Should Never-Smokers at Increased Risk for Lung Cancer Be Screened?

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Introduction: Lung cancer in never-smokers ranks among the 10 most common causes of death due to cancer worldwide and in the United States. However, it is unknown whether never-smokers at elevated risk for developing lung cancer may benefit from lung cancer screening.

Methods: The MIcrosimulation SCreening ANalysis (MISCAN)-Lung microsimulation model was used to assess the effects of lung cancer screening for simulated cohorts of never-smokers at different levels of relative risk (RR) for lung cancer compared with never-smokers at average risk. The benefits and harms of screening were estimated for each cohort and compared with those of a cohort of ever-smokers eligible for lung cancer screening according to the United States Preventive Services Task Force (USPSTF) criteria.

Results: The relative lung cancer mortality reduction in never-smokers was higher than the USPSTF eligible cohort (37% compared with 32%). However, the number of life-years gained per lung cancer death averted was lower (10.4 compared with 11.9) and the proportion of overdiagnosed cancers was higher (9.6% compared with 8.4%) for never-smokers compared with the USPSTF eligible cohort, as never-smokers are diagnosed at a later age. The estimated number of screens per lung cancer death averted ranged from 6162 for never-smokers at average risk to 151 for never-smokers with an RR of 35 compared with 353 for the USPSTF eligible cohort.

Conclusions: Never-smokers with RRs of 15 to 35 have similar to better trade-offs between benefits and harms compared with ever-smokers recommended for lung cancer screening by the USPSTF guidelines. For most never-smokers, lung cancer screening is not beneficial.

Key Words: Lung cancer, Screening, Never-smokers.

(*J Thorac Oncol.* 2015;10: 1285–1291)

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Disclosure: This publication was supported by Grant 5U01CA152956-04 from the National Cancer Institute as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. H.J. de Koning is the principal investigator of the Dutch–Belgian Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings onderzoek; the NELSON trial). K. ten Haaf is a researcher affiliated with the NELSON trial.

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DOI: 10.1097/JTO.0000000000000593

ISSN: 1556-0864/15/1009-1285

Although smoking is considered a main risk factor for developing lung cancer, 10% to 25% of all lung cancers occur in never-smokers.[1,2] Lung cancer in never-smokers is a significant public health problem, as it ranks among the 10 most common causes of death due to cancer worldwide and in the United States.[2–4]

The results of the National Lung Screening Trial (NLST) have indicated that lung cancer mortality can be reduced by screening ever-smokers with computed tomography (CT).[5] The United States Preventive Services Task Force (USPSTF) recently published the recommendation to implement annual lung cancer screening for ever-smokers aged 55 to 80 years who have smoked at least 30 pack-years and, if quit smoking, quit less than 15 years ago.[6] Other organizations have recommended screening using the NLST eligibility criteria or variations thereof.[7–9] To our knowledge, no organization currently recommends lung cancer screening for never-smokers.

Some lung cancer screening studies have included never-smokers, but these studies used chest radiography or were single-arm studies.[10–12] A survey on attitudes toward lung cancer screening in the United States showed that a large proportion of never-smokers were willing to consider lung cancer screening, even though few believed that they were at risk for developing lung cancer.[13]

In addition to tobacco smoking, various risk factors for developing lung cancer have been identified for ever- and never-smokers, such as environmental tobacco smoke (e.g., "second-hand smoking"), exposure to carcinogens (e.g., asbestos, radon gas, and ionizing radiation), and genetic susceptibility.[3,14–16] A number of risk models incorporate these and other risk factors to identify ever- and never-smokers at elevated levels of risk.[17–21] Recent studies have identified subpopulations within the NLST who were at a higher level of risk for developing lung cancer compared with the average population of the trial.[20,22,23] Screening was more effective for these subpopulations, which indicates that screening recommendations based on an individual's risk could lead to more effective screening programs.[20,22,23] Therefore, some researchers argue that lung cancer screening may be recommended for never-smokers, provided that they have a high risk for developing lung cancer.[24]

However, the long-term benefits and harms of implementing a lung cancer screening program for never-smokers are unknown. The USPSTF recommendations were in part based on modeling analyses, which investigated the trade-offs between the long-term benefits and harms of different screening policies for ever-smokers.[25] This study aims to investigate

the trade-offs between the benefits and harms of lung cancer screening for never-smokers at different levels of risk.

MATERIALS AND METHODS

MISCAN-Lung

The MIcrosimulation SCreening ANalysis (MISCAN)-Lung model is used in this investigation. MISCAN-Lung has been calibrated to the NLST, the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO), and data from the Surveillance, Epidemiology and End Results (SEER) Program, from which it derived information on the preclinical duration of lung cancer and CT screening effectiveness.[26,27] Lung cancer incidence and mortality in never-smokers in the PLCO were among the calibration targets of the model.[26,27] MISCAN-Lung aided in informing the USPSTF on their recommendations for lung cancer screening.[25,28]

Histologic Types

There are indications that smoking behavior affects not only a person's risk of developing lung cancer but also the histologic type that develops.[29,30] This suggests that the distribution of histological types of lung cancer in never-smokers may differ from ever-smokers. Subramanian and Govindan[16] provided an overview of the distribution of histological types of lung cancer in never-smokers across different studies. This overview was used to derive the distribution of histological types of lung cancer in never-smokers for this investigation, shown in Table 1.[16] To our knowledge, little information is available on differences in the distribution of histological types of lung cancer in never-smokers between sexes. Therefore, we assumed that the distribution of histological types of lung cancer in never-smokers did not differ by sex.

Lung Cancer Survival

It has been suggested that never-smokers may have a better response to certain treatments compared with ever-smokers, such as treatment with epidermal growth factor receptor inhibitors, which could lead to differences in survival.[31,32] Some studies suggest that never-smokers have a better survival compared with ever-smokers, whereas other studies indicate that no significant differences in survival exist.[33–36] To our knowledge, no study provides detailed data on lung cancer survival for never-smokers by stage, histology, and sex.[33–36] Therefore, survival data from SEER were used, which provides detailed information on survival by stage, histology, and sex for ever- and never-smokers combined.[37]

Lung Carcinogenesis

MISCAN-Lung uses the two-stage clonal expansion model (TSCE) to estimate a person's risk of developing lung cancer as a function of age and smoking history.[26,27,38,39] The TSCE has been used to investigate the age-specific incidence of lung cancer in never-smokers previously.[14,39,40] To assess whether MISCAN-Lung is suitable for investigating the effectiveness of lung cancer screening for never-smokers, the estimated age-group–specific mortality rates of lung cancer in never-smokers were compared with those reported by Thun et al.[41]

Considered Levels of Relative Risk

If lung cancer screening is to be considered for never-smokers, eligible individuals will need to be identified, for example, through the application of risk models. To our knowledge, the following lung cancer risk models consider never-smokers: the Spitz, PLCOm2011, PLCOm2014, and the Liverpool Lung Project (LLP) models.[17–20] The Spitz model incorporates environmental tobacco smoke exposure (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.20–2.69)) and a family history of any cancer in two or more first-degree relatives (OR, 2.00; 95% CI, 1.39–2.90).[18] Spitz et al[18] noted that the ORs of these variables closely approximated the relative risks (RRs). Thus, the Spitz model considers RRs up to 3.6. Recently, this model was extended to incorporate micronuclei in binucleated cells (BN-MN) (OR 16.72 per unit increase; 95% CI, 9.01–31.02) alongside environmental tobacco smoke exposure (OR, 1.12; 95% CI, 0.47–2.68) and a family history of cancer in two or more first-degree relatives (OR, 1.06; 95% CI, 0.47–2.43).[21] The average difference in BN-MN between cases and controls in the model's development and validation data sets was 1.78 to 1.79 units.[21] Assuming the ORs of the model variables closely approximate the RRs and an increase of 1.80 units of BN-MN compared with a never-smoker at average risk is considered, the model considers RRs up to at least 35.73 for never-smokers.

The PLCOm2011 model was the first model based on data from PLCO to provide risk estimates for never-smokers.[17] Recently, an updated version of this model (PLCOm2014) was published that incorporates five risk factors (excluding age and race) for never-smokers: education (OR 0.92 per one of six levels change; 95% CI, 0.87–0.96), body mass index (BMI) (OR 0.97 per one unit change; 95% CI, 0.95–0.99),

TABLE 1. Histological Types Considered in MISCAN-Lung

Histological Types Considered in MISCAN-Lung	Proportions Considered in Never-Smokers (Both Sexes)	Proportions Considered in Ever-Smokers (Men)	Proportions Considered in Ever-Smokers (Women)
Adenocarcinoma/large cell carcinoma/ bronchioloalveolar carcinoma	66.68%	41.01%	50.33%
Squamous cell carcinoma	13.68%	25.22%	15.78%
Small-cell carcinoma	2.53%	13.75%	13.26%
Other non–small-cell carcinoma	17.12%	20.02%	20.63%

MISCAN, Microsimulation Screening Analysis model.