Published in final edited form as:
Lung Cancer. 2013 November ; 82(2): . doi:10.1016/j.lungcan.2013.07.017.

Diagnostic evaluation following a positive lung screening chest radiograph in the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial

William G. Hocking[a,*], **Martin C. Tammemagi**[b], **John Commins**[c], **Martin M. Oken**[d], **Paul A. Kvale**[e], **Ping Hu**[f], **Lawrence R. Ragard**[g], **Tom L. Riley**[c], **Paul Pinsky**[f], **Thomas M. Beck**[h], and **Philip C. Prorok**[i]

[a]Department of Oncology/Hematology, Marshfield Clinic, Marshfield, WI

[b]Department of Community Health Sciences, Brock University

[c]Information Management Services, Rockville, MD

[d]Virginia Piper Cancer Institute, University of Minnesota, Minneapolis, MN

[e]Department of Pulmonary Diseases, Henry Ford Health System, Detroit, MI;387-5426

[f]Division of Cancer Prevention, National Cancer Institute, Bethesda, MD

[g]Westat, Inc., Rockville, MD

[h]Mountain States Tumor Institute at St. Luke's Regional Medical Center, Boise, ID

[i]Biometry Research Group, National Cancer Institute, Bethesda, MD

Abstract

Lung cancer is the major cause of cancer mortality. One of the aims of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) was to determine if annual screening chest radiographs reduce lung cancer mortality. We enrolled 154,900 individuals, aged 55–74 years; 77,445 were randomized to the intervention arm and received an annual chest radiograph for 3 or 4 years. Participants with a positive screen underwent diagnostic evaluation under guidance of their primary physician. Methods of diagnosis or exclusion of cancer, interval from screen to diagnosis, and factors predicting diagnostic testing were evaluated. One or more positive screens occurred in 17% of participants. Positive screens resulted in biopsy in 3%, with 54% positive for cancer. Biopsy likelihood was associated with a mass, smoking, age, and family history of lung cancer. Diagnostic testing stopped after a chest radiograph or computed tomography/magnetic resonance imaging in over half. After a second or subsequent positive screen, evaluation stopped after comparison to prior radiographs in over half. Of 308 screen-detected cancers, the diagnosis was established by thoracotomy/thoracoscopy in 47.7%, needle biopsy in 27.6%, bronchoscopy in 20.1% and mediastinoscopy in 2.9%. Eighty-four percent of screen-detected lung cancers were diagnosed within 6 months. Diagnostic evaluations following a

[*]**Corresponding author at:** Marshfield Clinic, Department of Oncology/Hematology, 1000 N Oak Avenue, Marshfield, WI 54449, USA. Tel.: +1 715-387-5426. Fax: +1 715-389-5757 hocking.william@marshfieldclinic.org.

Conflict of Interest Statement Drs. Hu, Pinsky, and Prorok are employed by the NIH. All other authors report no real or potential conflict of interest.

positive screen were conducted in a timely fashion. Lung cancer was diagnosed by tissue biopsy or cytology in all cases. Lung cancer was excluded during evaluation of positive screening examinations by clinical or radiographic evaluation in all but 1.4% who required a tissue biopsy.

Keywords

Lung Neoplasms/mortality; Radiography/screening/methods; Risk factors

1. Introduction

Lung cancer accounts for 13% of all cancers and causes an estimated 1.4 million deaths annually worldwide[1]. When diagnosed at an early stage, 5-year survival is as high as 60%– 70%[2,3], but only 30% of clinically detected lung cancers are potentially resectable at the time of diagnosis, and approximately 85% of lung cancer patients die from the disease[4].

Early trials of screening high-risk populations by chest radiography alone or with sputum cytology[5-9] did not demonstrate reduction in lung cancer mortality. In 1993, the National Cancer Institute (NCI) initiated the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)[10] to determine whether screening programs would reduce mortality from these four cancers. Screening results for the lung cancer intervention arm of this trial have been previously published[11], and comparison to the control arm demonstrated no mortality benefit from screening[12].

The goal of this study was to evaluate the diagnostic approach following a positive lung screening examination in PLCO. We were particularly interested in how the diagnosis of lung cancer was established or excluded, what factors influenced the diagnostic approach, and the outcome when a positive screen was followed by a negative diagnostic evaluation for cancer.

2. Methods

2.1. Ethics statement

Ethical approval was obtained by both the NCI and local institutional review boards (see appendix). All participants signed informed consent documents prior to enrollment.

2.2. Study design

Details of the PLCO design and operations have been previously reported[10]. Individuals between the ages of 55 and 74 were eligible. Between November 8, 1993 and July 2, 2001, a total of 154,900 participants were enrolled. Randomization and screening were carried out at ten screening centers[10].

The screening evaluation for lung cancer was a single view posterior-anterior chest radiograph (CXR). Current or former smokers underwent initial screening at baseline (T0), followed by three annual screens (T1-T3). Never-smokers initially followed the same protocol, but an amendment effective December 7, 1998 changed eligibility for the T3 CXR to current or former smokers only. Radiographs were defined as positive when the radiologist identified a mass (> 3 cm), nodule (< 3 cm), infiltrate, or other abnormality (atelectasis, pleural, hilar or mediastinal mass) that could represent cancer. Each screening radiograph was initially interpreted in isolation to determine positivity, but subsequently compared to previous CXR when available.

PLCO required that the participants and their primary care providers (PCPs) receive notification of results within 3 weeks. Participants were referred to their PCPs for management, and no standard diagnostic algorithm was recommended. Medical records were obtained to document follow-up. For the purpose of this analysis, a hierarchy of diagnostic procedures ranging from non-invasive to minimally invasive to major invasive was utilized (Table I). The method of establishing a diagnosis of lung cancer was inferred from procedures performed on the date of cancer diagnosis.

Screen-detected cancers were defined as those diagnosed within a window extending 9 months from a positive screen or from a diagnostic test linked to a positive screen. Other cancers were classified as either interval, if the participant had one or more screening examinations but the cancer was diagnosed outside of the screen-detected window, or post-screening if a lung cancer was diagnosed more than 12 months after screening ended.

Diagnosis of screen-detected lung cancer was considered an indicator of effectiveness of the diagnostic evaluation. Since the effectiveness of a negative diagnostic evaluation can only be determined by absence of a subsequent lung cancer diagnosis, the diagnosis of lung cancers within 3 years after a negative diagnostic evaluation was used as an indicator of possible false negative diagnostic evaluation.

Lung cancer pathology was obtained from pathology reports. Cancers were classified as non-small cell lung cancer (NSCLC), small cell, or carcinoid tumors. Carcinoids were excluded from this analysis.

2.3. Statistical analysis

Descriptive statistics were prepared with contingency table analysis and chi-squared test or Fisher's exact test when cell counts were small. Logistic regression analysis was employed to evaluate predictor variable associations with positive screen and highest diagnostic evaluation. Multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI). Predictor variables that were evaluated included age, sex, race/ethnicity, education, family history of lung cancer, emphysema, chronic bronchitis, smoking status, pack-years smoked, and radiographic characteristics. Predictor variables that had a p-value of <0.15 in univariate analysis were considered in multivariable models. Backward stepwise selection was used to remove variables from the model using a significance cutpoint of $p < 0.05$. Nonlinear effects in continuous variables were evaluated using lowess plots and restricted cubic splines. Selected interactions of variables in final models were evaluated by including main effects and interaction terms. Significance of the interaction terms was assessed by the likelihood ratio test. To control for clustering of data in study centers, centers were included in models with indicator variables (fixed effects). Clustering of repeat measures within individuals (more than one positive screen) was adjusted for by using Huber and White robust "sandwich" variance estimator[13].

Model fit and ability to predict were assessed by pseudo-R^2, the Hosmer-Lemeshow goodness-of-fit test, and receiver operator characteristic area under the curve[14]. All reported p-values are two-sided. Models and statistics were prepared using Stata/MP 12.1 (StataCorp; College Station, TX).

3. Results

3.1. Enrollment and baseline demographic features

PLCO randomized 77,445 participants to the intervention arm with nearly equal numbers of men and women. Table II shows baseline features of all participants and those with one or more positive screens versus no positive screen. A multivariable analysis demonstrated that

factors associated with a positive screen were age, male gender, family history of lung cancer, emphysema, being a current or former smoker, and pack-years smoked. A significant interaction existed between age and sex, indicating that the probability of positive screen increases with age more sharply for men than for women.

3.2. Screen results and diagnostic evaluation following a positive screen

There were 13,038 (16.8%) individuals with one or more positive screens and 17,645 total positive screens. There were 9,774 participants with one (75.0%), 2203 with two (16.9%), 779 with three (6.0%), and 282 with four (2.2%) positive screens. Data on the diagnostic evaluation is available on 16,361 (92.7%) of the positive screens (Table III). After a first positive screen the biopsy rate was 3.3% with 55.6% positive for cancer. After a second or subsequent positive screen, the biopsy rate was 2.4%, with 59.1% positivity.

Table IV shows the relationship of radiographic abnormalities and subsequent diagnostic evaluation after a first positive screen. Thoracotomy was performed most frequently after finding a mass, but overall was performed in only 1.2% of first positive screens. Overall, 1.6% underwent a major diagnostic procedure and 2.1% a minimally invasive procedure. Diagnostic evaluation was completed by an imaging study or lower procedure in 96.3%. Among participants not diagnosed with cancer, 0.7% underwent a major diagnostic procedure.

Fluordeoxyglucose (FDG)-positron-emission tomography (PET) scans were performed during diagnostic evaluations in 59 participants after a positive screen (0.3%) and in 16 of 308 participants (5.2%) later diagnosed with cancer. From 1993 to 1996, only one PET scan was performed. There were 19 (0.2% of positive screens) from 1997 to 2000, and 39 (1.3%) from 2001 to 2005, a significant increasing trend ($p<0.0001$). A PET scan was the highest diagnostic procedure in only 0.2% of all initial positive screens. After a PET scan was performed, the frequency of thoracotomy or thoracoscopy was 28.8%, versus 1.3% with no PET scan. In participants diagnosed with lung cancer who did not have a PET scan, 46.6% had a thoracotomy or thoracoscopy, and 28.8% had a needle biopsy; in those who had a PET scan, 68.8% had a thoracotomy or thoracoscopy, and only 6.3% underwent needle biopsy.

There were 308 screen-detected lung cancers, resulting in an overall positive predictive value (PPV) of 1.7%. Characteristics of these lung cancers have been reported[11]. Table V shows the diagnostic evaluation for participants with or without subsequently diagnosed lung cancer. All cancer diagnoses were based on histology or cytology. Bronchoscopic diagnoses include brushings, washings, and transbronchial biopsy. Biopsy to exclude lung cancer was required in only 1.4% of participants.

A multivariable model predicting the likelihood of having chest imaging after a positive screening exam shows female gender, family history of lung cancer, smoking exposure, and a mass on screening exam predict a higher likelihood and abnormalities other than a mass or nodule and multiple positive screens predict a lower likelihood of chest imaging (Table VI). Significant predictors for a biopsy included age, family history of lung cancer, being a current or former smoker, smoking exposure, having a mass, and having fewer preceding positive screens (Table VI).

For screen-detected lung cancers, the interval from a positive screen to diagnosis was <3 months in 61.0%, 3–6 months in 22.7%, 6–9 months in 8.4%, 9–12 months in 4.9%, and >12 months in 2.9%. Among 242 participants with screen-detected lung cancer and a single positive screen, the median time from screen to diagnosis was 2.0 months (range 0–17). For the 66 with two or more positive screens, the median time from first screen to diagnosis was 25.5 months (range 11–52), and from the last screen 3.0 months (range 0–18). Among

12,730 participants with a positive screen who were not diagnosed with a screen-detected lung cancer, there were 349 non-screen-detected lung cancers. Of these, 280 occurred more than 3 years after the last screen, with median time to diagnosis 87.5 months (range 36–153) after the first and 81.5 months (range 36-153) after the last positive screen. There were 69 non-screen-detected cancers diagnosed less than 3 years from the last positive screen. Of these, 38 were interval cancers. For these 69 cancers the median time to diagnosis was 26.0 months (range 9–64) from the first and 21 months (range 9–35) after the last positive screen.

4. Discussion

The National Lung Screening Trial (NLST) demonstrated that screening a high-risk population for lung cancer reduces mortality by 20%[15]. In PLCO, screening with chest radiograph did not result in mortality reduction[12]. This study examines the diagnostic approach taken after a positive screen, which could potentially impact the effectiveness of the screening program. In addition, these results are useful in considering the diagnostic approach to a CXR abnormality suspicious for lung cancer.

These results reflect the practice patterns at the screening centers and their surrounding medical communities. Nearly 17% of participants had one or more positive screens, and the biopsy rate after a positive screen was approximately 3%, of which over 55% were positive. A positive screen led to a diagnosis of cancer in 1.7%. The screen positivity rate in PLCO is substantially higher than that in earlier lung screening trials[5-7]. However, in these trials there was a 12%–15% “indeterminate” CXR interpretation, which led to further diagnostic evaluation of these participants to exclude cancer. The PPV in our trial is lower than in previous trials, probably due to inclusion of 46% never-smokers in PLCO[11].

Among the 308 screen-detected cancers, tissue diagnosis was established most frequently by thoracotomy, followed by needle biopsy, bronchoscopy, thoracoscopy, and mediastinoscopy. In a logistic model of PLCO participants with a first positive screen for lung cancer, independent risk factors for lung cancer included age >65 years, lower education, pack-years and duration of smoking, body mass index <30, family history of lung cancer, and radiographic findings of a mass, nodule, unilateral hilar or mediastinal adenopathy, lung infiltrate, or an upper to mid-chest lesion[16]. A logistic model utilizing clinical and radiographic features of solitary pulmonary nodules showed clinical factors associated with malignancy were age >65, smoking history, and personal history of cancer 5 or more years previously[17]. In a subsequent study, this model did not perform better than physician judgment in predicting malignancy, although physicians tended to overestimate the risk of cancer in low-risk nodules[18]. In our study, age, family history of lung cancer, smoking history, and presence of a mass were associated with higher likelihood of biopsy, suggesting that clinicians utilize these factors in the decision process.

PET scanning first became widely available for diagnostic and staging evaluation around the year 2000 and was only utilized toward the end of the follow-up window in PLCO. PET/CT imaging has recently been shown to improve discrimination of benign from malignant pulmonary nodules[19] and may be particularly useful when combined with a clinical prediction model[20]. There were 43 diagnostic PET scans performed in our cohort, with no diagnosis of lung cancer, but PET scan was the highest diagnostic procedure in only 0.2%. While PET scan usage was relatively limited, there was a >10-fold increase from early to later trial years. In our study, patients diagnosed with lung cancer who received a PET scan were more likely to have a thoracotomy or thoracoscopy and less likely to have a needle biopsy than those not having a PET scan, suggesting that a PET scan may have led more directly to a definitive surgical procedure.

Of the 13,038 participants with at least one positive screen, 12,730 did not have a diagnosis of lung cancer during the screening interval, indicating that 97.6% were false positive. Diagnostic evaluation stopped after comparison of the screening radiograph with a prior CXR in about one-third. A diagnostic CXR completed the evaluation in just under one-third and cross-sectional imaging in one-fifth, while only 1.4% underwent a tissue biopsy to exclude cancer. Despite this low rate of biopsy, 121 patients without cancer underwent invasive surgical procedures (Table V). In participants with more than one positive screen, the diagnostic evaluation was completed after comparison with previous CXRs in just over half, reflecting clinical judgment in evaluating a suspicious but stable radiographic finding.

One indication of diagnostic efficiency is the interval from a positive screen to diagnosis of lung cancer, which was within 3 months in over 60% and 6 months in over 80% of screen-detected cancers. The median time to diagnosis after one positive screen was 2 months, and after two or more positive screens 3 months from the last positive screen; whereas the interval after the last screen was 9–153 months for non-screen-detected cancers. Eighty percent of the non-screen-detected cancers occurred more than 3 years after the last positive screen. This long interval suggests these cancers were unlikely to have been present and missed on the screening radiographs, and for the most part represented post-screening cancers. Furthermore, nearly 60% of NSCLCs detected by screening were stage I-II, compared with 33% of interval cancers[11]. A recent study in a clinical, non-screening setting demonstrated the interval from suspicious CXR to diagnosis was 3-98 days[21]. While various groups have recommended specific intervals between initial suspicious radiograph and diagnosis or treatment, the effect of delay in diagnosis on prognosis remains unclear[22,23].

Our data set does not include nodule diameter, so it is not possible to compare the diagnostic evaluation precisely with American College of Chest Physicians (ACCP) guidelines[24] that are based, in part, on nodule diameter and growth rate. These guidelines emphasize the importance of comparison to prior radiographs, which was a major component of the diagnostic evaluation for PLCO participants, particularly after the baseline year. The approach to diagnostic evaluation for PLCO participants appears to be generally consistent with ACCP guidelines published in 2013, despite the fact that PLCO screening started in 1993.

5. Conclusion

In summary, a positive lung screen resulted in an appropriate and timely diagnostic evaluation, even prior to the availability of PET scanning. Participants diagnosed with cancer underwent a sequential diagnostic approach that resulted in a tissue diagnosis. Those who were not diagnosed with cancer usually underwent a more limited diagnostic evaluation, often terminated after comparison of the screening examination with prior radiographs or additional chest imaging, and invasive diagnostic procedures were infrequent.

Acknowledgments

The authors thank the participants who made the trial possible, and also thank Marie Fleisner of the Marshfield Clinic Research Foundation for editorial assistance with this article.

Funding Source This research was supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, and DHHS, Contract #NO1-CN-25518. The NCI participated in trial design and provided oversight during conduct of the study. Trial Registration: clinicaltrials.gov identifier: NCT00002540.

Appendix: IRB Committee Names and Project Approval Numbers for all Study Centers

Colorado Multiple Institutional Review Board #93-377

MedStar Health Research Institute-Georgetown University Oncology Institutional Review Board #1993-276

Department of Veterans Affairs VA Pacific Islands Health Care Systems Spark M. Matsunaga Medical Center #2010-03

Henry Ford Health System IRB #112

University of Minnesota IRB #9302M06411

Washington University in St. Louis IRB #201104130

University of Pittsburgh IRB #9262115

University of Utah IRB#00004389

Marshfield Clinic Research Foundation IRB #RED10110PLCO

University of Alabama-Birmingham IRB #0000726

References

[1]. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61:69–90. [PubMed: 21296855]

[2]. 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. [PubMed: 2842549]

[3]. Ginsberg RJ, Rubinstein LV, Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995; 60:615–23. [PubMed: 7677489]

[4]. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics 2009. CA Cancer J Clin. 2009; 59:225–49. [PubMed: 19474385]

[5]. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo Program. J Occup Med. 1986; 28:746–50. [PubMed: 3528436]

[6]. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer: Results of the Memorial Sloan-Kettering study in New York. Chest. 1984; 86:44–53. [PubMed: 6734291]

[7]. Frost JK, Ball WC Jr, Levin ML, Tockman MS, Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis. 1984; 130:549–54. [PubMed: 6091505]

[8]. Kubik A, Parkin DM, Khlat 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. [PubMed: 2404878]

[9]. Manser RL, Irving LB, Stone C, Byrnes G, Abramson M, Campbell D. Screening for lung cancer. Cochrane Database Syst Rev. 2004; (1):CD001991. [PubMed: 14973979]

[10]. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000; 21:273S–309S. [PubMed: 11189684]

[11]. Hocking WG, Hu P, Oken MM, Winslow SD, Kvale PA, Prorok PC, et al. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. J Natl Cancer Inst. 2010; 102:722–31. [PubMed: 20442215]

[12]. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, et al. Screening by chest radiograph and lung cancer mortality. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial. JAMA. 2011; 306:1865–73. [PubMed: 22031728]

[13]. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica. 1980; 48:817–38.

[14]. Hosmer, DW., Jr; Lemeshow, S. Applied Logistic Regression. 2nd ed. John Wiley & Sons, Inc.; New York: 1999.

[15]. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. New Engl J Med. 2011; 365:395–409. [PubMed: 21714641]

[16]. Tammemagi MC, Freedman MT, Pinsky PF, Oken MM, Hu P, Riley TL, et al. Prediction of true positive lung cancers in individuals with abnormal suspicious chest radiographs: a prostate, lung, colorectal, and ovarian cancer screening trial study. J Thorac Oncol. 2009; 4:710–21. [PubMed: 19404219]

[17]. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodule. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997; 157:849–55. [PubMed: 9129544]

[18]. Swensen SJ, Silverstein MD, Edell ES, Trastek VF, Aughenbaugh GL, et al. Solitary pulmonary nodules: clinical prediction model versus physicians. Mayo Clin Proc. 1999; 74:319–29. [PubMed: 10221459]

[19]. Bryant AS, Cerfolio RJ. The maximum standardized uptake values on integrated FDGPET/CT is useful in differentiating benign from malignant pulmonary nodules. Ann Thorac Surg. 2006; 82:1016–20. [PubMed: 16928527]

[20]. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglcose positron emission tomography. Chest. 2005; 128:2490–6. [PubMed: 16236914]

[21]. Yorio JT, Xie Y, Yan J, Gerber DE. Lung cancer diagnostic and treatment intervals in the United States: a health care disparity? J Thorac Oncol. 2009; 4:1322–30. [PubMed: 19752757]

[22]. Jensen AR, Mainz J, Overgaard J. Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncol. 2002; 41:147–52. [PubMed: 12102158]

[23]. Quarterman RL, McMillan A, Ratcliffe MB, Block MI. Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. J Thorac Cardiovasc Surg. 2003; 125:108–14. [PubMed: 12538992]

[24]. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of Lung Cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143:e93S–120S. [PubMed: 23649456]

Table I

Diagnostic testing hierarchy

Invasiveness of Procedure	Condensed Hierarchy	Extended Hierarchy
Major	Tissue biopsy	Thoracotomy
		Thoracoscopy
		Mediastinoscopy
		Needle Biopsy
		Bronchoscopy with biopsy
Minimal	Cytology	Thoracentesis
		Cytology (sputum, bronchial washings)
	Bronchoscopy	Bronchoscopy without biopsy
Non-Invasive	Imaging	PET Scan
		Chest CT/MRI
	Chest X-ray	Chest X-ray
	Comparison	Comparison
	Clinical exam	Clinical Exam
	Other procedure	Other – no biopsy
	No procedure	None – no procedures done
		None – missing data

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Table II

Demographics of participants with one or more positive screens, compared to those with no positive screens

		Ever Positive Screen		Never Positive			All Screened	
		N	%	N	%	*p*-value	N	%
Age	< 65	7740	59.4	37841	65.7	<.0001	45581	64.5
	≥ 65	5298	40.6	19754	34.3		.25052	35.5
Gender	Male	7041	54.0	28628	49.7	<.0001	35669	50.5
	Female	5997	46.0	28967	50.3	.	34964	49.5
Race/ethnicity	White, non-Hispanic	11435	88.2	50742	89.0	<.0001	62177	88.8
	Black, non-Hispanic	849	6.5	2622	4.6	.	3471	5.0
	Hispanic	220	1.7	1047	1.8	.	1267	1.8
	Asian	390	3.0	2177	3.8	.	2567	3.7
	Pacific Islander	39	0.3	309	0.5	.	348	0.5
	American Indian	35	0.3	145	0.3	.	180	0.3
Highest Education	High school or less	3956	30.5	16823	29.5	<.0001	20779	29.7
	Post high school	4563	35.2	19371	34.0	.	3934	34.2
	College grad or postgraduate	4432	34.2	20807	36.5	.	5239	36.1
Family History of Lung Cancer	No	10993	85.4	49258	86.9	<.0001	60251	86.6
	Yes	1482	11.5	5889	10.4	.	7371	10.6
	Maybe	398	3.1	1518	2.7	.	1916	2.8
Smoking Status	Never	5037	38.8	27543	48.3	<.0001	32580	46.5
	Former	6189	47.7	24058	42.2	.	30247	43.2
	Current	1746	13.5	5446	9.5	.	7192	10.3

Missing values were excluded for smoking status, race, family history, and education

Table III

Highest diagnostic procedure by number of positive screens

	Positive Screen				All	
	1st Positive		2nd–4th Positive			
	N	%	N	%	N	%
Highest Followup						
Thoracotomy	160	1.2	47	1.0	207	1.2
Thoracoscopy	39	0.3	8	0.2	47	0.3
Mediastinoscopy	15	0.1	8	0.2	23	0.1
Needle Biopsy	127	1.0	25	0.5	152	0.9
Bronchoscopy with biopsy	87	0.7	22	0.5	109	0.6
Thoracentesis	5	0.0	2	0.0	7	0.0
Cytology	37	0.3	14	0.3	51	0.3
Bronchoscopy without biopsy	8	0.1	2	0.0	10	0.1
PET Scan	25	0.2	6	0.1	31	0.2
Chest CT/MRI	2591	19.9	428	9.3	3019*	17.1
Chest X-ray	4765	36.5	705	15.3	5470	31.0
Comparison	3073	23.6	2574	55.9	5647	32.0
Clinical Exam	481	3.7	350	7.6	831	4.7
Other	7	0.1	2	0.0	9	.1
None	1618	12.4	414	9.0	2032	11.5
All	13038	100.0	4607	100.0	17645	100.0

*A total of 5 MRIs

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Table IV

Highest diagnostic procedure by type of radiographic abnormality on 1st positive screen

Invasiveness of Procedure	Highest Follow-up level	Abnormality type: Mass N	Mass %	Mass Cum. %	Nodule N	Nodule %	Nodule Cum. %	Other positive N	Other positive %	Other positive Cum. %	TOTAL N	TOTAL %	TOTAL Cum. %
Major	Thoracotomy	32	3.8	100.0	110	1.1	100.0	18	0.8	100.0	60	1.2	100.0
	Thoracoscopy	4	0.5	96.2	30	0.3	98.9	5	0.2	99.2	39	0.3	98.8
	Mediastinoscopy	3	0.4	95.8	8	0.1	98.6	4	0.2	99.0	15	.1	98.5
	Subtotal	39	4.7	100.0	148	1.4	100.0	27	1.2	100.0	214	1.6	100.0
Minimally	Needle Biopsy	41	4.8	95.4	67	0.7	98.5	19	0.8	98.9	127	1.0	98.4
	Bronchoscopy with biopsy	27	3.2	90.6	38	0.4	97.8	22	0.9	98.1	87	0.7	97.4
	Thoracentesis	1	0.1	87.3	1	0.0	97.3	3	0.1	97.1	5	0.0	96.7
	Cytology	3	0.4	87.3	19	0.2	97.4	15	0.6	97.0	37	0.3	96.7
	Bronchoscopy w/o biopsy	1	0.1	87.0	4	.0	97.2	3	0.1	96.4	8	0.1	96.4
	Subtotal	73	8.6	95.4	129	1.3	98.5	62	2.5	98.9	264	2.1	98.4
Non-invasive	PET Scan	1	0.1	86.9	23	0.2	97.2	1	0.0	96.2	25	0.2	96.3
	Chest CT/MRI	189	22.2	86.8	2054	20.9	96.9	348	14.8	96.2	2591	19.9	96.1
	Chest X-ray	248	29.1	64.6	3701	37.7	76.0	816	34.6	81.4	4765	36.5	76.3
	Comparison	158	18.5	35.5	2256	23.0	38.4	659	27.9	46.8	3073	23.6	39.7
	Clinical Exam	27	3.2	17.0	367	3.7	15.4	7	3.7	18.9	481	3.7	16.2
	Other w/o biopsy	.	.	.	6	0.1	11.7	1	0.0	15.2	7	0.1	12.5
	Subtotal	623	73.1	86.9	8407	85.5	97.2	1912	81.0	96.2	0942	84.0	96.3
	None	39	4.6	13.8	368	3.7	11.6	116	4.9	15.2	523	4.0	12.4
	Missing data	79	9.3	9.3	774	7.9	7.9	24	10.3	10.3	1095	8.4	8.4
	Total	853	100.0	.	9826	100.0	.	2359	100.0	.	13038	100.0	.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Table V

Highest follow-up by cancer diagnosis

Invasiveness of All Procedure	Highest Follow-up Level	Cancer No N	Cancer No %	Cancer Yes N	Cancer Yes %	All N	All %
Major	Thoracotomy	76	0.4	131	42.5	207	1.2
	Thoracoscopy	31	0.2	16	5.2	47	0.3
	Mediastinoscopy	14	0.1	9	2.9	23	0.1
	Subtotal	121	0.7	156	50.6	277	1.6
Minimally	Needle Biopsy	67	0.4	85	27.6	152	0.9
	Bronchoscopy with biopsy	47	0.3	62	20.1	109	0.6
	Thoracentesis	6	0.0	1	0.3	7	0.0
	Cytology	49	0.3	2	0.6	51	0.3
	Bronchoscopy w/o biopsy	10	0.1	.	.	10	0.1
	Subtotal	179	1.1	150	48.6	329	2.1
Non-invasive	PET Scan	31	0.2	.	.	31	0.2
	Chest CT/MRI	3019	17.4	.	.	3019	17.1
	Chest X-ray	5470	31.6	.	.	5470	31.0
	Comparison	5646	32.6	1	0.3	5647	32.0
	Clinical Exam	830	4.8	1	0.3	831	4.7
	Other	9	0.1	.	.	9	0.1
	Subtotal	15005	86.5	2	0.6	15007	84.9
	None	2032	11.7	.	.	2032	11.5
	All	17337	100.0	308	100.0	17645	100.0

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Table VI

Multivariable logistic regression models * predicting PLCO participants with an abnormal suspicious lung screens receiving imaging (model 1) and biopsy (model 2)

	Model 1 Outcome: Imaging	**Model 2 Outcome: Biopsy**
Variable	**Odds ratio (95% CI; *p*-value)**	
Age (per 10 years	NS	1.388 (1.162-1.657; $p < 0.001$)
Sex (male vs. female)	0.798 (0.736-0.865; $p < 0.001$)	NS
Family history of lung cancer	1.140 (1.011-1.284; $p = 0.032$)	1.462 (1.145-1.867; $p = 0.002$)
Smoking status (current vs. former; former vs. never)	NS	1.540 (1.306-1.817; $p < 0.001$)
Pack-years smoked (per 20 PKYR)	1.084 (1.057-1.111; $p < 0.001$)	1.201 (1.139-1.266; $p < 0.001$)
Abnormality Type		
Mass	1.541 (1.337-1.775; $p < 0.001$)	4.873 (3.860-6.153; $p < 0.001$)
Nodule	Referent group	Referent group
Pleural mass	0.822 (0.644-1.048; $p = 0.113$)	0.955 (0.553-1.744; $p = 0.880$)
Infiltrate	0.566 (0.483-0.662; $p < 0.001$)	1.104 (0.793-1.536; $p = 0.559$)
Atelectasis	0.480 (0.258-0.894; $p = 0.021$)	0.388 (0.055-2.748; $p = 0.343$)
Hilar lymphadenopathy	0.924 (0.772-1.107; $p = 0.394$)	1.339 (0.881-2.035; $p = 0.172$)
Number of positive screens	0.550 (0.506-0.599; $p < 0.001$)	0.758 (0.636-0.904; $p = 0.002$)
Model performance		
Pseudo-R^2	0.065	0.099
Hosmer-Lemeshow test	$p = 0.752$	$p = 0.413$
ROC AUC	0.677	0.739

* These models are adjusted for screening variables, including randomization year, study year of positivity, and study center; and also have variances adjusted for repeat measures in the same individual using the Huber and White robust “sandwich” variance estimator

Abbreviations: NS, not significant; PKYR, pack-years smoked; ROC AUC, receiver operator characteristic area under the curve