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

Kevin ten Haaf, MSc, and Harry J. de Koning, MD, PhD

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.

chronic obstructive pulmonary disease (OR, 1.41; 95% CI, 1.15–1.73), a personal history of cancer (OR, 1.62; 95% CI, 1.22–2.16), and a family history of lung cancer (OR, 1.80; 95% CI, 1.48–2.18).[20] The calculator provided by the authors was used to verify that the ORs closely approximate the RRs (available at http://www.brocku.ca/lung-cancer-risk-calculator). A BMI of 18 is the lowest for which the model is valid and assuming the base BMI and education levels are similar to those in the PLCOm2012 model (a BMI of 27 and "some college education"), implies that the PLCOm2014 model considers RRs up to 6.98 (disregarding age and race).[20,23]

The LLP model incorporates four risk factors for never-smokers: a history of pneumonia (OR, 1.83; 95% CI, 1.26–2.64), asbestos exposure (OR, 1.89; 95% CI, 1.35–2.62), a history of cancer (OR, 1.96; 95% CI, 1.22–3.14), and a family history of lung cancer (OR, 2.02 for age of onset <60; 95% CI, 1.18–3.45; and 1.18 for age of onset ≥60; 95% CI, 0.79–1.76).[19] The model was replicated in R software (version 3.0.1) and analyses indicate that the ORs of the risk factors closely approximate the RRs. Thus, the LLP model considers RRs up to 13.69.

Therefore, cohorts of never-smokers with the following levels of RR will be simulated: 1, 2, 5, 10, 15, 20, and 35. For cohorts with RRs higher than 1, the hazard function of the TSCE at each age was multiplied by the considered level of RR.[25] In addition, a "USPSTF eligible" cohort is simulated composed of individuals who would be eligible for at least one screening at some point in their life according to the USPSTF recommendations. The Smoking History Generator developed by the National Cancer Institute was used to generate the probability of death from causes other than lung cancer by smoking behavior (including never smoking).[42–44]

Considered Screening Programs, Benefits, and Harms

The investigated cohorts are assumed to be born in 1950 and followed from ages 45 to 90 years, similar to de Koning et al.[25] To allow comparison with the screening policy recommended by the USPSTF, never-smokers are assumed to be screened annually from ages 55 to 80 years with a perfect adherence to screening. The investigated benefits and harms of lung cancer screening include the relative reduction in lung cancer mortality, the number of life-years gained, and overdiagnosis.

RESULTS

The age-group–specific lung cancer mortality rates for never-smoking men and women estimated by MISCAN-Lung were compared with those reported by Thun et al[41] (Table S13 in their report), in Figure 1*A* and *B*, respectively. Overall, the model reproduced the reported

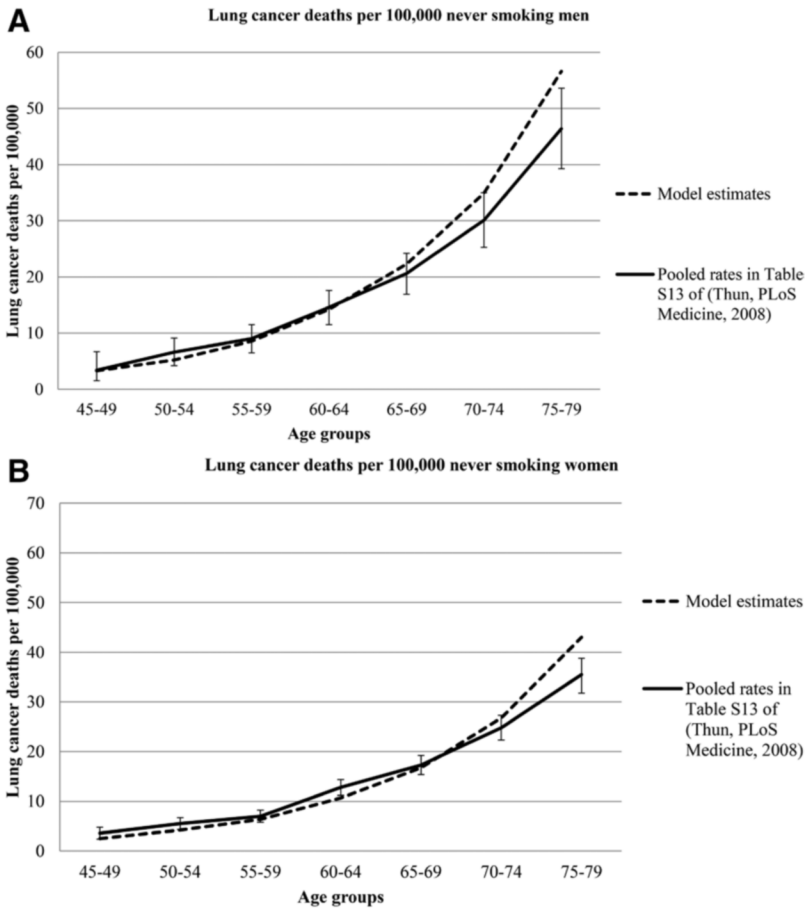

FIGURE 1. *A,* Observed and estimated lung cancer death rates in never-smoking men. Adapted from Thun et al.[41] Error bars denote 95% confidence intervals for the incidence rate difference. *B,* Observed and estimated lung cancer death rates in never-smoking women. Adapted from Thun et al.[41] Error bars denote 95% confidence intervals for the incidence rate difference.

age-group–specific lung cancer mortality rates well for both sexes but somewhat overestimated the lung cancer mortality rate for ages 75 to 79 years.

Table 2 shows the benefits of lung cancer screening for the investigated cohorts. The proportion of lung cancers detected at an early stage was higher for never-smokers compared with the USPSTF eligible cohort (65.8–65.9% of all cases compared with 59.4%). This may be a result of the higher proportion of adenocarcinomas in never-smokers (see Table 1), which have a longer preclinical sojourn time and are more likely to be detected at an early stage by CT screening compared with other histologies.[26] As a result of the larger proportion of lung cancers detected at an early stage, the relative reduction in lung cancer mortality was higher for never-smokers compared with the USPSTF eligible cohort: 37.0% to 37.3% compared with 32.7%. However, the number of lung cancer deaths averted (per 100,000) was lower for most cohorts of never-smokers, ranging from 354 deaths averted for never-smokers at average risk to 12,509 for never-smokers with an RR of 35 compared with 4305 for the USPSTF eligible cohort. The same holds for the number of life-years gained (per 100,000), which ranged from 3669 for never-smokers at average risk to 129,509 for never-smokers with an RR of 35 compared with 51,035 for the USPSTF eligible cohort.

The number of lung cancer deaths averted and life-years gained for never-smokers with an RR of 15 were higher compared with the USPSTF cohort. However, because of the high number of screens, the number of screens per life-year gained and the number of screens per lung cancer death averted were still higher compared with the USPSTF cohort. However, screening never-smokers with an RR of 20 leads to a slightly lower number of screens per life-year gained and a much lower number of screens per lung cancer death averted compared with the USPSTF cohort.

Table 3 shows the harms of lung cancer screening for the investigated cohorts. The number of screens (per 100,000) was much greater for the USPSTF eligible and never-smoker cohorts compared with the 1950 cohort examined in de Koning et al,[25] as in the latter cohort only 19.3% of the cohort received at least one screen. The number of screens was higher for the never-smoker cohorts compared with the USPSTF eligible cohort: approximately 1.8 to 2.1 million screens compared with 1.5 million screens. This is because of two reasons: first, never-smokers live longer compared with ever-smokers and will be able to attend more screenings during their lifetime.[43,45] Second, the USPSTF criteria indicate that ever-smokers may not be eligible for screening at the earliest starting age, as some current, continuing smokers may not reach the minimum number of pack-years at age 55

TABLE 2. Benefits of Screening

Scenario	Lung Cancers Detected at an Early Stage (Stage I–II) (%)	Lung Cancer Mortality Reduction (%)	Absolute Number of Lung Cancer Deaths Averted per 100,000	Life-Years Gained per 100,000	Life-Years Gained per Lung Cancer Death Averted	Screens per Life-Year Gained	Screens per Lung Cancer Death Averted
USPSTF (ever eligible only)	59.4	32.7	4,305	51,035	11.9	30	353
Never-smokers at average risk	65.8	37.1	354	3,669	10.4	594	6,162
Never-smokers at two times average risk	65.9	37.0	706	7,332	10.4	296	3,075
Never-smokers at five times average risk	65.8	37.0	1,764	18,359	10.4	117	1,216
Never-smokers at 10 times average risk	65.8	37.1	3,541	36,809	10.4	57	593
Never-smokers at 15 times average risk	65.8	37.1	5,322	55,247	10.4	37	387
Never-smokers at 20 times average risk	65.8	37.1	7,118	73,892	10.4	27	283
Never-smokers at 35 times average risk	65.9	37.3	12,509	129,786	10.4	15	151

USPSTF, United States Preventive Services Task Force.

TABLE 3. Harms of Screening

Scenario	Screens per 100,000	CT Examinations per 100,000 (Includes Screenings)	Average Screening Examinations per Person Screened	Percentage of Lung Cancers Overdiagnosed	Percentage of Screen-Detected Lung Cancers Overdiagnosed
USPSTF (ever eligible only)	1,520,632	1,776,046	16.2	4.6	8.4
Never-smokers at average risk	2,179,173	2,544,605	22.5	5.2	9.5
Never-smokers at two times average risk	2,170,544	2,534,532	22.5	5.2	9.6
Never-smokers at five times average risk	2,144,601	2,504,249	22.2	5.3	9.6
Never-smokers at 10 times average risk	2,101,248	2,453,645	21.9	5.3	9.6
Never-smokers at 15 times average risk	2,057,745	2,402,865	21.5	5.3	9.6
Never-smokers at 20 times average risk	2,014,118	2,351,940	21.1	5.3	9.6
Never-smokers at 35 times average risk	1,882,721	2,198,562	19.9	5.3	9.6

USPSTF, United States Preventive Services Task Force.

but at a later age. In addition, eligible former smokers may not complete the full screening program because of becoming ineligible by reaching the maximum years since cessation. As a result, the average number of screening examinations per person screened was higher for the cohorts of never-smokers compared with the USPSTF eligible cohort (20–22 compared with 16). As the never-smoker cohorts receive a higher number of screening examinations and are diagnosed at a later age (when no screening occurs), the proportion of overdiagnosis was higher compared with the USPSTF eligible cohort (9.5–9.6% of all screen-detected cases compared with 8.4%).

DISCUSSION

Suggestions to recommend lung cancer screening based on an individual's risk and the growing awareness of lung cancer in never-smokers have raised the question of whether never-smokers at high risk for lung cancer should be screened.[2–4,12,14,20,23,30,33,35,41,46] Our study is the first to provide indications whether never-smokers may benefit from lung cancer screening through quantifying the benefits and harms of screening never-smokers at different levels of risk.

Screening never-smokers at average risk or an RR of 2 compared with average risk has unfavorable trade-offs between benefits and harms, requiring 3000 to 6000 screens to prevent one death. However, the trade-off for never-smokers with an RR of 5 is more favorable than breast cancer screening: 1216 screens per death averted compared with 1558 (Model E in Mandelblatt et al[47]); however, the number of screens per life-year gained is less favorable: 117 compared with 91. Never-smokers with an RR of 10 have more favorable trade-offs in deaths prevented and life-years gained per screen compared with breast cancer screening but less favorable compared with ever-smokers for whom the USPSTF recommends screening.[25,47] However, never-smokers with an RR of 15 to 35 have similar to more favorable trade-offs between the benefits and the harms compared with smokers for whom the USPSTF recommends screening.

Lung cancer screening for never-smokers may lead to a higher relative reduction in lung cancer mortality compared with screening ever-smokers. However, although the cohorts of never-smokers have a higher relative reduction in lung cancer mortality compared with the USPSTF eligible cohort, the increase in number of life-years gained is less than one would anticipate. For example, the number of lung cancer deaths averted for never-smokers with an RR of 15 was 23.62% higher compared with the USPSTF eligible cohort, whereas the number of life-years gained was only 8.25% higher (Table 2). This can be explained by the lower number of life-years gained per lung cancer death averted, which was 11.9 years for the USPSTF eligible cohort compared with 10.4 for the never-smoker cohorts. This may seem counterintuitive, as ever-smokers have a higher all-cause mortality compared with never-smokers but can be explained through the differences in the average age of lung cancer diagnosis and average age of death between these groups.[43,45] Supplementary Table 1 (in Supplemental Digital Content, http://links.lww.com/JTO/A851) shows the average age of lung cancer diagnosis (given that the cancer is diagnosed after age 45) and the average age of death (given that the person is alive at age 45 years) for the investigated cohorts. Supplementary Table 1 (in Supplemental Digital Content, http://links.lww.com/JTO/A851) indicates that persons in the USPSTF eligible cohort die younger compared with never-smokers because of the detrimental effects of smoking.[43,45] However, because of the carcinogenic effects of smoking, patients in the USPSTF eligible cohort developed lung cancer at a younger age compared with never-smokers. In addition, the high proportion of adenocarcinoma in never-smokers, which have a longer preclinical sojourn time compared with other histologies, may further contribute to the later age of diagnosis.[26]

Our investigation has some limitations. We assume that the preclinical duration of lung cancer in never-smokers is similar to that of ever-smokers, whereas there are indications that lung cancer biology may differ in never-smokers.[3] However, although the carcinogenesis process may differ in never-smokers, to our knowledge, there are no indications that differences in the preclinical duration of lung cancer exist between never- and ever-smokers.[3]

Another limitation is that the investigated levels of RR are assumed to be constant over a person's life. Although the elevation in risk may be constant over a person's life for some risk factors, such as genetic susceptibility, this may not be the case for risk factors such as asbestos or radon exposure.[3,14,16] However, the benefits and harms of screening never-smokers at specific levels of RR are more easily interpreted by assuming that the RR is constant over a person's lifetime.

Finally, although our research indicates at what level of risk for developing lung cancer never-smokers could benefit from lung cancer screening, our findings are based on model-based extrapolations. Further research is needed to accurately identify never-smokers at high risk for developing lung cancer, which would allow us to further validate our findings. However, although a number of risk factors for developing lung cancer in never-smokers have been identified, the etiology of lung cancer in never-smokers is not well understood.[3,14–16,46] Although lung cancer risk models for never-smokers exist, the performance of the majority of these models is limited.[17–19,48]

This is further demonstrated by comparing the risk of developing lung cancer for an average 67-year-old (the age between the USPSTF recommended screening ages of 55–80 years) never-smoker (by sex) for different time frames in MISCAN-Lung (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/JTO/A851) with those of the investigated risk models (Supplementary Table 3 in Supplemental Digital Content, http://links.lww.com/JTO/A851). Supplementary Table 3 (in Supplemental Digital Content, http://links.lww.com/JTO/A851) indicates that the investigated lung cancer risk models for never-smokers generally predict higher lung cancer risks compared with MISCAN-Lung. However, the age-group–specific lung cancer mortality rates for never-smoking men and women estimated by MISCAN-Lung are comparable with those reported by Thun et al[41] (Table S13 in their report). This indicates that the majority of lung cancer risk models may overestimate the risk of lung cancer for never-smokers.

Finally, the proportion of never-smokers with RRs of 15 compared with never-smokers at average risk is uncertain as information on many risk factors (and the joint distribution thereof) is scarcely available at the population level. The application of the PLCOm2014 model to the PLCO data set and the application of the LLP model for recruiting participants for the UK Lung Cancer Screening Trial (UKLS) may currently provide the best information on the expected levels of risk for never-smokers.[20,49]

The PLCOm2014 model suggests that the maximum observed risk in 65,711 never-smokers in the PLCO was 1.47% over a 6-year period.[20] A white never-smoker attaining the highest level of RR (6.98, disregarding age and race) would not reach this level of risk until age 73 years (verified using the calculator provided by the authors, available at http://www.brocku.ca/lung-cancer-risk-calculator). The theoretical maximum possible 6-year risk of lung cancer for never-smokers in the PLCOm2014 model is 3.5%; however, the necessary combination of risk factors to achieve this level of risk is expected to be rare.[20]

The LLP model was used to recruit participants for the UKLS trial, including never-smokers.[49] Only four (0.04% of 10,697) never-smokers had a high LLP risk (a risk of 5% or higher over a 5-year period) and all were aged at least 73 years.[49] Analyses using the model (replicated in R software) suggest that both men and women can only achieve this absolute level of risk at this age at the highest level of RR (13.69).

In conclusion, this study is the first to investigate the long-term benefits and harms of lung cancer screening for never-smokers. Screening never-smokers at high levels of elevated risk for developing lung cancer (RRs of 15 or higher compared with average risk) is indicated to have similar or better trade-offs between benefits and harms as the population for which the USPSTF recommends screening. However, most lung cancer risk models for never-smokers consider RRs of lower than 15 for never-smokers at elevated risk compared with never-smokers at average risk. In addition, the majority of lung cancer risk models for never-smokers may overestimate the average risk of never-smokers. Applications of lung cancer risk models to populations of never-smokers suggest that few never-smokers attain high levels of risk.[20,49] Thus, few never-smokers are expected to attain RRs of 15 compared with never-smokers at average risk. Therefore, for most never-smokers, lung cancer screening is not beneficial.

ACKNOWLEDGMENTS

We thank M.C. Tammemägi for providing useful comments with regard to the PLCOm2011 and PLCOm2014 models. We thank our colleagues from the CISNET Lung working group (in particular J. Jeon) and F. van Hees (Department of Public Health, Erasmus MC) for providing useful comments.

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