

## ONLINE FIRST

# Screening by Chest Radiograph and Lung Cancer Mortality

## The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial

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**Context** The effect on mortality of screening for lung cancer with modern chest radiographs is unknown.

**Objective** To evaluate the effect on mortality of screening for lung cancer using radiographs in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

**Design, Setting, and Participants** Randomized controlled trial that involved 154 901 participants aged 55 through 74 years, 77 445 of whom were assigned to annual screenings and 77 456 to usual care at 1 of 10 screening centers across the United States between November 1993 and July 2001. The data from a subset of eligible participants for the National Lung Screening Trial (NLST), which compared chest radiograph with spiral computed tomographic (CT) screening, were analyzed.

**Intervention** Participants in the intervention group were offered annual postero-anterior view chest radiograph for 4 years. Diagnostic follow-up of positive screening results was determined by participants and their health care practitioners. Participants in the usual care group were offered no interventions and received their usual medical care. All diagnosed cancers, deaths, and causes of death were ascertained through the earlier of 13 years of follow-up or until December 31, 2009.

**Main Outcome Measures** Mortality from lung cancer. Secondary outcomes included lung cancer incidence, complications associated with diagnostic procedures, and all-cause mortality.

**Results** Screening adherence was 86.6% at baseline and 79% to 84% at years 1 through 3; the rate of screening use in the usual care group was 11%. Cumulative lung cancer incidence rates through 13 years of follow-up were 20.1 per 10 000 person-years in the intervention group and 19.2 per 10 000 person-years in the usual care group (rate ratio [RR]; 1.05, 95% CI, 0.98-1.12). A total of 1213 lung cancer deaths were observed in the intervention group compared with 1230 in usual care group through 13 years (mortality RR, 0.99; 95% CI, 0.87-1.22). Stage and histology were similar between the 2 groups. The RR of mortality for the subset of participants eligible for the NLST, over the same 6-year follow-up period, was 0.94 (95% CI, 0.81-1.10).

**Conclusion** Annual screening with chest radiograph did not reduce lung cancer mortality compared with usual care.

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**L**UNG CANCER IS THE LEADING cause of cancer death in the United States and worldwide. Screening for lung cancer has long been studied as an approach to reducing the burden of lung cancer. Randomized trials conducted in the 1970s and 1980s using screening spu-

tum cytology and chest radiographs failed to detect a significant reduction in lung cancer mortality in the group offered more extensive screening.<sup>1-4</sup>

Results of the National Lung Screening Trial (NLST), comparing screening with low-dose spiral computed tomography (CT) with chest radio-

graph, demonstrated a 20% reduction in lung cancer mortality in the CT group.<sup>5,6</sup>

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**For editorial comment see p 1916.**

Two of the early screening trials evaluated the effect of sputum cytology but provided no data on a mortality benefit from chest radiographic screening.<sup>1,2</sup> Of the other 2, one recommended annual chest radiographs to the control group.<sup>3,4</sup> These trials were relatively small, so an effect of chest radiographic screening could have been missed because of low power. This history led to the design of the lung component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, initiated 9 years before the NLST, to compare annual chest radiographic screening with usual care. Because the NLST did not have a usual care group, examining its findings in conjunction with those from PLCO is critical for addressing the benefit (and harms) of CT compared with usual care.

Findings from the lung cancer screening examinations in the intervention group of PLCO have been reported.<sup>7</sup> In this article, we report the mortality results of the lung component comparing the intervention and control groups. We also performed an analysis limited to those PLCO participants who would have met the NLST eligibility requirements. In addition to facilitating interpretation of the NLST results, the PLCO findings provide important information about the benefits and harms of annual chest radiographic screening.

## METHODS

The design of PLCO has been described previously.<sup>8</sup> Enrollment of men and women aged 55 through 74 years was initiated in 1993 and completed in 2001 at 10 screening centers nationwide. Each center obtained annual local institutional review board approval to conduct the study, and all participants provided written informed consent. The recruitment process targeted individuals from the general population residing in the catchment area of each center. The principal recruitment strategy was mass mailing. The ethnic diversity of the PLCO participants is a reflection of the geographic location of the centers.

Individual randomization to either the intervention or usual care group was within blocks that were stratified by screening center, sex, and age. Exclusion criteria at study entry included history of a PLCO cancer, current cancer treatment, and removal of 1 lung. Because PLCO was a screening trial for multiple cancers, not just lung cancer, there was no eligibility requirement concerning smoking; in this respect, the PLCO lung component is unique among lung cancer screening trials. At study entry, participants completed a self-administered baseline questionnaire that inquired about demographics (such as race/ethnicity classified as white, black, Asian/Pacific Islander, American Indian/Alaskan Native, or Hispanic origin), medical history, smoking history, and past screenings.

Participants randomized to the intervention group were offered a posterior-anterior chest radiograph at baseline and then annually for 3 more years. Never-smoker participants randomized after April 1995 were not offered the third screen. Participants and their health care practitioners were notified of chest radiographic results. A chest radiograph was considered positive if a nodule, mass, infiltrate, or other abnormality considered suspicious for lung cancer was noted. Those with positive examination results were advised to seek diagnostic evaluation. In accordance with standard US practice, diagnostic evaluation was decided by the patients and their primary physicians, not by trial protocol. The PLCO screening center staff obtained medical records related to diagnostic follow-up of positive screen results, and medical record abstractors recorded information on relevant diagnostic procedures and any associated complications.

Adherence with screening in the intervention group was defined as the number of participants screened divided by the number expected. Chest radiographic screening in the usual care group was assessed by surveying a random sample of just more than 1% of participants using biennial, and later annual, health status questionnaires

(HSQs), which inquired about the frequency and reason for use of various procedures, including the screening tests under evaluation. Intervention group participants were included in the HSQs for the postscreening study years (6 and beyond). For the purposes of this article, the chest radiographic contamination rate was defined as the proportion of HSQ-queried participants reporting a chest radiograph in the last year as part of a routine physical examination. Because the HSQ survey as a whole was cross-sectional (ie, participants were generally queried once), the contamination rate is an estimate of the average annual screening rate in the usual care group.

All diagnosed cancers of any site and all deaths occurring during the trial were ascertained, primarily by means of a mailed annual study update questionnaire, which asked about type and date of any cancers diagnosed in the prior year. Participants who did not return the questionnaire were contacted by repeat mailing or telephone. To enhance the completeness of end point verification, the active follow-up was supplemented by periodic linkage to the National Death Index. The TNM stage and stage group were determined by the fifth edition of the *American Joint Committee on Cancer's Cancer Staging Manual*.<sup>9</sup> Treatment data were abstracted from medical records for the 1-year period following diagnosis.

Death certificates were obtained to confirm the death and to determine the provisional cause of death. However, because the true cause was not always accurately recorded on the death certificate, the trial used an end point adjudication process to assign cause of death in a uniform and unbiased manner.<sup>10</sup> All deaths with causes potentially related to a PLCO cancer were reviewed, including any for which the participant had a prostate, lung, colorectal, or ovarian cancer or possible metastasis from 1 of these cancers and any of unknown or uncertain cause. Death reviewers were blinded to the trial group of the deceased participant. Cause-specific deaths were de-

defined as those with underlying cause of lung cancer or treatment for lung cancer.

Among intervention group participants, screen-detected cancers were defined as those diagnosed within a window extending 9 months from a positive screen result or 9 months from a diagnostic evaluation that was linked to the positive screen result. Non-screen-detected cancers diagnosed among participants who attended at least 1 screen were classified as interval if they occurred up to 1 year after the last scheduled screen or postscreening if they occurred more than 1 year after the last scheduled screen. Participants who never attended a screening but who were diagnosed with cancer were classified as never screened.

### Subanalysis of Participants Eligible for the NLST

The NLST is a randomized trial that compared the posterior and anterior view of the chest radiograph with low-dose spiral CT screening for lung cancer.<sup>6,11</sup> This ancillary analysis comparing chest radiograph vs usual care in the participants who would have been eligible for the NLST subset of the PLCO cohort was conceived as a complement to the primary NLST analysis of CT vs chest radiograph. To that end, the eligible subset of PLCO participants, ie, those with at least a 30-pack-year smoking history who were either current smokers or who had quit smoking within 15 years before randomization, was identified (the age range, 55-74 years, was the same for both trials). In addition to analyses on the entire PLCO study population, we also present the results of this post hoc analysis restricted to this subset to aid in the interpretation of the NLST results. Because the length of follow-up in the NLST was 6 years, we present an analysis of the PLCO subset restricted to a similar 6-year follow-up period.

### Statistical Methods

The primary analysis compared lung cancer mortality rates between the 2 groups by intention to screen. Secondary aims

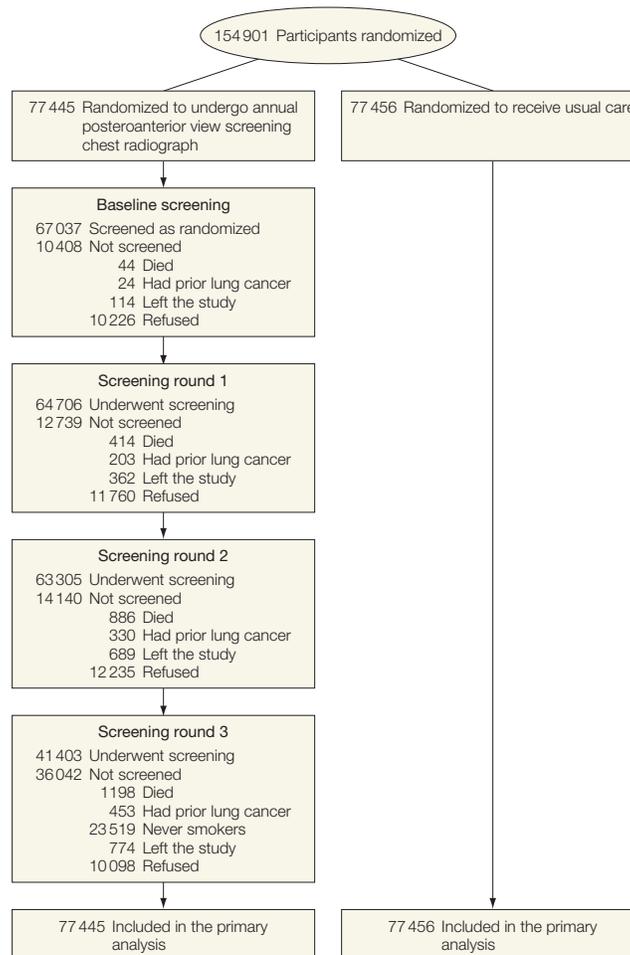
included comparison of lung cancer incidence, cancer stage, survival, potential harms of screening, and all-cause mortality between the 2 groups.

The trial was designed to have 90% power to detect a 10% or greater reduction in lung cancer mortality in the intervention than in the usual care group, assuming at least 85% adherence with the screening protocol among those in the intervention group and no more than 40% contamination in the usual care group.<sup>8</sup> Power was based on the assumed event rate of 3796 lung cancer deaths overall: 1998 in the usual care group and 1798 in the intervention group.

An interim analysis plan was used to monitor the primary end point for efficacy and futility. The plan used a weighted log-rank statistic with weights increasing in proportion to pooled lung cancer mortality. The weighted statistic was chosen because of the presumed delay in effect of screening on lung cancer mortality. The efficacy boundary was constructed via the Lan-DeMets approach using an O'Brien-Fleming spending function, and a non-binding futility boundary was constructed via stochastic curtailment.<sup>12</sup>

Since the start of the trial enrollment, an independent data and safety monitoring board has reviewed the ac-

**Figure 1.** Flow of Participants Through the Trial



The number of screened for eligibility was not obtained. The values shown for those who died or who had prior lung cancer are cumulative. Participants who refused in 1 round could participate in a subsequent round.

cumulating data and interim sequential analyses at least once each year. At its meeting on October 4, 2010, the board recommended reporting the end point results of the PLCO lung component. This recommendation was not the result of crossing a statistical futility boundary but rather because of a belief that the data provided an important public health message. The board also deemed that further follow-up was unlikely to change the conclusion and that the results should be published at the same time as those from the NLST.

Event rates were defined as the ratio of the number of events (cancer diagnoses or deaths) in a given period to the person-time at risk for the event. Person-time was measured from randomization to the earliest of the death date or date of last follow-up (censor-

ing date) for mortality rates and to the earliest of the diagnosis date, death date, or censoring date for incidence rates. Participants were censored at December 31, 2009, at the latest because the screening centers did not routinely collect data on events occurring after that point; participants were also censored at a maximum of 13 years from randomization because there was limited follow-up beyond that point.

Rate ratios (RRs) were derived as the ratio of event rates. Pointwise confidence intervals for incidence and mortality RRs were calculated assuming a Poisson distribution for the number of events and via asymptotic methods, assuming a normal distribution for the logarithm of the ratio.<sup>13</sup> The adjusted, sequential *P* value and confidence interval for the RR for the primary end

point of lung cancer mortality were derived in accordance with the sequential design and in the case of the confidence interval, according to the weighted method used to monitor the trial, which allows for a varying rate ratio.<sup>14</sup> Further details are provided in the supplemental material (eAppendix available at <http://www.jama.com>).

Analyses were performed using SAS/STAT software version 9<sup>15</sup> and R version 2.12.0.<sup>16</sup>

## RESULTS

Of the 154 901 participants enrolled, 77 445 were randomized to the intervention group and 77 456 to the usual care (control) group (FIGURE 1). The demographic characteristics and screening history of the trial population, by group, are shown in TABLE 1. The groups were similar: approximately half were women (50.5%); 64.1% were aged 55 through 64 years at baseline; about 45% were never smokers, 42% former smokers, and 10% current smokers. The median (mean) follow-up time was 11.9 (11.2) years in each group; the interquartile range (for each group) was 10.0 to 13.0 years.

Adherence to screening was 86.6% at the baseline screen, decreasing to 79% by year 3. The overall adherence rate was 83.5%, and 91.2% of participants had undergone at least 1 radiographic screening. Screen positivity rates were 8.9% at baseline, 7.1% at year 1, 6.6% at year 2, and 7.0% at year 3. Eighty-two percent of those screened at baseline and between 93% and 95% of those whose subsequent screens were positive for cancer were known to have had diagnostic follow-up. The most commonly performed follow-up procedures at baseline were repeat radiograph (43%) and chest CT (20%). At years 1 through 3, between 40% and 47% of participants' follow-up included a comparison with prior screens, whereas between 23% and 29% underwent another radiograph, and between 15% and 17% underwent a chest CT. In the usual care group, the contamination rate (ie, rate of chest radiograph screening) during the screening phase of the trial was estimated at 11%.

**Table 1.** Participant Demographics and Smoking History by Group

	No. (%) of Participants	
	Intervention Group	Usual Care Group
All	77 445	77 456
Men	38 340 (49.5)	38 345 (49.5)
Age, y		
55-59	25 850 (33.4)	25 839 (33.4)
60-64	23 784 (30.7)	23 773 (30.7)
65-69	17 457 (22.5)	17 473 (22.6)
70-74	10 354 (13.4)	10 371 (13.4)
Race/ethnicity		
White, non-Hispanic	66 874 (86.4)	65 708 (84.8)
Black, non-Hispanic	3883 (5.0)	3825 (4.9)
Hispanic	1421 (1.8)	1397 (1.8)
Asian	2791 (3.6)	2785 (3.6)
Other or unknown	2476 (3.2)	3741 (4.8)
Educational attainment		
<High school	5620 (7.3)	5461 (7.1)
High school	17 272 (22.3)	17 122 (22.1)
Some college	25 935 (33.5)	25 585 (33.0)
College graduate	26 659 (34.4)	25 915 (33.5)
Unknown	1959 (2.5)	3373 (4.4)
Smoking status		
Current	8078 (10.4)	7979 (10.3)
Former	32 555 (42.0)	32 136 (41.5)
Never	34 950 (45.1)	34 233 (44.2)
Unknown	1862 (2.4)	3108 (4.0)
National Lung Screening Trial-eligible <sup>a,b</sup>	15 183 (20.3)	15 138 (20.6)
Family history of lung cancer in first-degree relative <sup>b</sup>	7930 (10.6)	7729 (10.5)
Chest radiograph within 3 y prior to randomization <sup>b</sup>	40 126 (53.0)	39 213 (52.7)

<sup>a</sup>Thirty pack-years and current smoker or quit within 15 years of trial entry.

<sup>b</sup>There are patients with missing values. Percentages were calculated on the population with nonmissing data.

Of 12 718 participants without screen-detected cancer who had at least 1 screen positive for cancer (17 229 positive screens total), 15 445 were associated with a diagnostic procedure, and for 169 the information is incomplete. Of these 12 778 participants, 54 (0.4%) had a complication of a diagnostic follow-up procedure. Of 69 individual complications, the most common were pneumothorax (29%), atelectasis (15%), and infection (10%). Information about diagnostic procedures in the usual care group is not available.

Cumulative lung cancer incidence by study group is shown in FIGURE 2. Cumulative incidence rates (per 10 000 person-years) through 13 years were 20.1 in the intervention group and 19.2 in the usual care group (RR, 1.05; 95% CI, 0.98-1.12). Although incidence rates were dependent on smoking history (3.1 for never smokers, 23 for former smokers, 83 for current smokers), the RRs for incidence were similar according to smoking history: 1.06 for never smokers, 1.12 for former smokers, and 1.00 for current smokers.

Lung cancer characteristics are displayed in TABLE 2. Within the inter-

vention group during the screening period (excluding participants who were never screened), 307 of the 505 lung cancers (61%) ascertained were screen detected and 198 (39%) were detected during the interval. This means that during the entire 13-year follow-up period, 307 of the 1696 all lung cancers (18%) were detected by screening and 198 (12%) were interval cancers. Lung cancer histology was similar by group, with about 41% being adenocarcinoma, 20% squamous cell carcinoma, and 14% small cell carcinoma. However, within the intervention group, screen-detected cancers were more likely to be adenocarcinoma (56%) and less likely to be small cell carcinoma (7%) compared with cancers that were not detected by screening.

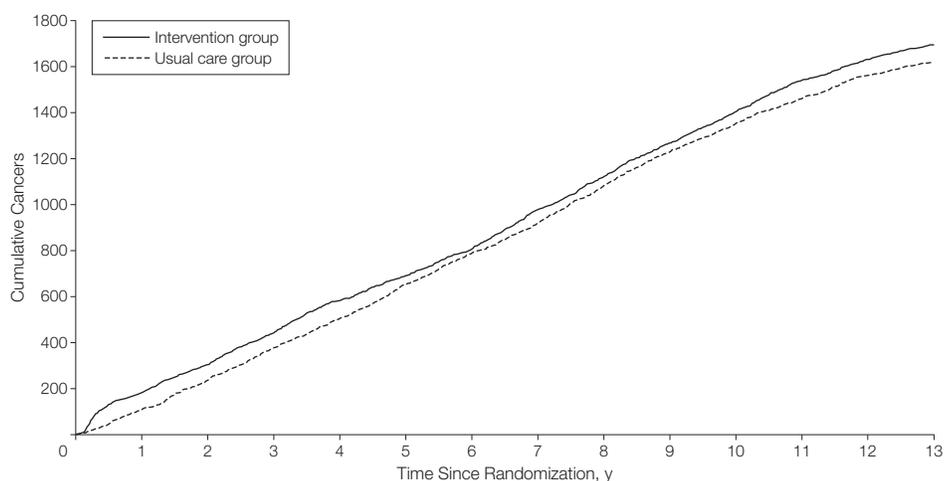
Among non-small cell lung cancers, the stage distribution was generally similar across groups, although intervention group cases compared with usual care were slightly more likely to be stage I (32% vs 27%) and slightly less likely to be stage IV (35% vs 38%). Within the intervention group, the screen detected non-small cell lung cancer cases differed substantially from

the rest, with 50% being stage I and only 17% stage IV. The absolute number of stage III and IV cancers was similar across groups, with 359 stage III and 514 stage IV in the intervention group compared with 365 stage III and 530 stage IV in the usual care group.

Cumulative deaths from lung cancer are displayed in FIGURE 3. A slight separation of the curves began just after 4 years that persisted through 11 years of follow-up. For the total 13-year follow-up period, 1213 lung cancer deaths were observed in the intervention group vs 1230 in the usual care group. Cumulative lung cancer mortality rates (per 10 000 person-years) were 14.0 in the intervention group and 14.2 in the usual care group for a lung cancer mortality RR of 0.99 (adjusted 95% CI, 0.87-1.22; adjusted  $P = .48$ ). Lung cancer mortality RRs were 0.94 (95% CI, 0.69-1.29) for never smokers, 1.02 (95% CI, 0.91-1.15) for former smokers, and 0.99 (95% CI, 0.88-1.12) for current smokers, and by sex, they were 1.02 (95% CI, 0.92-1.13) for men and 0.92 (95% CI, 0.81-1.06) for women.

Primary treatment for lung cancer was similar across groups, both over-

**Figure 2.** Lung Cancer Incidence by Year



Intervention group	
Cumulative cancers	181 304 441 583 692 808 981 1124 1268 1405 1544 1633 1696
Cumulative person-years	76617 152416 227322 301309 374374 446481 517521 587405 655538 718389 771188 812963 844011
Usual care group	
Cumulative cancers	109 235 377 504 653 790 923 1084 1232 1358 1465 1563 1620
Cumulative person-years	76597 152495 227549 301699 374873 446975 517940 587701 655718 718398 771147 812834 843762

all and by stage (TABLE 3). Resection without chemotherapy was the predominant therapy for stage I non-small cell lung cancers (75% intervention; 73% usual care), while stage III or IV non-small cell lung cancers primarily received chemotherapy without resection (53% intervention; 54% usual care).

**Table 2.** Histology and Stage of Lung Cancers by Group and Mode of Detection<sup>a</sup>

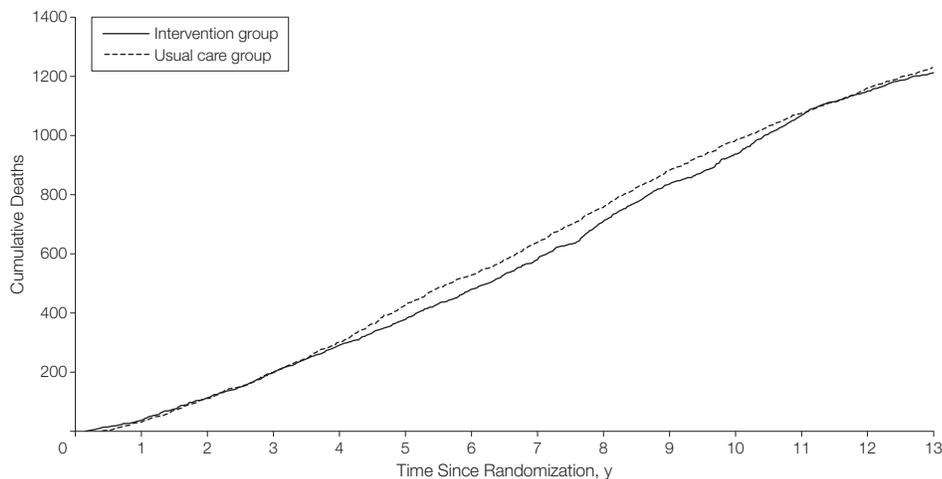
	No. (%) of Participants					
	Intervention Group				Total	Usual Care Group
	Screen Detected	Interval	Never Screened	After Screening		
All	307	198	193	998	1696	1620
Type						
Small cell	22 (7)	42 (21)	27 (14)	138 (14)	229 (14)	235 (15)
Squamous	63 (21)	37 (19)	51 (27)	195 (20)	346 (20)	329 (20)
Adenocarcinoma <sup>b</sup>	172 (56)	71 (36)	70 (36)	383 (38)	696 (41)	658 (41)
Large cell	21 (7)	12 (6)	5 (3)	39 (4)	77 (5)	53 (3)
Other Non-small cell lung cancer <sup>c</sup>	27 (9)	31 (16)	38 (20)	239 (24)	335 (20)	338 (21)
Unknown	2 (0.7)	5 (3)	2 (1)	4 (0.4)	13 (0.8)	7 (0.4)
Non-small cell lung cancer						
Total	283 (92)	151 (76)	164 (85)	856 (86)	1454 (86)	1378 (85)
Stage						
I	141 (50)	40 (26)	38 (23)	243 (28)	462 (32)	374 (27)
II	26 (9)	10 (7)	12 (7)	64 (8)	112 (8)	105 (8)
III	67 (24)	44 (29)	32 (20)	216 (25)	359 (25)	365 (26)
IV	49 (17)	54 (36)	82 (50)	329 (38)	514 (35)	530 (38)
Unknown	0	3 (2)	0	4 (0.5)	7 (0.5)	4 (0.3)
Stage of small cell						
Limited	12 (55)	11 (26)	11 (41)	44 (32)	78 (34)	74 (32)
Extensive	8 (36)	29 (69)	16 (59)	89 (65)	142 (62)	145 (62)
Unknown	2 (9)	2 (5)		5 (4)	9 (4)	16 (7)

<sup>a</sup>Percentages may not sum to 100 due to rounding.

<sup>b</sup>Includes bronchioalveolar adenocarcinoma.

<sup>c</sup>Includes spindle cell carcinoma, intermediate cell carcinoma, giant cell carcinoma, clear cell carcinoma, adenosquamous carcinoma, adenoid cystic carcinoma, nonsmall cell (not otherwise specified [NOS]), carcinoma (NOS), mixed small and nonsmall cell, neuroendocrine nonsmall cell (NOS).

**Figure 3.** Lung Cancer Mortality by Year



Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77268	154053	230270	305833	380691	454773	527937	600004	670274	735098	789540	832441	864227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77286	154116	230348	305902	380725	454719	527804	599790	669955	734523	788854	831678	863330

**Table 3.** Primary Lung Cancer Treatment by Stage and Group

Treatment	Non-Small Cell Lung Cancer, No. (%) of Participants					
	Stage I		Stage II		Stage III or IV	
	Intervention (n = 462)	Usual Care (n = 374)	Intervention (n = 112)	Usual Care (n = 105)	Intervention (n = 873)	Usual Care (n = 895)
Resection without chemotherapy	347 (75)	273 (73)	46 (41)	43 (41)	52 (6)	48 (5)
Resection with chemotherapy	43 (9)	35 (9)	33 (29)	32 (30)	61 (7)	56 (6)
Radiation alone	34 (7)	32 (9)	14 (13)	4 (4)	144 (16)	127 (14)
Chemotherapy without resection	14 (3)	13 (3)	13 (12)	17 (16)	467 (53)	487 (54)
Other	24 (5)	21 (6)	6 (5)	9 (9)	149 (17)	177 (20)

Treatment	Small Cell Lung Cancer, No. (%) of Participants			
	Limited		Extensive	
	Intervention (n = 78)	Usual Care (n = 74)	Intervention (n = 142)	Usual Care (n = 145)
Chemotherapy and radiation	56 (72)	51 (69)	31 (22)	39 (27)
Chemotherapy without radiation	18 (23)	20 (27)	79 (56)	76 (52)
Other	4 (5)	3 (4)	32 (23)	30 (21)

A total of 9091 participants (11.7%) in the intervention group and 9244 (11.9%) in the usual care group died of other causes (deaths from PLCO cancers are excluded). Cumulative mortality rates from other causes (per 10 000 person-years) were 105.2 in the intervention group and 107.1 in the usual care group (RR, 0.98; 95% CI, 0.95-1.01). The distribution of causes of death was similar in the 2 groups (TABLE 4).

The results of the ancillary analysis for the subset of PLCO participants who would have been eligible for the NLST are shown in TABLE 5. This subset included 15 183 participants in the intervention group and 15 138 in the usual care group. Approximately, 60% were men, 40% current smokers, and the median pack-year history was about 52. Through 6 years of follow-up, 518 lung cancer cases and 316 lung cancer deaths occurred in the intervention group compared with 520 lung cancer cases and 334 deaths in the usual care group.

Cumulative lung cancer incidence rates (per 10 000 person-years) through 6 years were 60.6 in the intervention group and 60.8 in the usual care group (RR, 1.00; 95% CI, 0.88-1.13). Cumulative lung cancer mortality rates (per 10 000 person-years) through 6 years were 36.1 in the intervention group and 38.3 in the usual care group (RR, 0.94; 95% CI, 0.81-1.10). The RRs through

**Table 4.** Cause of Death From Death Certificate by Group, Excluding Prostate, Lung, Colorectal, and Ovarian Cancer-Related Deaths

Cause of Death	No. (%) of Participants	
	Intervention Group	Usual Care Group
Non-prostate, lung, colorectal, or ovarian neoplasms	2258 (24.8)	2239 (24.2)
Ischemic heart disease	1616 (17.8)	1586 (17.2)
Cerebrovascular accident	542 (6.0)	540 (5.8)
Other circulatory disease	1327 (14.6)	1402 (15.2)
Respiratory illness	997 (11.0)	1007 (10.9)
Digestive disease	318 (3.5)	306 (3.3)
Infectious disease	202 (2.2)	191 (2.1)
Endocrine, nutritional, and metabolic diseases and immunity disorders	357 (3.9)	377 (4.1)
Diseases of the nervous system	356 (3.9)	374 (4.0)
Fatal injury	470 (5.2)	476 (5.1)
Other	648 (7.1)	746 (8.1)
Total	9091 (100.0)	9244 (100.0)

**Table 5.** Results for National Lung Screening Trial Subset

	Intervention Group (n = 15 183)	Usual Care Group (n = 15 138)	Rate Ratio (95% CI)
Men, No. (%)	9252 (60.9)	9110 (60.2)	
Current smoker, No. (%)	6146 (40.5)	6069 (40.3)	
Median pack-years	52.0	52.5	
Adherence with baseline screen, No. (%) <sup>a</sup>	13 035 (85.9)		
Overall adherence, No. (%) <sup>a</sup>	48 330 (81.4)		
Results through 6 y of follow-up			
Diagnosed cases, No.	518	520	1.00 (0.89-1.13)
Person-years for incidence	85 428	85 474	
Lung cancer deaths, No.	316	334	0.94 (0.81-1.10)
Person-years for death	87 473	87 198	

<sup>a</sup>Percentage of expected screens.

13 years were similar to those through 6 years. The corresponding RR for the total PLCO cohort at 6 years was 1.02 (95% CI, 0.93-1.13) for lung cancer incidence and 0.91 (95% CI, 0.80-1.03) for lung cancer mortality.

A retrospective power calculation for the NLST-eligible subset, assuming 334 expected usual care group deaths, yielded a power of 26% to detect a true mortality reduction with invitation to screening with chest radiograph of 10%, power of 52% to detect a 15% mortality reduction, and power of 77% to detect a 20% mortality reduction.

## COMMENT

Annual chest radiographic screening for up to 4 years did not have an effect on cumulative lung cancer mortality during 13 years of follow-up in the PLCO randomized screening trial. The randomized groups in PLCO were comparable at baseline, there was relatively high screening adherence in the intervention group and low contamination in the usual care group, and the treatment distributions across the groups were similar. Therefore, these findings provide good evidence that there is not a substantial lung cancer mortality benefit from lung cancer screening with 4 annual chest radiographs.

The Mayo Lung Project trial of chest radiograph and sputum cytology screening carried out in the late 1970s and early 1980s did not show a mortality benefit. In the Mayo Lung Project, however, there was a 17% overdiagnosis rate through approximately 20 years of follow-up (ie, 17% more lung cancers were diagnosed in the screened group than in the control group). Estimating overdiagnosis in PLCO is difficult because the large majority of lung cancers that cumulated in the intervention group were not screen detected. After 2 full years from the last scheduled chest radiographic screen (to account for catch up in the usual care group), the overall increase in incidence was a statistically nonsignificant 6% in the intervention group. The 7-year (and similar 13-year result) was calculated in the same way as the Mayo Lung Project overdiagnosis rate. However, this excess of 58 lung cancers in the intervention group at 7 years has to be related to 307 screen-detected cancers, resulting in an overdiagnosis rate of 19%. These estimates should be interpreted

with the recognition that the intervention participants in the Mayo Lung Project received chest radiographs at 4-month intervals together with sputum cytology while annual chest radiographs were recommended to control participants.

There was no evidence of a stage shift in PLCO, with the absolute number of stage III or IV cancers similar across groups. The histology of lung cancers was also similar, although within the intervention group there was a relative preponderance of adenocarcinomas among the screen-detected cases. This suggests that adenocarcinomas are preferentially identified by chest radiographic screening, which might be expected because adenocarcinomas commonly present as peripheral nodules that are more easily visualized on chest radiograph, in contrast to centrally located tumors such as most squamous cell carcinomas.

Because the PLCO follow-up extended through a maximum of 13 years, with median follow-up of almost 12 years—although the screening protocol was carried out for only the first 4 years—the issue of a possible dilution of screening effect arises. For instance, if the detectable presymptomatic phase (ie, the phase detectable in theory by screening) of any lung cancer with lethal potential was no more than  $X$  years, then deaths arising from cancers diagnosed after more than  $X$  years from the end of PLCO screening could not have been affected by this screening and the death rates for these cases would be expected to be the same in each group. The overall screening effect would then be the average of any true effect and 0, with 0 given roughly half the weight. This would serve to reduce the power of the trial to detect a true difference between groups.

The value of  $X$ , which can be thought of as the upper end of the “sojourn time” distribution for lung cancer, has been estimated to be 1 to 4 years.<sup>17-19</sup> Adding this time interval to the end of screening at 3 years from randomization would lead to examining mortality rates restricted to cases diagnosed

within 6 or 7 years of randomization (however, in these types of analyses the total person-years for the entire trial population are used for the denominator but deaths are restricted to those occurring, through the full 13 years of follow-up, from the above-specified cases). The mortality RRs using these cutoffs were 0.89 (95% CI, 0.80-1.00) for 6 years and 0.94 (95% CI, 0.84-1.04) for 7 years of case ascertainment.

Because these comparisons were not the primary analysis of the trial and because the choice of 6- or 7-year case group restriction was not stated a priori, the interpretation of this approach must be viewed with caution. Even taking these estimates at face value, however, the mortality decrease from chest radiographic screening for 3 to 4 years is marginal at best and is not statistically significant if adjusted for multiple statistical testing among participant subsets.

The absence of a stage shift in the intervention group might also result, at least in part, from the dilution effect described above. Because only about 20% of the total of intervention group cancers were screen detected, the large number of cancers unaffected by screening could be diluting any true effect. The RR for late stage (III or IV) cancers diagnosed through 6 years after randomization was 0.88 (95% CI, 0.78-0.99) and was 0.94 (95% CI, 0.84-1.05) for cases diagnosed 7 years after randomization. However, these were not stated a priori comparisons, so the nonstatistically significant finding through 6 years must be considered in this light.

The findings from the NLST, which demonstrated a 20% mortality benefit (RR, 0.80) for screening with low-dose spiral CT compared with chest radiograph, should be compared with the findings for chest radiograph vs usual care for the PLCO subgroup that would have been eligible for that trial. Through the approximate 6-year period, the mortality RR in the NLST-eligible PLCO cohort was quite close to 1 (RR, 0.94; 95% CI, 0.81-1.10). The 2 populations were similar with respect to median pack-years (48 vs 52) and sex distribution (59% men vs 61% women), with

slightly fewer current smokers in the PLCO group. The periods of screening overlapped but were on average later in the NLST, 2002-2006, than in PLCO, 1993-2004; furthermore, there were 3 annual screens in the NLST compared with 4 in the PLCO subcohort. Thus, although there were some modest differences between the 2 cohorts, it seems reasonable to consider the chest radiograph vs usual care comparison in the NLST-eligible cohort in PLCO to be an adequate surrogate for such a comparison within NLST. As such, the 20% mortality benefit of low-dose spiral CT vs chest radiograph observed in NLST is likely a good approximation of the mortality benefit that must have been observed of low-dose spiral CT vs usual care if this latter group had been added to NLST.

## CONCLUSION

Annual screening with chest radiographs over a 4-year period did not significantly decrease lung cancer mortality compared with usual care neither in the PLCO as a whole nor in the subset of participants who would have been eligible to enroll in the NLST.

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