

# Baseline Chest Radiograph for Lung Cancer Detection in the Randomized Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Martin M. Oken, Pamela M. Marcus, Ping Hu, Thomas M. Beck, William Hocking, Paul A. Kvale, Jill Cordes, Thomas L. Riley, Stephen D. Winslow, Steven Peace, David L. Levin, Philip C. Prorok, John K. Gohagan for the PLCO Project Team

**Background:** The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was initiated in 1992 to examine cause-specific mortality reduction from screening for these four cancers in men and women. We report lung cancer detection results of the baseline screening round. **Methods:** Of the 154 942 participants enrolled, who were aged 55–74 years with no history of PLCO cancers, 77 465 were randomly assigned to the intervention arm. Current or former smokers and never smokers in this arm received an initial single-view posterior-anterior chest radiograph. **Results:** In the initial screen, 5991 (8.9%, 95% confidence interval [CI] = 8.7% to 9.2%) of radiographs were suspicious for lung cancer: 8.2% (95% CI = 7.9% to 8.5%) for women and 9.6% (95% CI = 9.3% to 10.0%) for men. Rates were highest for older age groups and for smokers. Among those 5991 participants with a positive screen, 206 (3.4%, 95% CI = 3.0% to 3.9%) underwent biopsy examination, 126 (61.2%, 95% CI = 54.5% to 67.8%) of whom were diagnosed with lung cancer within 12 months of the screen (59 in women and 67 in men). The positive predictive value was 2.1% (95% CI = 1.7% to 2.5%), and 1.9 lung cancers were detected per 1000 screens. Among these cancers, 44% (95% CI = 35% to 52%) were stage I non-small-cell lung cancer. High rates of lung cancer were found in current smokers (6.3 per 1000 screens) and in former smokers who had smoked within the past 15 years (4.9 per 1000 screens). The lung cancer detection rate among never smokers was 0.4 per 1000 screens; this group accounted for 11% (95% CI = 5.6% to 16.6%) of the cancers identified. **Conclusions:** In the baseline screen, nearly half the cancers were stage I. Whether this experience results in a reduction in lung cancer mortality is yet to be seen. [J Natl Cancer Inst 2005;97:1832–9]

Lung cancer is a worldwide problem, estimated to cause nearly one million deaths annually (1). In the United States alone, lung cancer is the most common cause of cancer death in both men and women. By the time lung cancer produces symptoms, the disease is usually advanced and incurable. At present, treatment for advanced lung cancer is unsatisfactory, and nearly 90% of the approximately 170 000 patients newly diagnosed each year will die within 2 years (2). However, if the disease is diagnosed in its early stages, a time when it can still be treated with surgery, the 5-year survival rate is 70% (3). It is therefore possible that an improvement in the detection of lung cancer at an early stage when it can be resected might reduce the mortality rate from this disease.

Chest radiograph and sputum cytology have been the most common screens for lung cancer. These two methods are currently the only screening procedures that have been evaluated in controlled trials for the detection of early-stage asymptomatic lung cancer that used disease-specific reduction in mortality as the endpoint. Several studies of screening for lung cancer by chest radiograph with or without sputum cytology were conducted in both the United States and the United Kingdom in the 1950s and 1960s, but none found a reduction in lung cancer mortality rate (4–10).

The efficacy of screening for lung cancer has also been evaluated in four randomized controlled trials (11–15), three of which (11,13–15) were sponsored by the National Cancer Institute as part of the Cooperative Early Lung Cancer Detection Program (16). All enrolled male smokers only, and all had a primary endpoint of mortality from lung cancer. Two of these studies (11,12) compared periodic chest radiographs done at regular intervals with “no screening,” which, in practice, actually consisted of less frequent radiographs. In the other two studies (14,15), all participants received an annual chest radiograph, but the intervention arm participants also received sputum cytologic examinations every 4 months. The Mayo Lung Project (11,17–19), the most influential of these four studies, prevalence-screened 10 933 men ages 45 years or older who were current smokers of at least one pack per day and then enrolled and randomly assigned the 9211 who did not have lung cancer or other exclusionary conditions. Participants in the intervention arm received a chest radiograph and sputum cytologic examination every 4 months for 6 years; participants in the control arm received no additional study exams but, at trial entry, did receive standard Mayo advice to obtain annual chest radiographs and sputum cytologic examination for screening. In fact, approximately 50% of the men in the control

*Affiliations of authors:* Hubert H. Humphrey Cancer Center, North Memorial Medical Center, Robbinsdale, MN (MMO); Biometry Research Group (PMM, PH, DLL, PCP), Early Detection Research Group (JKG), Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD; Mountain States Tumor Institute, St. Luke’s Regional Medical Center, Boise, ID (TMB); Marshfield Clinic Research Foundation, Marshfield, WI (WH); Henry Ford Health System, Detroit, MI (PAK); Environmental and Occupational Health Studies Section, University of Minnesota, Minneapolis, MN (JC); Information Management Systems, Inc., Rockville, MD (TLR, SDW); Westat, Rockville, MD (SP).

*Correspondence to:* Martin M. Oken, MD, Hubert H. Humphrey Cancer Center, North Memorial Medical Center, 3300 Oakdale Ave. N, Plaza 100, Robbinsdale, MN 55422 (e-mail: martin.oken@northmemorial.com).

See “Notes” following “References.”

DOI: 10.1093/jnci/dji430

© The Author 2005. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

arm received a chest radiograph in the final year of the study (19). At the conclusion of the study in 1983, 13 years after the first participant and 7.5 years after the last participant were randomly assigned to a study arm, 206 lung cancers had been diagnosed in the screening group, and 160 lung cancers had been diagnosed in the control group. There was no difference in mortality rates between the two groups, even on reanalysis with a median follow-up of 20.5 years (20). For comparison, the Czechoslovakia lung cancer screening study enrolled a total of 6346 male smokers aged 40–64 years (12). Participants in the screened arm were evaluated every 6 months for 3 years with a chest radiograph and sputum cytologic examination. They were compared with a no-screen control arm after a baseline prevalence screen in all participants. Control subjects received a chest radiograph during the third study year, and all participants (intervention and control) received annual chest radiographs for an additional 3 years. In the final report (12) at the end of the 6-year screening period, there were 108 lung cancers and 85 deaths in the screening group and 82 lung cancers and 67 deaths in the control group, but there was no statistically significant difference in mortality. The Johns Hopkins and Memorial Sloan-Kettering Lung Projects together enrolled more than 20 000 male smokers older than 45 years (13–15). All participants in these studies received an annual chest radiograph and were randomly assigned to receive either sputum cytologic examination every 4 months or no sputum examination. The studies are therefore usually viewed as having assessed the usefulness of sputum cytologic examination. Neither study showed a reduction in lung cancer mortality.

The lack of an observed benefit in these trials led to the current belief that lung cancer screening by chest radiograph with or without sputum cytologic examination is ineffective for reducing lung cancer mortality. Nevertheless, screening with chest radiographs does detect more stage I cancers than are expected in the absence of screening (13–15). Longer survival of screened patients, compared with that of patients diagnosed through usual care, is observed as well, but lead time and overdiagnosis explain, at least in part, these apparent benefits (20). Because the chest radiograph is simple, widely available, noninvasive, and relatively inexpensive, it continues to be used as a screening modality, even in the absence of evidence demonstrating a definitive benefit.

Concern about insufficient size of previous studies (11–19), as well as difficulties in the interpretation of results of completed studies, raised the possibility that a small but important benefit from annual chest radiograph could have been missed (20). In 1992, the National Cancer Institute initiated the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, the largest and most ambitious cancer screening trial undertaken in the United States (21). This trial differed from the Mayo Lung Project in several key respects. The most important difference was that the Mayo Lung Project was limited to men only, whereas the PLCO included men and women in nearly equal numbers. Furthermore, the PLCO randomly assigned nearly 155 000 participants to a screening group or a control group and was, therefore, able to detect smaller, yet clinically meaningful, lung cancer mortality differences than these prior studies. In contrast to the Mayo Lung Project, there was also no prevalence or baseline screen for control subjects in the PLCO, and control subjects were not instructed at trial entry to obtain chest radiographs outside the study.

We report the results of the initial lung cancer screening round for the intervention arm of the PLCO Trial. The PLCO Trial is unique in that it presents the largest prevalence screen for lung cancer, one that was conducted in a population with a mixture of participants of different sexes, races, and smoking histories. The comparison of data across arms, including lung cancer mortality, will be reported at a later date.

## PARTICIPANTS AND METHODS

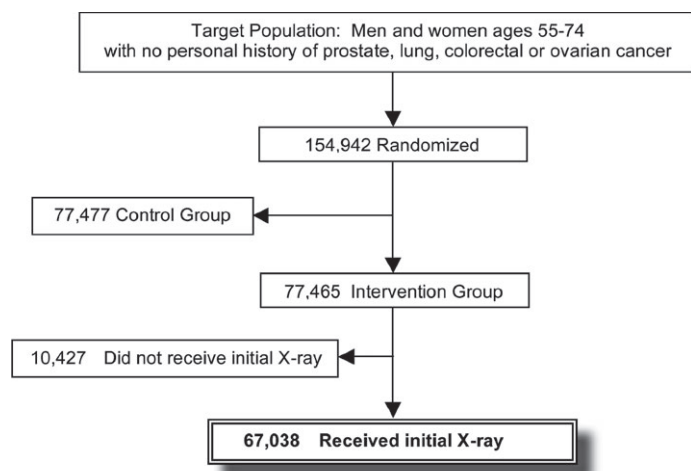
### Design Summary and Participants

The components of the PLCO Cancer Screening Trial, including a detailed description of the trial's design and operations, have been described elsewhere (21). The main objective of the study is to determine whether a screening program for prostate, lung, colorectal, or ovarian cancer in healthy subjects can reduce mortality from these diseases.

The study was open to persons between the ages of 55 and 74 years. Study participants could not have been diagnosed with prostate, lung, colorectal, or ovarian cancer at any time or be undergoing treatment for any cancer other than basal cell or squamous cell skin cancer. Exclusions included anyone participating in another cancer screening or primary prevention trial, men who had taken finasteride (Proscar) in the 6 months before entry or who had had more than one prostate-specific antigen blood test in the past 3 years, and individuals who had had colonoscopy, sigmoidoscopy, or a barium enema examination in the past 3 years. Individuals with previous surgical removal of the entire prostate, one lung, or the entire colon were also excluded from the study. Women with prior removal of both ovaries were initially excluded; however, as of 1996, they were allowed to enroll. Recruitment was directed toward volunteers in the general population, and direct mail was used primarily as the recruitment strategy. Enhanced recruitment methods were used to target minority populations. All participants signed informed consent documents approved by both the National Cancer Institute and their local institutional review board.

On entry in the study, subjects were given a self-administered baseline questionnaire that included questions about personal sociodemographic characteristics (age, race, sex, marital status, and education), family history of cancer, personal medical history, cigarette smoking history (status, age started and stopped, and amount smoked), and cancer screening history in the 3 years before entry. The questionnaire covered topics believed to be relevant to risk factors for the PLCO Trial cancers.

The PLCO was designed as a two-armed randomized trial with a target enrollment of 37 000 women and 37 000 men, aged 55–74 years at entry, in the screened arm and equal numbers of women and men enrolled in the control arm. The flow of participants into the trial is outlined in Fig. 1. A total of 154 942 participants have been enrolled, with 77 477 assigned to the control group and 77 465 assigned to the intervention group. Randomization and screening were carried out at the following 10 screening centers: University of Colorado Health Sciences Center, Denver, CO; Lombardi Cancer Research Center of Georgetown University, Washington, DC; Pacific Health Research Institute, Honolulu, HI; Henry Ford Health System, Detroit, MI; University of Minnesota School of Public Health, Minneapolis, MN; Washington University School of Medicine, St. Louis, MO; University of Pittsburgh/Pittsburgh Cancer Institute/Magee-Women's Hospital, Pittsburgh,



**Fig. 1.** Flow of participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

PA; University of Utah School of Medicine, Salt Lake City, UT; Marshfield Clinical Research Foundation, Marshfield, WI; and the University of Alabama at Birmingham, Birmingham, AL. Trial participants are to be followed for at least 13 years from entry.

The screening evaluation for lung cancer is a single-view posterior-anterior chest radiograph. Men and women who were current or former smokers (as defined in the baseline questionnaire) underwent an initial chest radiograph screening for lung cancer that was followed by three annual screens. Never smokers had an initial screening chest radiograph followed by two annual screens. Radiographs were defined as positive (i.e., suspicious for cancer) when the participating radiologist identified a nodule, infiltrate, or other abnormality that possibly could represent cancer. Cancers included in this analysis were diagnosed in participants in the screening arm within 12 months of a positive baseline screen.

When participants received a positive screen result, they were referred to their primary health care provider who then directed the follow-up and evaluation. Medical records were obtained to document follow-up activity.

## Statistical Analyses

We used proportions to measure screen positivity, lung cancer detection, and positive predictive value. Chi-square tests of independence (SAS Systems for Windows release 8.01, SAS, Cary, NC) were used to evaluate the statistical significance of differences in proportions. A normal approximation to the binomial distribution (22) was used to calculate 95% confidence intervals [CIs] for proportions. All statistical tests were two-sided.

## RESULTS

### Enrollment

The PLCO study randomly assigned 154 942 participants from November 8, 1993, through July 2, 2001 (as noted in Fig. 1), to intervention and control arms. Approximately half of the partici-

pants, 77 465, were randomly assigned to the intervention arm and were scheduled for an initial screening chest radiograph. Similar numbers of men and women were entered in the study. Consequently, this is also the largest randomized, controlled trial of screening for lung cancer in women, enrolling 78 234 and randomly assigning 39 115 female participants to the intervention (screening) arm.

The characteristics of the intervention arm participants are presented in Table 1. Sixty-four percent of the participants were 55–64 years old at enrollment, and 36% were 65 years or older. Most participants who enrolled in this study were white, with blacks accounting for only 5.1% of participants, despite a concerted effort to recruit individuals from minority populations. Other minority populations, including Hispanic, Asian, Pacific Islander, and Native American, accounted for 6.4% of participants.

At study entry, among participants who answered the baseline questionnaire, 46.8% classified themselves as never smokers,

**Table 1.** Baseline characteristics of participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial randomly assigned to the intervention arm ( $n = 77\,465$ )

Characteristic	No. (% of specified)
Age group	
55–59 y	25 840 (33.4)
60–64 y	23 797 (30.7)
65–69 y	17 472 (22.6)
70–74 y	10 356 (13.4)
Sex	
Female	39 115 (50.5)
Male	38 350 (49.5)
Race	
White, non-Hispanic	66 871 (88.5)
Black, non-Hispanic	3 883 (5.1)
Hispanic	1 421 (1.9)
Asian	2 793 (3.7)
Other	605 (0.8)
Not specified	1 892 (—)
Education	
≤11 y	5 620 (7.4)
Completed high school	17 270 (22.9)
Post-high school	9 373 (12.4)
Some college	16 549 (21.9)
Graduated college	12 864 (17.0)
Postgraduate	13 796 (18.3)
Not specified	1 993 (—)
Smoking status*	
Never smoker	35 018 (46.8)
Former smoker	32 392 (43.2)
≥15 y/<20 pk-y	13 946 (18.6)
≥15 y/20–29 pk-y	2 866 (3.8)
≥15 y/≥30 pk-y	3 421 (4.6)
≥15 y/not specified	107 (—)
<15 y/<20 pk-y	2 641 (3.5)
<15 y/20–29 pk-y	2 309 (3.1)
<15 y/≥30 pk-y	6 542 (8.7)
<15 y/not specified	19 (—)
Not specified/<20 pk-y	357 (—)
Not specified/20–29 pk-y	95 (—)
Not specified/≥30 pk-y	73 (—)
Not specified/not specified	16 (—)
Current smoker	8 181 (10.9)
<20 pk-y	1 865 (2.5)
20–29 pk-y	913 (1.2)
≥30 pk-y	5 381 (7.2)
Not specified	22 (—)
Not specified	1 874 (—)

\*Former smokers are divided into groups who last smoked ≥15 years and who last smoked <15 years before randomization. Smoking status is shown as the number of years since last smoked/number of pack-years (pk-y).

and 43.2% classified themselves as former smokers. Only 10.9% of participants reported that they were current smokers, compared with 22.5% smokers in the general population in 2002 (23). Sixty-four percent of men and 45% of women in the trial were current or former smokers. Twenty-nine percent of enrollees had a smoking history of at least 20 pack-years (38% for men and 20% for women). A family history of lung cancer in one or more first-degree relatives was self-reported by 10.5% of participants.

### Compliance

A total of 10 427 trial participants randomly assigned to the screening arm did not receive their initial chest radiograph. Overall compliance for the first chest radiograph was 86.5% (89.0% for men and 84.1% for women). There was no strong association of age with compliance in this study, although the rate was lowest (84.1%) in subjects aged 70–74 years. Compliance was slightly lower among current smokers (84.0%) and among heavy smokers (85.9%) than among other enrolled participants, but overall a compliance rate of more than 85% was generally maintained, as assumed in the original study design and statistical power calculations (21).

### Screening Results

The rate of positive results for initial chest radiographs was 8.9% (95% CI = 8.7% to 9.2%). The rate was statistically significantly higher ( $P < .001$ ) in men (9.6%, 95% CI = 9.3% to 10.0%) than in women (8.2%, 95% CI = 7.9% to 8.5%) (Table 2). The rate of a positive screen result increased with age for both sexes. Men had a higher rate of positive screen results than women in each age group and for each smoking status (data not shown). The rate of positive screen results was different ( $P < .001$ ) for the various smoking status categories, from never smoker (8.0%, 95% CI = 7.6% to 8.2%), to former smoker (9.5%, 95% CI = 9.2% to 9.9%), to current smoker (11.0%, 95% CI = 10.3% to 11.8%). Never smokers account for 46.8% of the study population and 46.6% of the subjects screened. Their positivity rate of 8.0% is surprisingly high when compared with that of current smokers of at least 30 pack-years (11.6%, 95% CI = 10.7 to 12.6).

Of those 5991 subjects with an initial positive screen, 4754 (79%) subsequently received some diagnostic evaluation. This evaluation included a repeat chest radiograph for 3187 (53%) participants, a comparison of the screening film with previous films for 1061 (18%), and a more detailed clinical evaluation for 2203 (37%); 1375 (23%) of the participants with an initial positive screen went on to have a computed tomography scan of the chest, and 190 (14%) of these participants then went on to a biopsy examination. Overall, 206 (3.4%, 95% CI = 3.0% to 3.9%) subjects with a positive screen went on to receive a biopsy examination (Table 3); 126 participants (61%, 95% CI = 54.4% to 67.8%) had biopsies that were positive for lung cancer (59 in women and 67 in men).

Women with a positive initial screen result were slightly more likely than men to have a computed tomography scan (25.5% vs. 21.3%) or a biopsy examination (3.7% vs. 3.2%). There was no consistent variation in follow-up with age, but the two oldest age groups (65–69 years and 70–74 years) had the highest biopsy rates (each of 4.0%). Never smokers had the lowest biopsy rates

**Table 2.** Results of baseline chest radiograph screen by participant characteristics in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

Group	No. screened	No. positive	% positive
All participants	67038	5991	8.9
Sex			
Female	32899	2700	8.2
Male	34139	3291	9.6
Age group			
55–59 y	22458	1668	7.4
60–64 y	20777	1816	8.7
65–69 y	15089	1494	9.9
70–74 y	8714	1013	11.6
Smoking status*			
Never smoker	31257	2485	8.0
Former smoker†	28771	2741	9.5
≥15 y/<20 pk-y	12573	1080	8.6
≥15 y/20–29 pk-y	2591	269	10.4
≥15 y/≥30 pk-y	3076	313	10.2
<15 y/<20 pk-y	2286	194	8.5
<15 y/20–29 pk-y	2066	182	8.8
<15 y/≥30 pk-y	5630	643	11.4
Current smoker†	6876	758	11.0
<20 pk-y	1580	166	10.5
20–29 pk-y	788	67	8.5
≥30 pk-y	4493	522	11.6
Partially or not specified	698	70	10.0

\*Former smokers are divided into groups who last smoked ≥15 years and who last smoked <15 years before randomization. Smoking status is shown as the number of years since last smoked/number of pack-years (pk-y).

†Summary categories for smokers include subjects without information on pack-years smoked and years since quitting (former smoker only).

(2.1%), compared with current smokers (7.0%) or smokers who smoked 30 pack-years or more (6.3%).

Among those 5991 participants with a positive initial screen, we detected 126 lung cancers within 12 months of the initial chest radiograph (47% in women and 53% in men). Thus, the positive predictive value observed for chest radiograph was 2.1%; i.e., 2.1% (95% CI = 1.7% to 2.5%) of positive screens led to a diagnosis of lung cancer, with a total of 1.9 lung cancers detected for every 1000 initial screening chest radiographs. Despite an apparent sex-related difference in the radiograph positivity rate (Table 2), men and women had similar rates of lung cancer diagnosis, similar positive predictive values, and similar numbers of lung cancers diagnosed per 1000 screens (Table 3).

**Table 3.** Evaluation and diagnostic outcome of positive screens by sex

Result	Baseline screening chest radiograph		
	All	Women	Men
No. screened	67038	32899	34139
No. positive screens	5991	2700	3291
% positive of total screened	8.9	8.2	9.6
No. patients examined by biopsy	206	100	106
% of positive screens examined by biopsy	3.4	3.7	3.2
No. lung cancers diagnosed	126	59	67
PPV of screening test, %	2.1	2.2	2.0
(95% CI for PPV)*	(1.7 to 2.5)	(1.6 to 2.7)	(1.6 to 2.5)
% of biopsy examinations positive	61.2	59.0	63.2
No. lung cancers per 1000 screens	1.9	1.8	2.0

\*PPV = positive predictive value (i.e., cancer diagnoses as a percentage of positive screens); CI = confidence interval.

**Table 4.** Baseline screening results by smoking status at entry

Smoking status*	No. screened	% positive screens	% of positive screens examined by biopsy	No. cancers diagnosed	PPV (95% CI)†	No. cancers diagnosed per 1000 screens
Never smoker	31 257	8.0	2.1	14	0.6 (0.3 to 0.9)	0.4
Former smoker‡	28 771	9.5	3.7	69	2.5 (1.9 to 3.1)	2.4
≥15 y/<20 pk-y	12 573	8.6	1.8	6	0.6 (0.1 to 1.0)	0.5
≥15 y/20–29 pk-y	2 591	10.4	4.5	8	3.0 (0.9 to 5.0)	3.1
≥15 y/≥30 pk-y	3 076	10.2	3.2	6	1.9 (0.4 to 3.4)	2.0
<15 y/<20 pk-y	2 286	8.5	3.6	6	3.1 (0.7 to 5.5)	2.6
<15 y/20–29 pk-y	2 066	8.8	5.5	7	3.8 (1.1 to 6.6)	3.4
<15 y/≥30 pk-y	5 630	11.4	6.8	36	5.6 (3.8 to 7.4)	6.4
Current smoker‡	6 876	11.0	7.0	43	5.7 (4.0 to 7.3)	6.3
<20 pk-y	1 580	10.5	6.6	9	5.4 (2.0 to 8.9)	5.7
20–29 pk-y	788	8.5	4.5	3	4.5 (0.0 to 9.4)	3.8
≥30 pk-y	4 493	11.6	7.5	31	5.9 (3.9 to 8.0)	6.9

\*Former smokers are divided into groups who last smoked ≥15 years and who last smoked <15 years before randomization. Smoking status is shown as the number of years since last smoked/number of pack-years (pk-y).

†PPV = positive predictive value (i.e., cancer diagnoses as a % of positive screens).

‡Summary categories for smokers include subjects without information on years since quitting (former smokers only) and pack-years smoked.

Among current smokers, lung cancer was diagnosed in 6.3 participants per 1000 screens (Table 4). Former smokers had 4.9 and 1.1 cancers per 1000 screens, respectively, depending on whether they did or did not smoke within the prior 15 years. Fourteen (11.1%, 95% CI = 5.6% to 16.6%) of the 126 cancers were diagnosed in the never smoker population, all but two of which were found in women. Among the 31 257 never smokers, the positive predictive value for a positive chest radiograph was only 0.6% (95% CI = 0.3% to 0.9%), and the lung cancer detection rate was only 0.4 per 1000 screens. There was a pattern of more frequent lung cancer diagnosis among men who were current smokers (8.0 cancers per 1000 screens) than among women who were current smokers (4.0 cancers per 1000 screens) (Table 5). This pattern was not observed in former or never smokers.

An analysis of the effect of smoking cessation over time (i.e., years since quitting smoking) on the likelihood of detecting lung cancer in the baseline screen is presented in Table 6. Fifty-one percent of the lung cancers detected at baseline were identified in never smokers or former smokers who reported that they quit smoking 5 years or more before enrollment. Among current smokers and those who reported quitting less than 2 years before

enrollment, the number of cancer diagnoses per 1000 screens was 5.9 for women and 7.3 for men. Thus, the number of cancers detected per 1000 chest radiograph screens remained at more than 4.0 for up to 10 years after smoking cessation and remained more than threefold that of never smokers (0.5%) thereafter.

Histopathologic data are presented in Tables 7 and 8. For our tabulation of these data, we combined adenocarcinoma and its variants (acinar adenocarcinoma, bronchoalveolar carcinoma, and adenosquamous carcinoma) into one group, “adenocarcinoma,” which accounts for 57% of all cancer diagnoses. Women were more likely than men to have adenocarcinoma (68% vs. 48%, respectively) (Table 7). All other histologic types were observed equally in both sexes or were more prevalent in men than in women. Overall, 86% of the lung cancers detected after a positive baseline screen were non–small-cell lung cancers. Of the 14 cancers diagnosed in never smokers, 12 were adenocarcinoma and two were malignant carcinoid tumors. Small-cell, squamous cell, and large-cell undifferentiated carcinoma types were found only in current or former smokers. Fifty-five (52%) of the 107 non–small-cell lung cancers or 44% (95% CI = 35% to 52%) of all 126 lung cancers diagnosed presented as stage I disease (Table 8).

**Table 5.** Baseline screening diagnosis of lung cancer by sex and smoking status at entry

Smoking status*	Women			Men		
	No. screened	No. cancers diagnosed	No. cancers diagnosed per 1000 screens	No. screened	No. cancers diagnosed	No. cancers diagnosed per 1000 screens
Never smoker	18 559	12	0.6	12 698	2	0.2
Former smoker†	11 255	35	3.1	17 516	34	1.9
≥15 y/<20 pk-y	5 407	2	0.4	7 166	4	0.6
≥15 y/20–29 pk-y	722	6	8.3	1 869	2	1.1
≥15 y/≥30 pk-y	654	2	3.1	2 422	4	1.7
<15 y/<20 pk-y	1 426	4	2.8	860	2	2.3
<15 y/20–29 pk-y	952	5	5.3	1 114	2	1.8
<15 y/≥30 pk-y	1 861	16	8.6	3 769	20	5.3
Current smoker†	3 022	12	4.0	3 854	31	8.0
<20 pk-y	928	5	5.4	652	4	6.1
20–29 pk-y	418	1	2.4	370	2	5.4
≥30 pk-y	1 669	6	3.6	2 824	25	8.9

\*Former smokers are divided into groups who last smoked ≥15 years and who last smoked <15 years before randomization. Smoking status is shown as the number of years since last smoked/number of pack-years (pk-y).

†Summary categories for smokers include subjects without information on pack-years smoked and years since quitting (former smoker only).

**Table 6.** Baseline lung cancer incidence by sex and time since cessation of smoking

Characteristic	Current smoker	Former smoker: time since cessation*				Never smoker	Incomplete history
		<2 y	2-5 y	5-10 y	≥10 y		
<b>Female</b>							
No. screened	3022	516	722	1443	8385	18 559	252
% positive screens	10.3	11.0	8.6	9.4	8.1	7.7	9.5
No. cancers diagnosed	12	9	3	8	15	12	0
No. cancers per 1000 screens	4.0	17.4	4.2	5.5	1.8	0.6	0
<b>Male</b>							
No. screened	3854	649	949	1826	13 828	12 698	335
% positive screens	11.6	12.8	11.1	12.4	9.7	8.3	9.9
No. cancers diagnosed	31	2	5	8	19	2	0
No. cancers per 1000 screens	8.0	3.1	5.3	4.4	1.4	0.2	0
<b>All participants</b>							
No. screened	6876	1165	1671	3269	22 213	31 257	587
% positive screens	11.0	12.0	10.0	11.1	9.1	8.0	9.7
No. cancers diagnosed	43	11	8	16	34	14	0
No. cancers per 1000 screens	6.3	9.4	4.8	4.9	1.5	0.4	0

\*Excludes former smokers with no information on time since quit.

## DISCUSSION

We enrolled 154 942 participants in this study, 77 465 of whom were randomly assigned to the intervention arm and 67 038 of whom received their initial baseline radiograph screening exam. At the initial screening, 5991 (8.9%) of these chest radiographs were positive and required additional evaluation. Although this additional evaluation was frequently limited to a standard chest radiograph and its comparison to previous radiographs, 1375 (23%) of those participants with positive screens went on to receive a computed tomography scan of the chest. Overall, 126 (2.1%) of the 5991 participants with a positive baseline screen were found to have cancer in the 12 months after their baseline screen. The number of cancers found among men and among women was comparable, and there was a high rate of adenocarcinoma, especially in women. In this screened population, 44% of lung cancers were diagnosed as stage I, and 12% were diagnosed as stage IV. Although such a distribution could be indicative of a stage shift compared with an unscreened population, it is possible that characteristics of the participants, such as healthier lifestyles or attentiveness to medical concerns, could be responsible. Therefore, the meaning of the apparently high proportion of early-stage cancers will not be fully understood until further data become available.

The rate of lung cancer detection in the initial PLCO screen was similar to that in the prevalence screen of the Mayo Lung Project. The PLCO detected 8.0 lung cancers per 1000 baseline screens of male smokers, compared with 8.3 in the Mayo Lung Project (11).

We detected a high rate of cancer in former smokers but an extremely low rate in never smokers, even though the never smoker group accounted for 41.5% of the positive screens found at baseline. The concerns raised by positive interpretations of screening chest radiographs in never smokers will have to be resolved by additional studies if screening were to become widely practiced.

One premise of any screening effort is that it will lead to earlier detection of cancer so that the cancer can be diagnosed and treated at an earlier, more curable stage. It is well documented (24-26) that the 5-year survival rate in stage I non-small-cell lung cancer is 50%-70%, which is considerably higher than the rate in stage II non-small-cell lung cancer. These more advanced

lung cancers are usually fatal within 2 years of diagnosis. If a beneficial stage shift does occur, it would be reflected in the central analysis in this trial, the comparison of lung cancer mortality among participants in the screening arm with that among participants in the control arm. These data will be reported at a later date when sufficiently mature.

An important feature of this study is that 39 115 women were accrued and randomly assigned to the intervention arm. The PLCO is the first major controlled study to evaluate screening for lung cancer in women. It was therefore important, in this preliminary analysis, to compare the results among women with those among men. We found that the incidence of positive screens was lower among women (8.2%) than among men (9.6%). This trend was found in every age group, in current and former smokers, in never smokers, and in smokers with a smoking history of less than 30 pack-years or of 30 or more pack-years. In an analysis of the relationship of sex and smoking status with lung cancer detection among all groups, we found a somewhat higher incidence of lung cancer among men (2.0 lung cancers per 1000 screens) than among women (1.8 lung cancers per 1000 screens). By smoking category, it was only among current smokers that we found a lower incidence of lung cancer among women (4.0 per 1000 screens) than among men (8.0 per 1000 screens) (Table 5). This result may merely reflect a dose difference per category, as suggested by the fact that women represent 59% of the group of current smokers with a smoking

**Table 7.** Histologically confirmed cancers after a positive baseline screen

Histologic type	Total	Women	Men
Total No. (%)	126 (100)	59 (100)	67 (100)
Non-small-cell	108 (86)	51 (86)	57 (85)
Adenocarcinoma*	72 (57)	40 (68)	32 (48)
Squamous cell	20 (16)	5 (8)	15 (22)
Large-cell undifferentiated	9 (7)	3 (5)	6 (9)
Other non-small-cell	7 (6)	3 (5)	4 (6)
Small cell	9 (7)	3 (5)	6 (9)
Carcinoid	7 (6)	4 (7)	3 (4)
Carcinoma, not otherwise specified	2 (2)	1 (2)	1 (1)

\*Includes acinar adenocarcinoma, bronchoalveolar carcinoma, and adenosquamous carcinoma.

**Table 8.** Stage of non-small-cell (NSC) lung cancers after a positive baseline screen

Stage	No.	% of NSC lung cancers	% of all cancers*
IA	34	32	27
IB	21	20	17
II	13	12	10
III	24	22	19
IV	15	14	12
Unavailable	1	—	—
Total No.	108	100	85

\*The one participant with NSC lung cancer and unavailable stage was excluded from percentage calculations.

history of less than 30 pack-years and only 37% of the group of current smokers with a smoking history of 30 pack-years or more. The observation that 12 of the 14 lung cancers among nonsmokers were found in women could also reflect exposure to passive smoking or other risk factors more prevalent among women. This speculation, however, needs to be substantiated in additional studies.

The histologic type of cancer most frequently identified was adenocarcinoma, which was found in 68% of women and in 48% of men diagnosed with lung cancer. These values are in keeping with prior observations of a temporal shift in the histologic distribution of non-small-cell lung cancer, with increased prevalence of lung adenocarcinoma in women and with an increase in the proportion of adenocarcinoma in both sexes accompanied by a gradual decrease in the proportion of squamous cell carcinoma (27,28). The tendency of adenocarcinoma to present as a peripheral lesion suggests the possibility that these cancers might be more readily detected on a chest radiograph than the more centrally located squamous cell carcinomas.

Epidemiologic data support the conclusion that smoking causes lung cancer, accounting for nearly 90% of lung cancer cases diagnosed in the United States and other countries in which cigarette smoking is common (29-31). This observation is reflected in the current study, in which 89% of the lung cancers found in the first 12 months after a positive screen occurred in smokers. Lung cancer risk among cigarette smokers increases with the number of cigarettes smoked per day and with the duration of smoking (32). In one study, models were derived to estimate the quantitative risk as a function of the number of cigarettes smoked, the duration of smoking, and the age of the smoker (32). According to these models, smoking duration appears to be a greater risk factor than the number of cigarettes smoked per day (32).

Conversely, smoking cessation is likely to reduce the risk of developing lung cancer, regardless of the age at which the smoker quits. A longer duration of smoking cessation is associated with a reduced risk of developing lung cancer (33). The data in Table 6 therefore are of interest. Current smokers and former smokers who smoked within the past 2 years had an incidence of 6.7 lung cancers per 1000 screens. Former smokers who quit 2-10 years earlier had an incidence of 4.9 cancers per 1000 screens. Among former smokers who quit more than 10 years earlier, the incidence dropped to 1.5 per 1000 screens. This incidence is still more than triple that identified in never smokers (0.4 cancer per 1000 screens). It has been, however, well documented by others (34) that, even 40 years after smoking cessation, former smokers have a higher risk of developing lung cancer than never smokers.

The question of whether screening by chest radiograph reduces mortality from lung cancer awaits the analysis and comparison of both randomization arms of the PLCO Screening Trial. The National Lung Screening Trial (NLST), which is comparing low-dose computed tomography scans with chest radiographs, builds in part on the experience of the PLCO Trial for generating and managing a very large accrual. It will offer a relevant comparison, regardless of whether the final results of the PLCO Trial support chest radiography as an effective screening modality.

In summary, our results from the baseline lung cancer screening round of the PLCO Trial demonstrate that massive participant accrual can be accomplished in a multi-institutional program with good compliance. Two limitations of the study are the disproportionate numbers of minority participants and never smokers as compared with the U.S. population. Nevertheless, the data suggest a high rate of early detection and possibly important differences between screening for lung cancer in women and in men. The answer to the important question of reduction in lung cancer mortality must await analysis of the two study arms as these data mature.

## REFERENCES

- (1) Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999;49:33-64.
- (2) Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003;53:5-26.
- (3) Ginsberg RJ, Rubinstein LV, Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Ann Thorac Surg* 1995;60:615-23.
- (4) Boucot KR, Weiss W. Is curable lung cancer detected by semiannual screening? *JAMA* 1973;224:1361-5.
- (5) Lillienfeld A, Archer PG, Burnett CH, Chamberlain EW, Chazin BJ, Davies D. An evaluation of radiologic and cytologic screening for the early detection of lung cancer: a cooperative pilot study of the American Cancer Society and the Veterans Administration. *Cancer Res* 1966;26:2083-121.
- (6) Nash FA, Morgan JM, Tomkins JG. South London Lung Cancer Study. *Br Med J* 1968;2:715-21.
- (7) Brett GZ. The value of lung cancer detection by six-monthly chest radiographs. *Thorax* 1968;23:414-20.
- (8) Brett GZ. Earlier diagnosis and survival in lung cancer. *Br Med J* 1969;4:260-2.
- (9) Dales LG, Friedman GD, Collen MF. Evaluating periodic multiphasic health checkups: a controlled trial. *J Chronic Dis* 1979;32:385-404.
- (10) Friedman GD, Collen MF, Fireman BH. Multiphasic health checkup evaluation; a 16-year follow-up. *J Chronic Dis* 1986;39:453-63.
- (11) Fontana RS, Sanderson DR, Taylor WF, Woolner LB, Miller WE, Muhm JR, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis* 1984;130:561-5.
- (12) Kubik A, Parkin DM, Khat M, Erban J, Polak J, Adamec M. Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. *Int J Cancer* 1990;45:26-33.
- (13) Stitik FP, Tockman MS, Khouri NF. Chest radiology. In: Miller AB, editor: *Screening for cancer*. New York (NY): Academic Press, 1985. p. 163-91.
- (14) Tockman M. Survival and mortality from lung cancer in a screened population: The John Hopkins study. *Chest* 1986;89 Suppl:325S-6S.
- (15) Melamed MR, Flehinger RJ, 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.
- (16) Berlin NI, Buncher CR, Fontana RS, Frost JK, Melamed MR. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: introduction. *Am Rev Respir Dis* 1984;130:545-9.

- (17) Fontana R, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo Program. *J Occup Med* 1986;28:746–50.
- (18) Fontana RS. Screening for lung cancer: Recent experience in the United States. In: Hansen HH, editor. *Lung cancer: basic and clinical aspects*. Boston (MA): Martinus Nijhoff Publishers; 1986. p. 91–111.
- (19) Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR, et al. Screening for lung cancer: a critique of the Mayo Lung Project. *Cancer* 1991;67 Suppl:1155–64.
- (20) Marcus PM, Bergstrath EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst* 2000;92:1308–16.
- (21) Gohagan JK, Levin DL, Prorok PC, Sullivan D, editors. *The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial*. *Control Clin Trials* 2000;21(6 Suppl):249S–406S.
- (22) Snedecor GW, Cochran WG. *Statistical methods*. 8th ed, Ames (IA): Iowa State University Press; 1989.
- (23) Centers for Disease Control and Prevention. *Cigarette smoking among adults—United States, 2002*. *MMWR Morb Mortal Wkly Rep* 2004;53:427–31.
- (24) Bulzebruck H, Bopp R, Drings P, Drings P, Bauer E, Krysa S, et al. New aspects in the staging of lung cancer: prospective validation of the International Union Against Cancer TNM classification. *Cancer* 1992;70:1102–10.
- (25) Naruke T, Goya T, Tsuchiya R, Suemasu K. Prognosis and survival in resected lung carcinoma based on the new international staging system. *J Thorac Cardiovasc Surg* 1988;96:440–7.
- (26) Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710–7.
- (27) Zheng T, Holford TR, Boyle P, Chen Y, Ward BA, Flannery J, et al. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960–1989. *Cancer* 1994;74:1556–67.
- (28) Beard CM, Jedd MB, Woolner LB, Richardson RL, Bergstrath EJ, Melton LJ 3rd. Fifty-year trend in incidence rates of bronchogenic carcinoma by cell type in Olmsted County, Minnesota. *J Natl Cancer Inst* 1988;80:1404–7.
- (29) Peto R, Lopez AD, Boreham J, Thun M. Mortality from smoking in developed countries, 1950–2000: Indirect estimates from national vital statistics. Oxford (U.K): Oxford University Press; 1994.
- (30) Schottenfeld D, Fraumeni JF Jr, editors. *Cancer Epidemiology and Prevention*. 2nd ed. New York (NY): Oxford University Press; 1996.
- (31) Gazdar AF, Minna JD. Cigarettes, sex and lung adenocarcinoma. *J Natl Cancer Inst* 1997;89:1563–5.
- (32) Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health* 1978;32:303–13.
- (33) Hrubec Z, McLaughlin JK. Former cigarette smoking and mortality among US veterans: A 26-year follow-up, 1954–1980. In: Burns DM, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their*

implication for prevention and control. *Smoking and Tobacco Control Monograph 8*. National Institutes of Health, National Cancer Institute. Bethesda (MD): U.S. Government Printing Office; 1997. p. 501–30.

- (34) Wynder EL, Muscat JE. The changing epidemiology of smoking and lung cancer histology. *Environ Health Perspect* 1995;103 Suppl 8:143–8.

## NOTES

As of June 2005, the PLCO Project Team includes more than 1000 dedicated staff who are actively involved in the PLCO Trial. Key personnel from the 10 screening centers, the National Cancer Institute, and support staff are noted below. A more complete list as of December 2000 can be found elsewhere (21). Primary authors on this manuscript are noted with an asterisk. Other titles are in parentheses after the name of the investigator (PI = Principal Investigator or co-PI, C = Screening Center Coordinator, PO = Project Officer).

**Screening Centers: Birmingham, AL**—Mona Fouad, MD, MPH (PI); Albert Oberman, MD, MPH; Edward Partridge, MD; Donald A. Urban, MD; Darlene Higgins (C); **Denver, CO**—E. David Crawford, MD (PI); Sheryl L. Ogden, RN, BSN (C); **Detroit, MI**—Paul A. Kvale,\* MD (PI); Christine C. Johnson, PhD, MPH (PI); Karen Broski (C); Lois Lamerato, PhD, MS; **Honolulu, HI**—Lance Yokochi, MD, MPH (PI); Victoria Jenkins, BSN, MEd (C); **Marshfield, WI**—Douglas Reding, MD, MPH (PI); William Hocking,\* MD (PI); Karen Lappe, BSN (C); **Minneapolis, MN**—Timothy R. Church, PhD, MS (PI); Martin M. Oken,\* MD (PI); Deborah Engelhard, MA (C); Jill Cordes,\* BSN, RN (C); **Pittsburgh, PA**—Joel L. Weissfeld, MD, MPH (PI); Robert E. Schoen, MD, MPH (PI); Betsy Gahagan, RN, BSN (C); **Salt Lake City, UT**—Saundra S. Buys, MD (PI); Thomas M. Beck,\* MD (PI); Lisa H. Gren, MSPH (C); Jeffery C. Childs; Bonita Wohlers, RN, MSN (C); **St Louis, MO**—Gerald L. Andriole, MD (PI); Heidi Lowery, RN, MS (C); **Washington, DC**—Edward P. Gelmann, MD (PI); Colleen McGuire, RN, MSN (C).

**National Cancer Institute: Division of Cancer Prevention**—Christine D. Berg, MD (PO); Philip C. Prorok,\* PhD (PO); John K. Gohagan,\* PhD; Barnett S. Kramer, MD, MPH; Richard M. Fagerstrom, PhD; David L. Levin,\* MD, MS; Pamela M. Marcus,\* PhD, MS; Ping Hu,\* ScD; Paul F. Pinsky, PhD; Jian-Lun Xu, PhD; Grant Izmirlian, PhD; Anthony B. Miller, MB (consultant); **Division of Cancer Epidemiology and Genetics**—Richard B. Hayes, PhD.

**Coordinating Center, Westat Inc.**—Barbara O'Brien, MT, MPH (PI); Lawrence R. Ragard, MD; Susan Yurgalevitch, MS, MPH; Keith Umbel; Beth Bridgeman; **Statistical Center, Information Management Systems, Inc.**—Thomas L. Riley\* (PI); Jonathan D. Clapp; Joseph H. Austin; Jerome Mabie; Craig Williams; Stephen D. Winslow\*; **Specimen Laboratory**—David Chia, PhD (PI); Jean Reiss, MT.

Supported by individual contracts from the National Cancer Institute to each of the 10 screening centers and to the coordinating center.

Manuscript received October 1, 2004; revised October 6, 2005; accepted November 8, 2005.