Research Article

Cancer Epidemiology, Biomarkers & Prevention

Lung Cancer Detectability by Test, Histology, Stage, and Gender: Estimates from the NLST and the PLCO Trials

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Abstract

Background: Implementing optimal lung cancer screening programs requires knowledge of the natural history and detectability of lung cancer. This information can be derived from the results of clinical trials with the aid of microsimulation models.

Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) program and individual-level data from the National Lung Screening Trial (NLST) and the Prostate, Lung, Colon, and Ovarian Cancer Screening trial (PLCO) were used to investigate the sensitivity (by histology and stage) of CT and chest radiography (CXR) and the mean preclinical sojourn time (MPST) of lung cancer (by gender, histology, and stage). The MISCAN-Lung model was used to reproduce the lung cancer incidence by method of detection (clinically or screen-detected), gender, histology, and stage in both trials and SEER, by calibrating CT and CXR sensitivity and natural history parameters.

Results: CT sensitivity ranges from 8.83% to 99.35% and CXR sensitivity from 2.51% to 97.31%, depending on histology and stage. CT sensitivity for stage IA is more than 3-fold higher compared with CXR, for all histologies. The total MPST estimates for lung cancer progressing through preclinical stages IA to IV range from 3.09 to 5.32 years for men and 3.35 to 6.01 years for women. The largest difference in total MPST between genders was estimated for adenocarcinoma.

Conclusions: We estimate longer MPSTs for lung cancer compared with previous research, suggesting a greater window of opportunity for lung cancer screening.

Impact: This study provides detailed insights into the natural history of lung cancer and CT screening effectiveness. *Cancer Epidemiol Biomarkers Prev; 24(1); 154–61. ©2014 AACR.*

Introduction

Lung cancer causes 1.4 million deaths per year globally, accounting for 18% of the total number of cancer deaths (1). Randomized controlled trials, which evaluated the benefits of lung cancer screening with chest radiography (CXR), such as the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO), did not show a significant reduction in lung cancer mortality (2). In contrast, the results of the National Lung Screening Trial (NLST) show that lung cancer mortality may be reduced by screening with CT (3). However, the knowledge of the natural history and detectability of lung cancer remains limited. Information on the natural history and detectability of lung cancer cannot be derived directly from observed data, as the onset and progression of preclinical disease is unobservable. This information can only be obtained by modeling disease onset, progression, and detection. With the aid of microsimulation models, results of clinical trials can be used to derive information on the natural history and detectability of lung cancer.

Estimates of the mean preclinical sojourn times (MPST) and sensitivities of screening modalities for lung cancer are essential for the extrapolation of clinical trials. These extrapolations allow the investigation of screening policies that deviate from those investigated in the trials, which may aid policy makers in developing optimal screening policies, as was shown recently (4). Furthermore, studies on other cancers have shown that both the MPST of the disease and the sensitivity of the screening test influence the efficiency of screening policies (5).

Previous studies obtained estimates for the MPST and detectability of lung cancer based on data from epidemiologic studies and clinical trials, using simulation or analytical modeling (6–9). However, these studies did not investigate differences in lung cancer MPST by gender, histology, and stage or investigate the detectability by histology and stage.

Because of the large number of participants and the use of CT and CXR as screening modalities, the NLST and PLCO provide detailed data, which allow in-depth analyses on the natural history and detectability of lung cancer. In this study, we estimate the MPST by gender, histology and stage, and CT and CXR sensitivity for lung cancer by histology and stage using the MISCAN-Lung model, based on data from the Surveillance, Epidemiology, and End Results (SEER) Program and individual-level data from the NLST and PLCO.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Materials and Methods

Data

NLST. The NLST was a randomized controlled screening trial, which compared lung cancer screening with low-dose CT to CXR (10). Fifty-three thousand four hundred fifty-four current or former smokers (who had quit within the previous 15 years) ages 55 to 74 years with a smoking history of at least 30 pack-years were randomized to three annual screenings with CT or CXR. The NLST showed a relative reduction in lung cancer mortality of 20% by screening with CT compared with CXR, after six years of follow-up (3). NLST data were available on the individual level.

PLCO. The PLCO was a randomized controlled screening trial which investigated screening for prostate, lung, colorectal, and ovarian cancer (11). The lung component of the trial randomized 154,901 participants ages 55 to 74 years to either receive four annual CXR screenings or usual care (i.e., no screening). The data from the PLCO control arm provide information on the natural history of lung cancer when screening does not occur. A combination of detailed data from screened and nonscreened populations is essential to accurately assess the lead-time achieved by screening and the potential for overdiagnosis. The PLCO had no eligibility criteria with regard to smoking history; however, participants who had never smoked and were randomized after April 1995 were not invited to the fourth screening round (2). The PLCO did not show a significant reduction in lung cancer mortality by screening with CXR compared with usual care after 13 years of follow-up (2). Data from the lung component of the PLCO were available on the individual level.

SEER. SEER is a source for cancer statistics from various U.S. states, providing information on the incidence of lung cancer in the absence of screening. Data on lung cancer incidence by 5-year age groups for ages 25 to 84, stage, histology, and gender were extracted from the SEER-17 database for years 2004 to 2008 (12).

MISCAN-Lung

The MISCAN-Lung model used in this analysis was developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) and is an extension of the model used to evaluate the impact of tobacco control on U.S. lung cancer mortality (13). The model was used to simulate NLST and PLCO, using individual-level data on smoking behavior, for six and 13 years of follow-up, respectively (14). The SEER-17 population was simulated for years 2004 to 2008, using the National Cancer Institute's Smoking History Generator to generate smoking behavior (15). These data were used to modify the population parameters to reflect the populations of the NLST and PLCO trials and SEER-17.

The calibration targets for NLST, PLCO, and SEER-17 have been described previously and can be found in the Supplementary Material (14). All model parameters were calibrated simultaneously using the Nelder-Mead optimization algorithm (16). The MISCAN-Lung model was first calibrated to the NLST and then validated on the NLST-eligible individuals in the PLCO, as demonstrated in Fig. 7 in Meza and colleagues (14). However, additional calibration was required to adequately replicate the outcomes in never smokers and light smokers in the PLCO (14). The recent analyses of the CISNET-Lung working group incorporated the version of the MISCAN-Lung model described in this investigation (4, 14, 17).

Lung carcinogenesis

Lung carcinogenesis is modeled using the two-stage clonal expansion model (TSCE) as described by Heidenreich, in contrast to an earlier version of MISCAN-Lung, which implemented an approximation of this model (13, 18, 19). The TSCE estimates a person's risk of lung cancer, as a function of age and smoking history. The TSCE parameters were estimated by Meza, using data from the Nurses' Health Study and the Health Professionals Follow-up Study (19). However, the gender-specific parameters for malignant transformation were recalibrated to NLST, PLCO, and SEER-17 (14). In SEER-17 simulations, we accounted for the lower age-adjusted incidence in the SEER-17 states compared with the U.S. population (6.1% for women and 10.9% for men; refs. 20, 21).

Histologies

The model distinguishes four histologies (compared with three histologies in the previous version of MISCAN-Lung), based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3): adenocarcinoma, squamous cell carcinoma, other non–small cell carcinoma, and small cell carcinoma (22). An overview of the histology classifications by ICD-O-3 codes is given in the Supplementary Material.

Large cell carcinomas were included in the adenocarcinoma histology as "a significant proportion of large cell carcinoma has immunohistochemical, cytogenetic, mutational, and gene expression profiles that overlap with adenocarcinomas, which may reflect a common cell of origin" (23).

Recent guidelines reclassify bronchioalveolar carcinoma (BAC) into adenocarcinoma *in situ* (AIS), invasive adenocarcinoma, and minimally invasive adenocarcinoma (MIA; ref. 24). Therefore, BACs were included in the adenocarcinoma histology. One hundred forty-seven cancers were denoted as BACs in NLST, 45 stage IB or higher, and thus invasive adenocarcinoma. Of 102 persons with stage IA BACs (79.41% screen-detected), 101 received treatment and eight died from lung cancer. One hundred eighty-eight cancers were denoted as BACs in PLCO, 109 stage 1B or higher. Of 79 persons with stage IA BACs (24.05% screen-detected), 75 were known to have received treatment and 11 died from lung cancer.

Most stage IA BACs found in PLCO were detected clinically, which suggests most of these cases were invasive adenocarcinoma. Although most IA BACs in NLST were detected by screening, it is unknown what proportion may have been AIS or MIA, as only a subset of BACs in NLST were reanalyzed using the recent guidelines (25). Therefore, it is unclear which stage IA BACs in NLST and PLCO would have been classified as AIS or MIA, which precludes these categories from separate analysis.

Stage progression

Cancers are assumed to progress sequentially from less advanced to more advanced preclinical stages, as shown in Supplementary Fig. 1S. Six stages are distinguished (compared with two stages in the previous version of MISCAN-Lung), based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition: IA, IB, II, IIIA, IIIB, and IV (26). Stages IA1

and IA2 were not considered in this edition. Stage IA was not divided into stages IA1 and IA2 because data for these stages were available for NLST, but not for PLCO or the extracted SEER-17 data.

The probability that a cancer progresses to a more advanced preclinical stage or is diagnosed clinically (e.g., diagnosed due to symptoms) is detailed by histology and stage in Supplementary Table 1S. Only lung cancers with known stages were taken into account, with the exception of small cell carcinoma in PLCO. Small cell carcinomas in PLCO were distinguished as either limited or extensive instead of stages based on the AJCC criteria. Therefore, we did not distinguish small cell carcinoma by stage for PLCO.

Mean preclinical sojourn times

The preclinical duration (in the absence of screening) of each stage (by histology) is assumed to follow a Weibull distribution, for which the mean and shape parameters are estimated. The MPST for each stage and histology is modeled as a multiplicative function of stage, histology, and gender-specific duration parameters. The duration parameters for men and other non–small cell carcinoma serve as the baseline durations. For example, the mean duration of stage IA adenocarcinoma for men is modeled as

$$Duration\_AD\_IA\_M = DurationAD * DurationIA,$$

whereas the mean duration for women is modeled as

$$Duration\_AD\_IA\_F = DurationAD * DurationIA * DurationWomenAD,$$

where *DurationWomenAD* measures the relative difference in MPST between women and men for adenocarcinoma.

The shape parameters and the dependence between the durations of the preclinical states within an individual were assumed to be similar for all stages, histologies, and both genders; the values of these parameters are shown in Supplementary Table 2S.

Sensitivities

The probability that a lung cancer is detected by screening (including additional diagnostic evaluations) is modeled as a mathematical function of the screening modality, histology, stage, and screening round. Screening round was included as a dichotomous predictor variable in this model to account for the fact that participants with abnormalities detected in the third round of NLST may have been evaluated more aggressively compared with previous rounds (27). These parameters were assumed not to differ by histology, stage, or gender. The sensitivity of each screening modality is restricted to be higher for more advanced stages, i.e., the CT sensitivity for stage IB adenocarcinoma is higher than stage IA adenocarcinoma. This is accomplished by modeling the sensitivity indices as additive functions of model parameters. For example, the stage-specific CT sensitivity index for stage IB adenocarcinoma is modeled as the sum of the parameters for the CT sensitivity of stages IB adenocarcinoma and IA adenocarcinoma:

$$SensADIB\_CT = Sensitivity\_AD\_IB\_CT + Sensitivity\_AD\_IA\_CT.$$

The sensitivity is further restricted between 0 and 1 by incorporating the stage-specific sensitivity parameters in inverse-logit (expit) functions of the sensitivity indices. Thus, the CT sensitivity for stage IB adenocarcinoma in round 2 is modeled as

$$\frac{\exp(SensADIB\_CT)}{1 + \exp(SensADIB\_CT)}.$$

Table 1. Sensitivity estimates by screening modality

	AD	SQ	SM	OTH
CXR				
IA	16.91%	9.72%	2.51%	6.27%
IB	27.13%	28.90%	4.25%	7.57%
II	27.26%	30.02%	6.64%	7.57%
IIIA	48.11%	46.31%	14.74%	29.78%
IIIB	49.29%	47.96%	53.18%	34.40%
IV	96.31%	78.62%	97.31%	36.94%
CT				
IA	56.63%	30.95%	8.83%	20.78%
IB	64.12%	38.05%	10.28%	24.75%
II	64.48%	39.19%	11.19%	24.78%
IIIA	75.93%	69.67%	41.58%	60.40%
IIIB	80.21%	79.39%	87.06%	68.27%
IV	98.88%	97.66%	99.35%	95.67%

Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

Assessment of statistical uncertainty

Profile likelihood confidence intervals were calculated using an approach similar to Wever's (28).

Results

The sensitivity estimates, shown in Table 1 (for the four screening rounds of the PLCO and the first two rounds of the NLST), indicate that CT sensitivity ranges from 8.83% to 99.35% and CXR sensitivity from 2.51% to 97.31%. The profile likelihood confidence intervals suggest that the plausible range of the CT sensitivities ranges from 2.32% lower to 4.06% higher compared with the sensitivities shown in Table 1 (e.g., the estimated CT sensitivity of stage IA adenocarcinoma is 56.63%, but may vary between 54.31% and 60.69%). The profile likelihood confidence intervals suggest that the plausible range of the CXR sensitivities ranges from 0.48% lower to 1.79% higher compared with the sensitivities shown in Table 1 (e.g., the estimated CXR sensitivity of stage IA adenocarcinoma is 16.91%, but may vary between 16.43% and 18.70%). CT and CXR sensitivity varies greatly by histology, particularly for the early stages. For example, CT sensitivity for stage IA squamous cell carcinoma is 30.95% compared with 20.78% for stage IA other non–small cell carcinoma, whereas CXR sensitivity for stage IA adenocarcinoma is 16.91% compared with 2.51% for stage IA small cell carcinoma. However, CT is more sensitive for each stage and histology compared with CXR. This is especially notable for stage IA, where CT sensitivity is more than 3-fold higher compared with CXR, for all histologies. Furthermore, even at advanced stages such as IIIA and IIIB, a 23% to 34% difference in sensitivity remains. There is a notable difference in CXR sensitivity for stage IV other non–small cell carcinoma compared with other histologies, which may reflect an atypical presentation that may be difficult to detect using CXR.

The sensitivity for the third round of NLST is estimated to have been up to 14.77% and 0.10% higher for CT and CXR respectively compared with previous rounds, as shown in Supplementary Table 3S.

Table 2. MPST estimates (in years) of preclinical stages by gender[a]

	AD	SQ	SM	OTH
Men				
IA	1.82	2.16	1.25	1.96
IB	0.64	0.76	0.44	0.69
II	0.46	0.55	0.32	0.50
IIIA	0.46	0.55	0.32	0.50
IIIB	0.36	0.42	0.25	0.39
IV	0.74	0.88	0.51	0.80
Total mean preclinical duration[b]	4.48	5.32	3.09	4.84
Women				
IA	2.44	2.15	1.36	2.31
IB	0.86	0.76	0.48	0.81
II	0.62	0.55	0.34	0.59
IIIA	0.62	0.55	0.35	0.59
IIIB	0.48	0.42	0.27	0.45
IV	0.99	0.88	0.55	0.94
Total mean preclinical duration[b]	6.01	5.31	3.35	5.69

Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

[a]The MPST estimates should be interpreted as follows: the time for an adenocarcinoma cancer to progress from preclinical stage IA to preclinical stage II (or be clinically detected in stage IB) in a male is on average 2.46 (1.82 + 0.64) years, of which 1.82 years are spent in the preclinical state of stage IA and 0.64 years are spent in the preclinical state of stage IB.

[b]If discovered clinically in stage IV.

Table 2 shows the MPST by gender, histology, and stage. The MPST estimates in Table 2 should be interpreted as follows: the time for an adenocarcinoma cancer to progress from preclinical stage IA to preclinical stage II (or be clinically detected in stage IB) in a male is on average 2.46 (1.82 + 0.64) years, of which 1.82 years is spent in the preclinical state of stage IA and 0.64 years is spent in the preclinical state of stage IB. The profile likelihood confidence intervals suggest that the plausible range of the MPST estimates ranges from 1.95% shorter to 10.60% longer compared with the estimates shown in Table 2 (e.g., the estimated MPST for stage IA adenocarcinoma in men is 1.82 years, but may vary between 1.78 and 2.01 years). The total MPST estimates of lung cancer progressing through preclinical stages IA to IV range from 3.09 to 5.32 years for men and 3.35 to 6.01 years for women. Small cell carcinomas are estimated to have the shortest MPST for both genders: the MPST in the preclinical stages IA to IV was estimated to be 3.09 years for men compared with 3.35 for women. The largest difference between genders was estimated for adenocarcinoma, for which the MPST in the preclinical stages IA to IV was estimated to be 4.48 years for men compared with 6.01 years for women. In contrast, there is little difference between genders for squamous cell carcinoma. The MPST for all histologies is estimated to be the longest in stage IA followed by stage IV. The MPST ranges for stage IA are estimated to be 1.25 to 2.16 years for men and 1.36 to 2.44 years for women, depending on the histology. An overview of the estimates of the histology and gender-specific duration parameters can be found in Supplementary Table 2S.

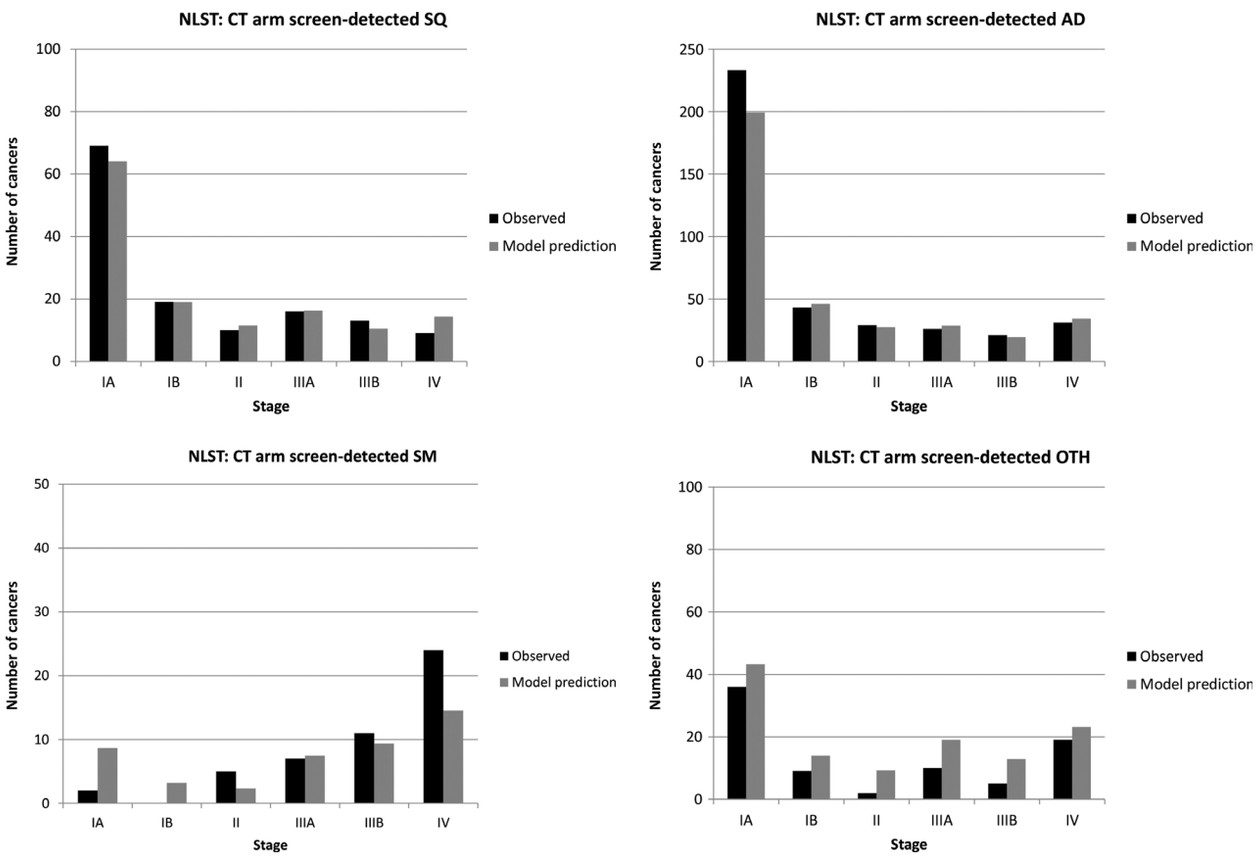

Figure 1.
NLST CT arm screen-detected lung cancers by histology and stage. Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

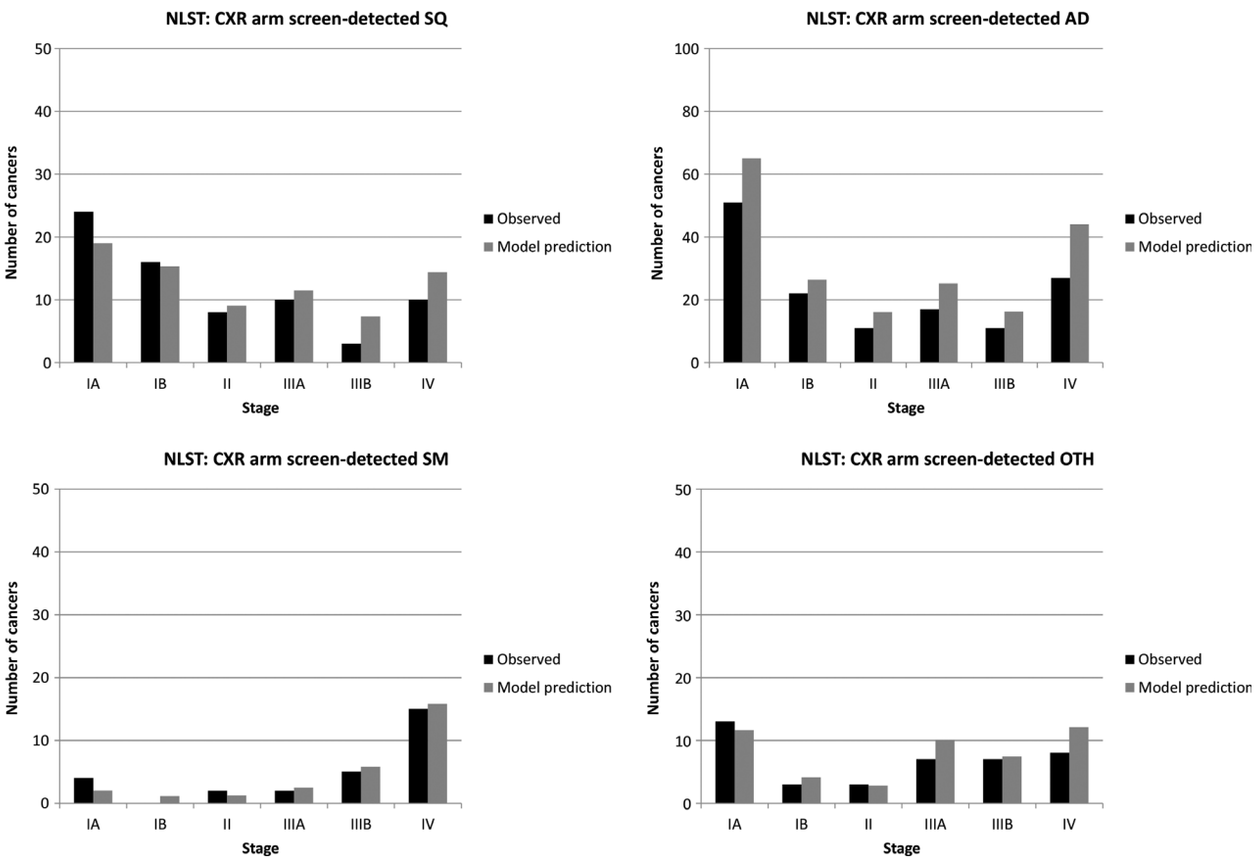

Figure 2.
NLST CXR arm screen-detected lung cancers by histology and stage. Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

Figures 1–3 show the model fit to the screen-detected lung cancers in NLST and PLCO. The results for the number of otherwise detected cancers for both trials, the PLCO control arm and SEER, are shown in Supplementary Figs. 2S–7S. The ranges of plausible values for the sensitivities and MPST estimates can be found in Supplementary Material.

Discussion

The NLST and PLCO indicated that lung cancer mortality may be reduced by screening with CT, in contrast to screening with CXR, which may be due to a difference in sensitivity between CT and CXR. However, differences in sensitivity by stage and histology cannot be easily derived from the observed data. Our model enables us to quantify the differences in CT and CXR sensitivity by histology and stage. The main differences between CT and CXR sensitivity are found for the early stages, in particular stage IA. This difference may partially explain the difference in lung cancer mortality reduction between the CT and CXR arms of NLST, as even between stages IA and IB substantial differences in survival exist: persons diagnosed in stage IA have a median survival of 59 months compared with a median survival of 42 months for persons diagnosed in stage IB as indicated in Fig. 7A of Groome and colleagues (29).

The differences between histologies indicate that the effects of screening may depend on the relative incidence of the histologies present in the screened population. The low CT sensitivity for early-stage small cell carcinoma combined with its short MPST suggests that the relative benefits of screening may be lower in populations with a large proportion of small cell carcinoma.

Our study gives some indication on the effects of varying screening intervals. Stage IA cancers could be more difficult to detect with biennial or triennial strategies, as the MPST estimates for stage IA range from 1.25 to 2.16 years for men and 1.36 to 2.44 years for women, depending on the histology. As the survival of stage IA is considerably higher compared with other stages, this suggests that annual screening could lead to higher lung cancer mortality reductions compared with biennial or triennial screening (29). This was also suggested in a recent analysis by the CISNET-Lung models, including MISCAN-Lung (4).

This study is the first to present sensitivity and MPST estimates for lung cancer by stage, histology, and gender. However, the detectability of lung cancer has been investigated earlier. Pinsky estimated an MPST of 1.8 years for subjects clinically presenting with early-stage disease (stages I–II) and an MPST of 0.85 and 1.05 years in the early and late preclinical states respectively, for subjects clinically presenting with late-stage disease (stages III–IV;

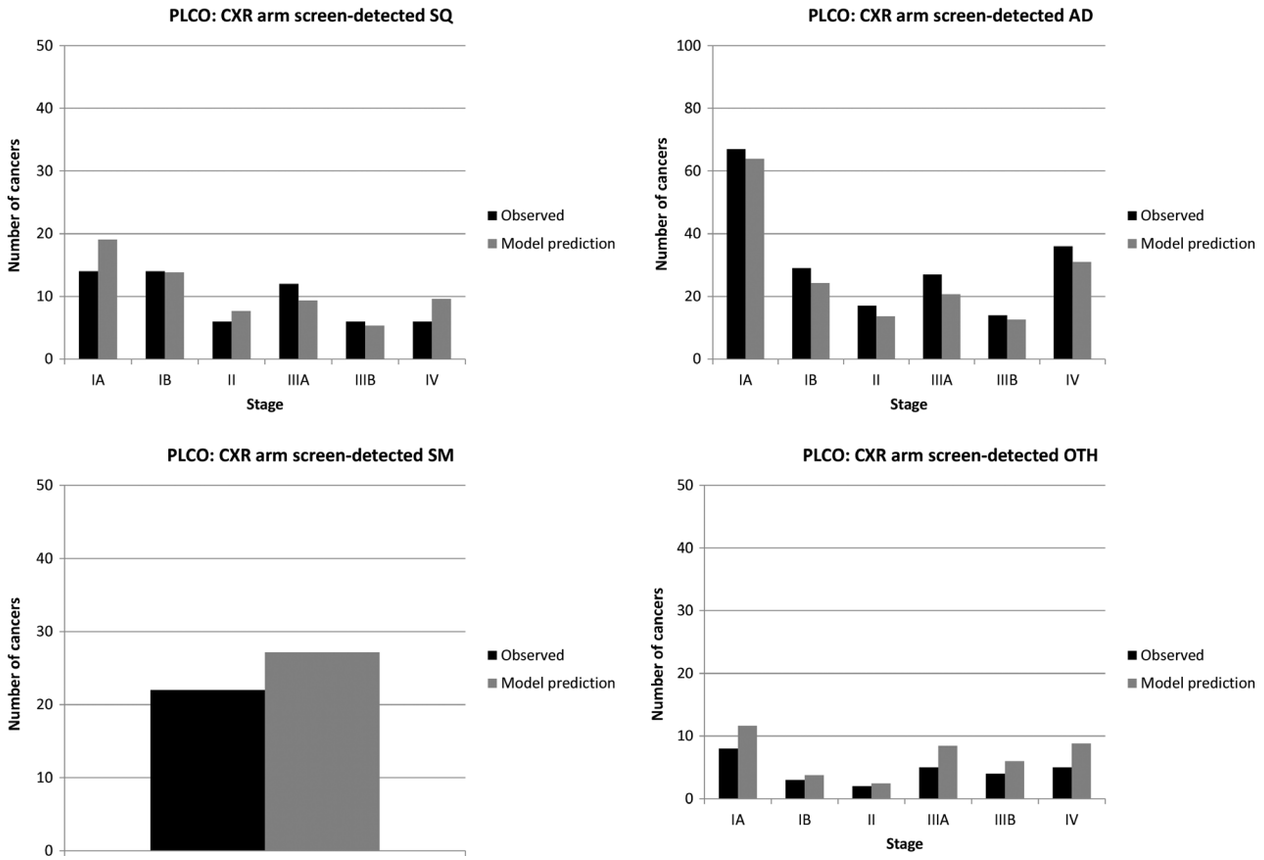

Figure 3.
PLCO CXR arm screen-detected lung cancers by histology and stage. Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

ref. 6). CXR sensitivity estimates were 73% for early-stage cases and 93% for late-stage cases. Wu estimated an MPST of 2.24 years and a mean sensitivity of 89.4% for CXR, using Mayo Lung Project data. Chien estimated a median sojourn time of 2.06 years and a median CT sensitivity of 97%, based on a systematic literature review (7).

Patz estimated an MPST of 3.6 years for non–small cell lung cancers (excluding BACs) with mean CT and CXR sensitivities of 83% and 33% and an MPST of 32.1 years for BACs, with mean CT and CXR sensitivities of 38% and 4%, based on NLST (9). The MPSTs for BACs are noticeably longer and the sensitivity estimates lower compared with other non–small cell lung cancers. However, these estimates are solely based on NLST, where both arms received screening. The lack of detailed data from a nonscreened population prevents an accurate assessment of the lead-time achieved by screening and the potential for overdiagnosis. As noted previously, most BACs found in NLST were screen-detected, found at an early stage and treated. This altered their natural history and may have influenced the BAC estimates. The same holds for non-BAC, non–small cell lung cancers found in NLST, but to a lesser extent, as 46.44% of them were screen-detected compared with 73.47% of BACs (9). Furthermore, some adenocarcinomas found in NLST may have originated from BACs which progressed to adenocarcinoma, which is not taken into account in their investigation. Finally, due to the statistical dependence between the MPST and the sensitivity of the screening modality, a model estimating a low sensitivity and a long MPST may provide a similar fit compared with a model estimating a high sensitivity and a short MPST (30). With higher sensitivity and shorter MPST estimates for BAC, a similar fit to NLST could have been obtained.

We estimate longer MPSTs for lung cancer compared with previous research, suggesting a greater window of opportunity for lung cancer screening. Noticeably, in contrast to previous studies, our model incorporates smoking history in the carcinogenesis process.

A limitation of our study is the uncertainty in the parameter estimates caused by the statistical dependence between the MPST and sensitivity of the screening modalities (30). However, we believe the joint fit of the natural history of lung cancer and the sensitivities of two different screening modalities on multiple trials helps limit this uncertainty. Moreover, the incorporation of data from historical registries and the detailed individual-level data of the control arm of the PLCO in the calibration provides information on the natural history of lung cancer in the absence of screening, which is essential to accurately assess the lead-time achieved by screening and potential for overdiagnosis. Another limitation is that the estimated screening sensitivities and MPSTs are largely based on NLST

and PLCO. However, these are the largest studies on lung cancer screening with CT and CXR, which makes them invaluable in investigating the natural history and detectability of lung cancer. Although differences in smoking prevalence exists between the NLST and the PLCO, the TSCE accounts for these differences in estimating a person's risk of lung cancer, through the use of individual-level data on smoking history, which allows us to adjust for differences in smoking prevalence between the two trials.

The model presented here has been used to analyze the harms and benefits of CT lung cancer screening for a 1950 birth cohort in the United States and will be used to investigate other populations (4). Another topic for future research will be to validate the model on other lung cancer screening trials such as the Dutch–Belgian Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings onderzoek; the NELSON trial), which will provide information on the generalizability of our model (31).

In conclusion, this study provides detailed information on the detectability of lung cancer by histology, stage, and gender, in contrast to previous studies which had less detailed analyses, did not incorporate smoking in their models' carcinogenesis process, and used less extensive data sources (6–9). This information will aid in the development of public health policies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by NCI.

Authors' Contributions

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Development of methodology: K. ten Haaf, J. van Rosmalen, H.J. de Koning
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Writing, review, and/or revision of the manuscript: K. ten Haaf, J. van Rosmalen, H.J. de Koning
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. ten Haaf
Study supervision: J. van Rosmalen, H.J. de Koning

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