified through the Tobacco Use Supplement with those of NLST participants.

Results

Study Accrual

NLST enrollment began on September 18, 2002 and was completed on April 26, 2004, 4 months before the targeted completion date. The study enrolled 53 456 individuals, with 9016 subjects being enrolled in 2002, 38 584 in 2003, and 5856 in 2004. Of the 53 456 participants, 34 614 (65%) were accrued from Lung Screening Study sites and 18 842 (35%) from ACRIN sites (Table 1). As of November 30, 2009, 192 enrolled persons who were thought to be eligible at the time of randomization were determined to be ineligible. Common reasons for ineligibility included computerized tomography within 18 months before enrollment (n = 68), nonsmoker or quit more than 15 years before randomization (n = 23), participation in another cancer screening trial (n = 28), recent antibiotic use (n = 17), insufficient pack-years (n = 12), diagnosis of cancer in the 5 years before randomization (n = 14), and age older or younger than the required range (n = 12). These randomized but ineligible subjects are included in the study and in the current analysis.

Comparison of the Lung Screening Study and ACRIN study populations showed that the two groups were quite similar with respect to demographics: 13 630 (72%) of 18 842 ACRIN and 25 604 (74%) of 34 614 Lung Screening Study subjects were younger than 65 years and 8440 (45%) of ACRIN and 13 483 (39%) of Lung Screening Study subjects were women. A total of 9514 (50%) of ACRIN and 16 265 (47%) of Lung Screening Study subjects were current smokers.

Demographic Characteristics

Of the total of 53 456 participants, 26 733 were randomly assigned to chest radiograph screening and 26 723 were randomly assigned to computerized tomography. The distribution of sex and age by study arm is shown in Table 2. A total of 31 533 (59%) of participants were men and 39 234 (73%) were younger than 65 years. Mean age of the entire cohort was 61.4 years (standard deviation = 5.0 years). Median age was 60 years (interquartile range = 57–65 years). Because randomization was stratified by sex and 5-year age group, the participant numbers are virtually identical within these categories across study arms.

The distribution of race, Hispanic or Latino ethnicity, marital status, educational status, and body mass index by study arm is shown in Table 2. The distribution of these characteristics was similar across study arms. Most individuals (48 549 or 91%) in the cohort were white, 2378 (4.4%) were black, and 935 (1.7%) were of Hispanic or Latino ethnicity. Only 3252 (6%) did not have a high school degree, and 16 839 (approximately 32%) had at least a college degree. A total of 15 017 (28%) of the NLST subjects were obese by Center for Disease Control criteria (ie, body mass index ≥ 30 kg/m^2).

Smoking History

Details of smoking history in these subjects are presented in Tables 2 and 3. Smoking patterns were similar across study arms. A total of 27 677 (52%) of the cohort of 53 456 participants were former smokers and 25 779 (48%) were current smokers. Among the 27 677 former smokers, 7891 (29%) reported quitting within 4 years of study entry. Smoking status showed a strong age trend, with the percentage of current smokers decreasing from 54% among those aged 55–59 years to 47% among those aged 60–64 years, 41% among those aged 65–69 years, and 38% among those aged 70–74 years. Median pack-year history of smoking was similar for current smokers (48 pack-years) and former smokers (50 pack-years). Duration of smoking was similar for current smokers and for former smokers, with a median of 43 years for both arms.

Occupational Exposure and Medical History

Information concerning work experience in occupations and industries thought to increase risk of lung disease or lung cancer is

Table 1. National Lung Screening Trial accrual data by study group and screening center*

Study group	Screening center	Location	Accrual, No. of participants
ACRIN	1. Beth Israel Deaconess Medical Center	Boston, MA	629
	2. Brigham and Women's Hospital	Boston, MA	540
	3. Brown University, Rhode Island Hospital	Providence, RI	827
	4. The Cancer Institute of New Jersey	New Brunswick, NJ	88
	5. Dartmouth-Hitchcock Medical Center	Lebanon, NH	575
	6. Emory University	Atlanta, GA	1231
	7. Jewish Hospital Rudd Heart and Lung Center	Louisville, KY	1971
	8. Johns Hopkins University	Baltimore, MD	1670
	9. Mayo Clinic, Jacksonville	Jacksonville, FL	288
	10. Mayo Clinic, Rochester	Rochester, MN	1183
	11. Medical University of South Carolina	Charlestown, SC	578
	12. Moffitt Cancer Center	Tampa, FL	787
	13. Northwestern University	Chicago, IL	426
	14. Ochsner Medical Center	New Orleans, LA	504
	15. St. Elizabeth Health Center	Youngstown, OH	1046
	16. University of California, Los Angeles	Los Angeles, CA	1587
	17. University of California, San Diego	San Diego, CA	155
	18. University of Iowa	Iowa City, IA	1154
	19. University of Michigan Medical Center	Ann Arbor, MI	857
	20. University of Pennsylvania	Philadelphia, PA	386
	21. University of Texas M.D. Anderson Cancer Center	Houston, TX	782
	22. Vanderbilt University	Nashville, TN	465
	23. Wake Forest University	Winston-Salem, NC	1113
	Total		18 842
LSS	24. Georgetown University Medical Center	Washington, DC	1827
	25. Henry Ford Health System	Detroit, MI	3395
	26. Marshfield Clinic Research Foundation	Marshfield, WI	2520
	27. Pacific Health Research & Education Institute†	Honolulu, HI	2359
	28. University of Alabama at Birmingham	Birmingham, AL	5052
	29. University of Colorado Denver	Aurora, CO	3743
	30. University of Minnesota School of Public Health	Minneapolis, MN	6618
	31. University of Pittsburgh Medical Center	Pittsburgh, PA	2177
	32. University of Utah Health Sciences Center	Salt Lake City, UT	3159
	33. Washington University School of Medicine	St Louis, MO	3764
	Total		34 614
Total			53 456

* ACRIN = American College of Radiology Imaging Network; LSS = Lung Screening Study.

† Formerly known as Pacific Health Research Institute.

shown in Table 4. Approximately 28% of participants in each arm reported working in at least one of the listed industries and/or occupations that have been associated with increased risk of lung disease or cancer. The most common of these industries and occupations were farming (10.7% or 5699 participants), chemicals or plastics manufacturing (6.2% or 3317 participants), welding (5.6% or 2975 participants), and painting (5.3% or 2813 participants). Approximately 5% of participants had worked with asbestos. The median duration of employment was 10 years or less for each industry and occupation, except for firefighting (which was 12 years in computerized tomography arm and 11 years in chest radiograph arm). Work history differed by sex, with 11 957 (38%) of the 31 533 men vs 3048 (14%) of the 21 923 women reporting a work history in any of the listed occupations.

The history of selected diseases, including respiratory, cardiovascular and malignant diseases, as well as family history of cancer, is presented in Table 5. Results were similar across arms. With respect to respiratory diseases, 9326 (17%) of the 53 456 subjects reported a history of chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema and approximately 22% in each arm reported a history of pneumonia. A history of cardiovascular disease was quite common, with 18 930 (35%) reporting a history of hypertension and 6797 (13%) reporting a history of heart disease or heart attack; in addition, 5174 (10%) reported a history of diabetes.

Data on family history of lung cancer were reported by each participant (Table 5). A family history of lung cancer (in a parent, sibling, or child) was reported by 11 621 (22%) of the 53 546 subjects, with 1748 (3%) reporting two or more relatives with a lung cancer history. This prevalence was similar in the two study arms.

Characteristics of the NLST population as compared with those of the overall NLST-eligible US population as measured with the Tobacco Use Supplement are shown in Table 6. The NLST population was younger than the US eligible population (73% were younger than 65 years vs 65%, respectively), but the populations were similar in terms of sex (59% of both populations were men). The proportions of blacks and Hispanics were roughly similar in the two populations. NLST subjects were substantially more educated, with the percentage having less than a high school education being 6% in the NLST cohort and 21% in the Tobacco

Table 2. Demographic factors and baseline smoking status of participants in the National Lung Screening Trial by screening arm*

Characteristic	Spiral CT, No. (%)	X-ray, No. (%)	Total, No. (%)
Total	26 723 (100.0)	26 733 (100.0)	53 456 (100.0)
Age at randomization			
<55,† y	2 (0.0)	3 (0.0)	5 (0.0)
55–59 y	11 440 (42.8)	11 421 (42.7)	22 861 (42.8)
60–64 y	8170 (30.6)	8198 (30.7)	16 368 (30.6)
65–69 y	4756 (17.8)	4762 (17.8)	9518 (17.8)
70–74 y	2352 (8.8)	2345 (8.8)	4697 (8.8)
>74,† y	1 (0.0)	3 (0.0)	4 (0.0)
Missing	2 (0.0)	1 (0.0)	3 (0.0)
Sex			
Male	15 770 (59.0)	15 763 (59.0)	31 533 (59.0)
Female	10 953 (41.0)	10 970 (41.0)	21 923 (41.0)
Race			
White	24 289 (90.9)	24 260 (90.7)	48 549 (90.8)
Black or African American	1196 (4.5)	1182 (4.4)	2378 (4.4)
Asian	559 (2.1)	536 (2.0)	1095 (2.0)
American Indian or Alaskan Native	92 (0.3)	98 (0.4)	190 (0.4)
Native Hawaiian or other Pacific Islander	91 (0.3)	102 (0.4)	193 (0.4)
More than one race	333 (1.2)	346 (1.3)	679 (1.3)
Missing	163 (0.6)	209 (0.8)	372 (0.7)
Hispanic ethnicity			
Hispanic or Latino	479 (1.8)	456 (1.7)	935 (1.7)
Neither Hispanic nor Latino	26 080 (97.6)	26 040 (97.4)	52 120 (97.5)
Missing	164 (0.6)	237 (0.9)	401 (0.8)
Marital status			
Never married	1255 (4.7)	1203 (4.5)	2458 (4.6)
Married or living as married	17 815 (66.7)	17 775 (66.5)	35 590 (66.6)
Widowed	1985 (7.4)	1982 (7.4)	3967 (7.4)
Separated	338 (1.3)	330 (1.2)	668 (1.2)
Divorced	5194 (19.4)	5238 (19.6)	10 432 (19.5)
Missing	136 (0.5)	205 (0.8)	341 (0.6)
Educational status			
≤8th grade	363 (1.4)	392 (1.5)	755 (1.4)
9th–11th grade	1279 (4.8)	1218 (4.6)	2497 (4.7)
High school graduate or GED	6274 (23.5)	6437 (24.1)	12 711 (23.8)
Post–high school training, excluding college	3768 (14.1)	3726 (13.9)	7494 (14.0)
Associate's degree or some college	6262 (23.4)	6152 (23.0)	12 414 (23.2)
Bachelor's degree	4506 (16.9)	4442 (16.6)	8948 (16.7)
Graduate school	3927 (14.7)	3964 (14.8)	7891 (14.8)
Other	227 (0.8)	241 (0.9)	468 (0.9)
Missing	117 (0.4)	161 (0.6)	278 (0.5)
CDC categories			
Underweight (<18.5 kg/m^2)	245 (0.9)	252 (0.9)	497 (0.9)
Normal (18.5–24.9 kg/m^2)	7517 (28.1)	7331 (27.4)	14 848 (27.8)
Overweight (25–29.9 kg/m^2)	11 265 (42.2)	11 491 (43.0)	22 756 (42.6)
Obese (≥30 kg/m^2)	7555 (28.3)	7462 (27.9)	15 017 (28.1)
Missing	141 (0.5)	197 (0.7)	338 (0.6)
Smoking status			
Current smokers	12 869 (48.2)	12 910 (48.3)	25 779 (48.2)
Former smokers	13 854 (51.8)	13 823 (51.7)	27 677 (51.8)
Quit within 4 y of study entry	3944 (14.8)	3947 (14.8)	7891 (14.8)
Quit 4–9.9 y before study entry	4598 (17.2)	4645 (17.4)	9243 (17.3)
Quit 10–15 y before study entry	5257 (19.7)	5165 (19.3)	10 422 (19.5)
Missing	55 (0.2)	66 (0.2)	121 (0.2)

* CDC = Center for Disease Control; CT = computerized tomography; GED = General Equivalency Diploma.

† Participants in the age groups of younger than 55 years and older than 74 years were ineligible.

Use Supplement cohort and the percentage with at least a college degree being 32% in the NLST cohort and 14% in the Tobacco Use Supplement cohort. NLST subjects were also slightly more likely to be married (67% vs 60%, respectively). Geographically, the NLST cohort, compared with the Tobacco Use Supplement cohort, had a greater proportion of Midwesterners (39% vs 29%, respectively) and smaller percentages of Southerners (24% vs 33%, respectively) and Northeasterners (16% vs 21%, respectively). With respect to smoking history, subjects in the NLST cohort were less likely to be current smokers than those in the Tobacco

Table 3. Baseline smoking frequency per pack-year history of participants in the National Lung Screening Trial by study arm*

Screening group and characteristic	No. of pack-years smoked: Current smoker	Former smoker	Entire cohort	No. of cigarettes smoked per day: Current smoker	Former smoker	Entire cohort	No. of years of smoking: Current smoker	Former smoker	Entire cohort
Spiral CT									
No.	12 869	13 854	26 723	12 869	13 854	26 723	12 868	13 853	26 721
Mean	55.52	56.52	56.04	25.98	30.77	28.47	43.44	42.74	43.08
Minimum	18	21	18	10	10	10	13	12	12
First quartile	40.0	38.8	39.0	20.0	20.0	20.0	40.0	38.0	39.0
Median	48.0	49.0	48.0	20.0	30.0	25.0	43.0	43.0	43.0
Third quartile	66.0	67.5	66.0	30.0	40.0	35.0	47.0	48.0	47.0
Maximum	235	295	295	100	140	140	67	69	69
X-ray									
No.	12 910	13 823	26 733	12 910	13 823	26 733	12 910	13 823	26 733
Mean	55.30	56.51	55.93	25.90	30.76	28.41	43.41	42.77	43.08
Minimum	25	15	15	10	10	10	16	10	10
First quartile	40.0	38.0	39.0	20.0	20.0	20.0	40.0	38.0	39.0
Median	48.0	49.5	48.0	20.0	30.0	25.0	43.0	43.0	43.0
Third quartile	64.5	68.0	66.3	30.0	40.0	35.0	47.0	48.0	47.0
Maximum	412	568	568	201	258	258	70	69	70
Total									
No.	25 779	27 677	53 456	25 779	27 677	53 456	25 778	27 676	53 454
Mean	55.41	56.52	55.98	25.94	30.77	28.44	43.43	42.75	43.08
Minimum	18	15	15	10	10	10	13	10	10
First quartile	40.0	38.3	39.0	20.0	20.0	20.0	40.0	38.0	39.0
Median	48.0	49.5	48.0	20.0	30.0	25.0	43.0	43.0	43.0
Third quartile	65.0	68.0	66.0	30.0	40.0	35.0	47.0	48.0	47.0
Maximum	412	568	568	201	258	258	70	69	70

* CT = computerized tomography.

Use Supplement cohort (48% vs 57%, respectively), but both cohorts had similar median pack-years of cigarette smoking (48 pack-years vs 47 pack-years, respectively).

Discussion

The validity of a randomized controlled trial rests on the ability of the randomization process to produce study arms that are similar with regard to characteristics that are or could be related to the outcome of interest. Our analysis of the baseline characteristics of the NLST population has demonstrated that the randomization process in NLST produced two very similar groups of participants (Tables 2–5). For example, the distributions of smoking characteristics, past occupational exposure, disease history, and family history of lung cancer were essentially indistinguishable between the two study arms. Demographically, the baseline age and sex distributions in the two arms were virtually identical because of stratified randomization on these factors. In addition, the race,

Table 4. Work experience of participants in the National Lung Screening Trial by screening arm*

Type of work	Spiral CT: No. (%)	Spiral CT: ME, y	X-ray: No. (%)	X-ray: ME, y	Total: No. (%)	Total: ME, y
Asbestos work	1238 (4.6)	8.0	1288 (4.8)	10.0	2526 (4.7)	9.0
Baking	603 (2.3)	3.0	551 (2.1)	3.0	1154 (2.2)	3.0
Butchering/meat packing	572 (2.1)	3.0	593 (2.2)	4.0	1165 (2.2)	3.0
Chemicals or plastics manufacturing	1642 (6.1)	8.0	1675 (6.3)	7.0	3317 (6.2)	8.0
Coal mining	169 (0.6)	8.0	162 (0.6)	9.0	331 (0.6)	8.0
Cotton or jute processing	194 (0.7)	4.0	201 (0.8)	4.0	395 (0.7)	4.0
Farming	2837 (10.6)	10.0	2862 (10.7)	10.0	5699 (10.7)	10.0
Firefighting	477 (1.8)	12.0	513 (1.9)	11.0	990 (1.9)	12.0
Flour, feed, or grain milling	290 (1.1)	4.0	297 (1.1)	4.0	587 (1.1)	4.0
Foundry or steel milling	1159 (4.3)	6.0	1089 (4.1)	5.0	2248 (4.2)	5.0
Hard rock mining	205 (0.8)	5.0	213 (0.8)	5.0	418 (0.8)	5.0
Painting	1382 (5.2)	5.0	1431 (5.4)	5.0	2813 (5.3)	5.0
Sandblasting	456 (1.7)	4.0	457 (1.7)	4.0	913 (1.7)	4.0
Welding	1505 (5.6)	10.0	1470 (5.5)	10.0	2975 (5.6)	10.0
Any of the above occupations	7448 (27.9)		7557 (28.3)		15 005 (28.1)	

* CT = computerized tomography; ME = median exposure.

Table 5. History of selected respiratory and cardiovascular diseases, selected malignancies, and family history of lung cancer, among participants in the National Lung Screening Trial by screening arm*

Disease	Spiral CT, No. (%)	X-ray, No. (%)	Total, No. (%)
Respiratory and cardiovascular disease			
Asbestosis	276 (1.0)	257 (1.0)	533 (1.0)
Asthma first diagnosed as an adult	1666 (6.2)	1653 (6.2)	3319 (6.2)
Asthma first diagnosed as a child	935 (3.5)	974 (3.6)	1909 (3.6)
Bronchiectasis	854 (3.2)	901 (3.4)	1755 (3.3)
Chronic bronchitis	2592 (9.7)	2545 (9.5)	5137 (9.6)
COPD	1347 (5.0)	1343 (5.0)	2690 (5.0)
Emphysema	2056 (7.7)	2037 (7.6)	4093 (7.7)
Chronic bronchitis, emphysema, or COPD	4674 (17.5)	4652 (17.4)	9326 (17.4)
Diabetes	2594 (9.7)	2580 (9.7)	5174 (9.7)
Fibrosis of the lung	70 (0.3)	58 (0.2)	128 (0.2)
Heart disease or heart attack	3445 (12.9)	3352 (12.5)	6797 (12.7)
Pneumonia	5930 (22.2)	5879 (22.0)	11 809 (22.1)
Sarcoidosis	48 (0.2)	49 (0.2)	97 (0.2)
Silicosis	30 (0.1)	27 (0.1)	57 (0.1)
Tuberculosis	281 (1.1)	296 (1.1)	577 (1.1)
Hypertension	9378 (35.1)	9552 (35.7)	18 930 (35.4)
Stroke	753 (2.8)	759 (2.8)	1512 (2.8)
Any of the above diseases	17 567 (65.7)	17 552 (65.7)	35 119 (65.7)
Malignancies			
Bladder cancer	112 (0.4)	128 (0.5)	240 (0.4)
Breast cancer†	352 (3.2)	396 (3.6)	748 (3.4)
Cervical cancer†	364 (3.3)	404 (3.7)	768 (3.5)
Breast or cervical cancer†	703 (6.4)	783 (7.1)	1486 (6.8)
Colorectal cancer	111 (0.4)	119 (0.4)	230 (0.4)
Esophageal cancer	12 (0.0)	8 (0.0)	20 (0.0)
Kidney cancer	37 (0.1)	31 (0.1)	68 (0.1)
Cancer of the larynx	20 (0.1)	26 (0.1)	46 (0.1)
Nasal cancer	11 (0.0)	10 (0.0)	21 (0.0)
Oral cancer	51 (0.2)	52 (0.2)	103 (0.2)
Cancer of the pharynx	3 (0.0)	5 (0.0)	8 (0.0)
Any head and neck cancer	82 (0.3)	89 (0.3)	171 (0.3)
Pancreatic cancer	4 (0.0)	3 (0.0)	7 (0.0)
Stomach cancer	12 (0.0)	15 (0.1)	27 (0.1)
Thyroid cancer	36 (0.1)	47 (0.2)	83 (0.2)
Any of the above cancers	1073 (4.0)	1194 (4.5)	2267 (4.2)
Family history of lung cancer			
Any first-degree relative‡	5815 (21.8)	5806 (21.7)	11 621 (21.7)
Two or more first-degree relatives	885 (3.3)	863 (3.2)	1748 (3.3)

* COPD = chronic obstructive pulmonary disease; CT = computerized tomography.

† Female participants only.

‡ A first-degree relative was defined as a parent, brother, sister, or children of an individual (National Cancer Institute—http://www.cancer.gov/dictionary/).

ethnicity, education, and marital status profiles were similar in the two arms.

It is useful to evaluate whether the results of a randomized controlled trial are generalizable to the population from which the study participants were drawn, also known as the "base population." Generalizability can be assessed in part by examining whether certain characteristics of the study sample are distributed similarly to those in the base population. To assess generalizability, we compared distributions of characteristics that are known or suspected to affect risk of lung cancer–specific death among NLST participants with those from respondents to the Tobacco Use Supplement of the Current Population Survey from the Census Department who met the NLST age and smoking eligibility criteria (11). For several key factors, including sex, race, ethnicity, and pack-years of smoking, the NLST and Tobacco Use Supplement populations were quite similar. The similarity of the percentages of black and Hispanic subjects indicated that targeted minority recruitment efforts were quite successful. Although there was no specific criterion in NLST to ensure that screening centers were selected to ensure geographic representativeness, the distribution of NLST subjects across the four regions of the country was generally reflective of the eligible population, with a modest overweighting of the Midwest and slight underweighting of the other regions. There is no reason to believe, however, that these minor geographic differences will affect findings in such a manner that results are not able to be generalized.

Research participants are often healthier than those to whom study results are to be generalized. Such a phenomenon can bias study outcomes if the fact that study participants are healthier results in a different outcome than would have been observed if the health of participants was similar to that of the base population. Distribution of certain characteristics did suggest that the NLST

Table 6. Comparison of the National Lung Screening Trial (NLST) cohort with the NLST-eligible US population from the Tobacco Use Supplement (TUS) of the US Census Bureau Current Population Surveys*

Characteristic	NLST	TUS
Male, %	59.0	58.5
Age group, %		
55–59 y	42.8	35.2
60–64 y	30.6	29.3
65–69 y	17.8	20.8
70–74 y	8.8	14.7
Race/ethnicity, %		
Black	4.4	5.5
Hispanic or Latino, %	1.7	2.4
Education, %		
Less than high school	6.1	21.3
College degree or higher	31.5	14.4
Married, %	66.6	60.0
Current smoker, %	48.2	57.1
Median pack-years of cigarette smoking	48.0	47.0
US region, %		
Northeast	16.3	21.1
Midwest	39.2	28.8
South	23.9	33.0
West	20.6	17.2

* Estimates were derived from the TUS of the US Bureau Current Population Survey for the years of NLST enrollment and were calculated by restricting the survey population to those respondents who met the NLST age and smoking eligibility criteria.

population might be healthier than the base population. For example, NLST subjects were somewhat younger (73% were younger than age 65 years vs 65% in the base population), were less likely to be current smokers (48% vs 57%, respectively), and were better educated (6% with less than a high school education vs 21%, respectively). Whether these differences will affect the generalizability of study findings is unknown, but it seems unlikely that these relatively minor differences will result in a meaningful bias. Adjustments for such differences can be made through statistical modeling. Other randomized prevention or screening trials, such as the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, have shown similar effects (12) (13). For example, in the PLCO Trial, the participants were better educated than the overall eligible population (12).

NLST data collected on smoking, family history of lung cancer, occupation and/or industry experience, and specific previous diseases will be used for epidemiological analyses of lung cancer incidence and mortality. The relationship of smoking, the strongest risk factor, to lung cancer will be explored in great detail. Numerous inhalational exposures, either known or suspected to be associated with lung cancer (14), will also be investigated. However, details of inhalational exposure were not recorded. More than 2500 of the NLST participants reported work-related exposure (median duration = 9 years) to asbestos, the environmental inhalational exposure most definitively and strongly associated with lung cancer (15). This cohort is one of the largest groups of asbestos-exposed subjects being actively followed for lung cancer (16,17) and will permit further evaluation of the well-known relationships among asbestos exposure, cigarette smoking, and lung cancer.

A family history of lung cancer is also associated with an increased risk of lung cancer. A systematic review of case–control and cohort studies (18) indicated that the presence of a relative with lung cancer is associated with a statistically significantly increased risk of lung cancer. Risk appears to be greatest in relatives of persons diagnosed at a young age and in those with multiple affected family members. However, it remains unclear how much of this increased risk can be attributed to genetics and how much to the fact that relatives of smokers are more likely to be cigarette smokers or exposed to second-hand smoke. Twenty-two percent of NLST participants had a family history of lung cancer, and 3% had two or more first-degree relatives with lung cancer. This large cohort may permit further evaluation of the role of family history in the etiology of lung cancer. The NLST also will generate data to evaluate several medical conditions known to be associated with lung cancer. Among these conditions, the most salient is COPD (15), present by self-report (including reports of chronic bronchitis and emphysema) in more than 9300 NLST participants. The presence of emphysema (self-reported in almost 4100 NLST participants) appears to be a greater risk factor for lung cancer than chronic airway obstruction (19,20). NLST ancillary studies should assist in confirming the extent of increased risk that is associated with the diagnosis of COPD and with computerized tomography–determined emphysema. Other risk factors for lung cancer present in the NLST cohort include asbestosis (reported by 533 participants), lung fibrosis (128 participants), silicosis (57 participants), and history of head and neck cancer (171 participants).

Limitations of the NLST as an epidemiological cohort include the fact that data on personal, family, and occupational history are self-reported and collected by use of a self-administered questionnaire. However, these limitations are common to most large studies of this type, and there was excellent participant compliance (99.6%) with completion of questionnaires.

We conclude that the NLST cohort is at high risk of lung cancer and is broadly reflective of the general US smoking population. The randomization process in the NLST resulted in study arms that have similar distributions of many known and suspected risk factors for lung cancer. In addition to evaluating the relative impact of chest radiographic and chest computerized tomography screening on lung cancer–specific mortality, the NLST cohort can also be used to clarify other important questions regarding lung cancer epidemiology.

Appendix

Writers and Major Contributors of the National Lung Screening Trial (NLST)

NLST Executive Committee: Denise R. Aberle, MD; Christine D. Berg, MD; William C. Black, MD; Timothy R. Church, PhD, MS; Richard M. Fagerstrom, PhD; Barbara Galen, MSN, CRNP, CNMT; Ilana F. Gareen, PhD; Constantine Gatsonis, PhD; Jonathan Goldin, MD, PhD; John K. Gohagan, PhD*; Bruce Hillman, MD*; Carl Jaffe, MD*; Barnett S. Kramer, MD, MPH; David A. Lynch, MD; Pamela M. Marcus, PhD; Mitchell Schnall, MD, PhD; Daniel C. Sullivan, MD*; Dorothy Sullivan; and Carl J. Zylak, MD.

Major contributing investigators: Project Officer, Christine D. Berg, MD. Principal Investigator, Denise R. Aberle, MD. Chief Statisticians, Richard M. Fagerstrom, PhD and Constantine Gatsonis, PhD. Lead Epidemiologists, Ilana F.

Gareen, PhD and Pamela M. Marcus, PhD. Lead Medical Physicists, Christopher Cagnon, PhD; Dianna Cody, PhD; Glenn Fletcher, PhD; Michael J. Flynn, PhD; Philip F. Judy, PhD; Randell Kruger, PhD; Frederick J. Larke, MS; DABR, Michael McNitt-Gray, PhD, Thomas Payne, PhD, J. Anthony Seibert, PhD, and Xizeng Wu, PhD. Lead Site Investigators for American College of Radiology Imaging Network (ACRIN): Gerald Abbott, MD; Denise R. Aberle, MD; Judith K. Amorosa, MD; Richard G. Barr, MD, PhD; William C. Black, MD; Phillip M. Boiselle, MD; Caroline Chiles, MD; Robert Clark, MD; Lynn Coppage, MD; Robert Falk, MD; Elliot K. Fishman, MD; David Gemmel, PhD; Jonathan G. Goldin, MD; Eric Goodman, MD; Eric M. Hart, MD; Todd Hazelton, MD; Elizabeth Johnson, MD; Philip F. Judy, PhD, Ella Kazerooni, MD; Barbara McComb, MD; Geoffrey McLennan, PhD, MBBS, FRACP; Reginald F. Munden, MD; James Ravenel, MD; Michael Sullivan, MD; Stephen J. Swensen, MD; Drew A. Torigian, MD, MA; Kay H. Vydareny, MD; and John A. Worrell, MD. Lead Site Investigators for the Lung Screening Study: Peter Balkin, MD; Timothy R. Church, PhD; Mona Fouad, MD; Matthew T. Freedman, MD, MBA; Kavita Garg, MD; Edward P Gelmann, MD*; David S. Gierada, MD; William Hocking, MD; Subbarao Inampudi, MD; Claudine Isaacs, MD; Paul Kvale, MD; David Lynch, MD; Howard Mann, MB, BCh; William Manor, DO; Hrudaya Nath, MBBS, DMR, MD; Douglas Reding, MD, MPH; David L. Spizarny, MD; Diane C. Strollo, MD; and John Waltz, MD. Supporting Statisticians, Mei-Hsiu Chen, PhD; Grant Izmirilian, PhD; Paul Pinsky, PhD; and Philip C. Prorok, PhD.

A full list of all staff for the trial with their role, title, and institutional affiliation has been presented previously (10).

*Former members: JKG, Founding Project Officer and Co-chair Executive Committee, BH and DCS, Former Director, Cancer Imaging Program.

References

1. American Cancer Society. *Cancer Facts and Figures*. Atlanta, GA: American Cancer Society; 2007.
2. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Program (ELCAP): overall design and findings from baseline screening. *Lancet*. 1999;354:99–105.
3. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med*. 2006;355(17):1763–1771.
4. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol*. 2002;20(4):911–920.
5. Sone S, Li F, Yang ZG, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. *Br J Cancer*. 2001;84(1):25–32.
6. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology*. 2005;235(1):259–265.
7. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest*. 2002;122(1):15–20.
8. Diederich S, Thomas M, Semik M, et al. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. *Eur Radiol*. 2004;14(4):691–702.
9. Blanchon T, Brechot JM, Grenier PA, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer*. 2007;58(1):50–58.
10. The National Lung Screening Trial. Overview and study design: The National Lung Screening Trial Research Team. *Radiology*. 2010. doi:10.1148/radiol.10091808.
11. US Department of Commerce, Census Bureau (2006). National Cancer Institute and Centers for Disease Control and Prevention Co-sponsored Tobacco Use Special Cessation Supplement to the Current Population Survey (2003). http://riskfactor.cancer.gov/studies/tus-cps/info.html Accessed October 18, 2010.
12. Pinsky PF, Miller A, Kramer BS, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am J Epidemiol*. 2007;165(8):874–881.
13. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ*. 1992;147(10):1477–1488.
14. Gottschall EB. Occupational and environmental thoracic malignancies. *J Thorac Imaging*. 2002;17(3):189–197.
15. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines. (2nd edition). *Chest*. 2007;132(3 suppl):29S–55S.
16. Mastrangelo G, Ballarin MN, Bellini E, et al. Feasibility of a screening programme for lung cancer in former asbestos workers. *Occup Med (Lond)*. 2008;58(3):175–180.
17. Tiitola M, Kivisaari L, Huuskonen MS, et al. Computed tomography screening for lung cancer in asbestos-exposed workers. *Lung Cancer*. 2002;35(1):17–22.
18. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*. 2005;93(7):825–833.
19. de Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest*. 2007;132(6):1932–1938.
20. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med*. 2007;176(3):285–290.

Funding

This research was supported by contracts from the Division of Cancer Prevention, National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services, and by grants (U01 CA80098 and CA79778) to support the American College of Radiology Imaging Network (ACRIN) under a cooperative agreement with Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, NCI. The NCI and ACRIN were actively involved in the design of the study and collection of data, but the authors had full responsibility for the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Notes

The authors thank the Screening Center investigators and staff of the National Lung Screening Trial. Most importantly, the individuals who chose to participate in the National Lung Screening Trial deserve our heartfelt thanks for their dedication and commitment.

Affiliations of authors: Department of Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA (DRA); Department of Community Health, Center for Statistical Sciences, Brown University, Providence, RI (AMA); Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (CDB); Information Management Services, Inc., Rockville, MD (JDC); Westat, Rockville, MD (KLC); Department of Community Health, Center for Statistical Sciences, Brown University, Providence, RI (IFG); Division of Radiology, National Jewish Health, Denver, CO (DAL); Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (PMM); Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (PFP).