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Interval lung cancers not detected on screening chest X-rays: How are they different?

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ABSTRACT

Background: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial provides us an opportunity to describe interval lung cancers not detected by screening chest X-ray (CXR) compared to screen-detected cancers.

Methods: Participants were screened for lung cancer with CXR at baseline and annually for two (never smokers) or three (ever smokers) more years. Screen-detected cancers were those with a positive CXR and diagnosed within 12 months. Putative interval cancers were those with a negative CXR screen but with a diagnosis of lung cancer within 12 months. Potential interval cancers were re-reviewed to determine whether lung cancer was missed and probably present during the initial interpretation or whether the lesion was a "true interval" cancer.

Results: 77,445 participants were randomized to the intervention arm with 70,633 screened. Of 5227 positive screens from any screening round, 299 resulted in screen-detected lung cancers; 151 had potential interval cancers with 127 CXR available for re-review. Cancer was probably present in 45/127 (35.4%) at time of screening; 82 (64.6%) were "true interval" cancers. Compared to screen-detected cancers, true interval cancers were more common among males, persons with <12 years education and those with a history of smoking. True interval lung cancers were more often small cell, 28.1% vs. 7.4%, and less often adenocarcinoma, 25.6% vs. 56.2% ($p < 0.001$), more advanced stage IV (30.5% vs. 16.6%, $p < 0.02$), and less likely to be in the right upper lobe, 17.1% vs. 36.1% ($p < 0.02$).

Conclusion: True interval lung cancers differ from CXR-screen-detected cancers with regard to demographic variables, stage, cell type and location.

ClinicalTrials.gov number: NCT00002540.

Abbreviations: CXR, chest X-ray; LDCT, low dose helical computed tomography; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; NIOSH, National Institute of Occupational Safety and Health; FET, Fisher's exact test; CI, confidence interval; OR, odds ratio; LRT, likelihood ratio test; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; L, left; R, right.

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1. Introduction

Lung cancer is the most common lethal cancer, expected to account for 159,260 deaths in the USA in 2014 [1] and for 1,400,000 deaths in the world in 2008 [2]. Low-dose helical computed tomography (LDCT) was reported in 2011 to reduce lung cancer mortality when it was used to screen high-risk persons [3], but screening with chest radiographs (CXR) has failed to demonstrate reduced mortality compared to historic controls or to usual care in numerous settings [4–9].

The lung component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was a comparison of annual screening with CXR to usual care in both never- and ever-smokers. PLCO provided an opportunity to describe characteristics of lung cancers that were not detected by screening CXR and were judged to have developed between screening tests, deemed "interval cancers". Our objective was to better characterize the nature of interval cancers. We first identified, by re-reviewing the CXR images of putative interval cancers, those that were detectable on the screen but missed ("probably present") during the original screening review in order to designate the "true interval" cancers. We then analyzed what factors were associated with true interval cancers (and probably present cancers) compared to screen-detected cancers.

We hypothesized that true interval lung cancers are distinct from screen-detected cancers, which would have implications in the development of new screening methodologies. In this report we have performed a detailed comparison of the characteristics of the true interval and screen-detected lung cancers diagnosed during the screening phase in the intervention arm of PLCO.

2. Materials and methods

2.1. Trial design

The design of PLCO has been described previously [9]. Males and females aged 55–74 were recruited between 1993 and 2001 at ten screening centers nationwide. Each institution obtained local Institutional Review Board approval to conduct the study; all participants provided written informed consent. Subjects were randomized to the intervention arm or to usual care within blocks stratified by screening center, sex and age. Exclusion criteria at study entry were history of a PLCO cancer, current cancer treatment and previous removal of one lung. Participants completed a baseline questionnaire at study entry that inquired about socio-demographics, medical history, smoking history, and past screenings.

Intervention arm participants were offered a postero-anterior (PA) CXR at baseline and then annually for three more years; participants who were randomized after April 1995 and who had never smoked were not offered the fourth screen. Subjects and their health care providers were notified of CXR results. A CXR was classified as "abnormal, suspicious for lung cancer" if a nodule, mass, infiltrate or other abnormality suspicious for lung cancer was noted. Those with abnormal suspicious exams were advised to seek diagnostic evaluation. Follow-up was determined by the participants and their physicians, and not by trial protocol. PLCO screening center staff obtained medical records related to diagnostic follow-up of positive screens and certified medical record abstractors recorded information to document lung cancer diagnosis. In addition, an annual questionnaire was completed by all subjects or next-of-kin until 2010, and medical records documenting follow-up also were obtained and abstracted when a lung cancer was reported and was not associated with a positive screen.

2.2. Definition of interval cancers in the PLCO Screening Arm

Among intervention arm subjects, screen-detected cancers were defined as those diagnosed after any positive screen within a window extending twelve months from the positive screen; additionally, a gap of no more than 9 months between screen and first procedure, or between procedures, could be present. Potential interval cancers were defined as those diagnosed within 12 months of a negative or "abnormal but not suspicious for lung cancer" PLCO screening CXR. Cancers diagnosed after the screening phase (more than 12 months after the last scheduled screening CXR) were denoted as "post-screening" and were not included in this analysis. Subjects with carcinoid tumors were also excluded.

After completion of the screening phase of PLCO, CXR that subsequently had been digitized from subjects who had potential interval lung cancers were re-interpreted to determine if there were findings suspicious for lung cancer that were missed at the first interpretation. Two physicians with extensive experience reading CXR (PAK, CJZ)[1] performed the second interpretations separately, blinded to the location of the cancer, and then compared interpretations with each other. If an abnormality that was suspicious for lung cancer was identified and was in the same lung as the cancer on this second reading by both reviewers, the image was characterized as a missed positive screen and the tumor was characterized as "probably present" at the last PLCO screening. If both reviews agreed with the initial interpretation that the image was not suspicious for cancer, the subsequent cancer was characterized as a "true interval cancer". Differences of opinions were resolved by discussion between the two reviewers, or with input from a third reviewer (DLS)[1] if consensus could not be reached.

2.3. Statistical analysis

Descriptive statistics were prepared using contingency table analysis and Fisher's exact test (FET). The 95% confidence intervals (CI) for proportions were estimated using the binomial exact method. Multivariable models were constructed to identify factors or characteristics associated with having a true interval lung cancer vs. screen detected cancer. This was done using two models, one with socio-demographic and exposure predictor variables which preceded diagnosis of lung cancer, and one for the tumor characteristics observed at lung cancer diagnosis. The direction, magnitude and precision of associations were estimated with odds ratios (OR) and their 95% confidence intervals (CI). Logistic regression modeling assumptions were evaluated. Nonlinear effects of continuous variables were evaluated graphically using loess plots and in modeling by using restricted cubic splines. The assumption of additivity of explanatory variables was evaluated by assessing interactions of predictors in final models by including the interaction term along with main effect terms. The added benefit of interactions and categorical variables were assessed by applying the likelihood ratio test (LRT) in the full and nested models with and without the term of interest. Because data were clustered in study centers, all models were adjusted for center as an indicator variable, which is tantamount to fixed effects models. All reported p-values are two-sided. Because the number of true interval cancers is limited, we did not restrict reporting of results to associations with p-values <0.05.

The comparison group of screen-detected lung cancers, which included screen-detected cancers ascertained at the baseline

[1] PAK is a board-certified pulmonologist who has been certified for 28 years as a "B" reader by the National Institute of Occupational Safety and Health (NIOSH), and CJZ and DLS are board-certified radiologists with added proficiency in thoracic radiology.