



Trends in lung cancer risk and screening eligibility affect overdiagnosis estimates



Erik F. Blom*, Kevin ten Haaf, Harry J. de Koning

Department of Public Health, Erasmus MC University Medical Center Rotterdam, Internal Postal Address Na-2401, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands

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ABSTRACT

Objectives: The degree of overdiagnosis due to lung cancer screening in the general US population remains unknown. Estimates may be influenced by the method used and by decreasing smoking trends, which reduce lung cancer risk and screening eligibility over time. Therefore, we aimed to estimate the degree of overdiagnosis due to lung cancer screening in the general US population, using three distinct methods.

Material and methods: The MISCAN-Lung model was used to project lung cancer incidence and overdiagnosis in the general US population between 2018–2040, assuming perfect adherence to the United States Preventive Task Force recommendations. MISCAN-Lung was calibrated to the NLST and PLCO trials and incorporates birth-cohort-specific smoking trends and life expectancies. We estimated overdiagnosis using the cumulative excess-incidence approach, the annual excess-incidence approach, and the microsimulation approach.

Results: Using the cumulative excess-incidence approach, 10.5 % of screen-detected cases were overdiagnosed in the 1950 birth-cohort compared to 5.9 % in the 1990 birth-cohort. Incidence peaks and drops due to screening were larger for older birth-cohorts than younger birth-cohorts. In the general US population, these differing incidence peaks and drops across birth-cohorts overlap. Therefore, annual excess-incidence would be absent between 2029–2040, suggesting no overdiagnosis occurs. Using the microsimulation approach, overdiagnosis among screen-detected cases increased from 7.1 % to 9.5 % between 2018–2040, while overdiagnosis among all lung cancer cases decreased from 3.7 % to 1.4 %.

Conclusion: Overdiagnosis studies should use appropriate methods to account for trends in background risk and screening eligibility in the general population. Estimates from randomized trials, based on the cumulative excess-incidence approach, are not generalizable to the general population. The annual excess-incidence approach does not account for trends in background risk and screening eligibility, and falsely suggests no overdiagnosis occurs in the general population. Using the microsimulation approach, overdiagnosis was limited but not nil. Overdiagnosis increased among screen-detected cases, while overdiagnosis among all cases decreased.

1. Introduction

Overdiagnosis is considered to be one of the main harms of cancer screening, and is typically defined as a screen-detected cancer that would not have become symptomatic during an individual's lifetime [1]. There are two ways overdiagnosis can happen. First, a patient with a progressive screen-detected cancer may die of other causes before their cancer would have progressed to a point at which it would cause symptoms (i.e. before clinical presentation). This becomes more likely when the chances of dying from competing causes are higher, for example when screening elderly persons [2] or those with many comorbidities. Second, some screen-detected cancers may not be progressive (i.e. indolent or regressing), and would thereby never reach a

point at which they would cause symptoms. In both cases, it is impossible to determine whether an individual screen-detected case has been overdiagnosed.

There are several methods for estimating overdiagnosis [3]. A commonly used method is the cumulative excess-incidence approach, in which the difference in cumulative incidence between a screened group and a matched control group is attributed to overdiagnosis. Several studies used this approach to estimate the degree of overdiagnosis in low-dose computed tomography screening for lung cancer. Using data from the National Lung Screening Trial, Patz et al. reported that 18.5 % of screen-detected lung cancers in the low-dose computed tomography arm were overdiagnosed at 7 years of follow-up [4]. The Danish Lung Screening Trial reported that 67.2 % of screen-detected cancers were

Abbreviations: USPSTF, United States Preventive Task Force; MISCAN-Lung, Microsimulation Screening Analysis - Lung

* Corresponding author.

E-mail addresses: e.f.blom@erasmusmc.nl (E.F. Blom), k.tenhaaf@erasmusmc.nl (K. ten Haaf), h.dekoning@erasmusmc.nl (H.J. de Koning).

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overdiagnosed at 11 years of follow-up [5]. Finally, researchers from the ITALUNG trial reported no overdiagnosis at 9 years of follow-up [6].

The variation in overdiagnosis estimates between these randomized trials has been suggested to be due to several factors, including a different number of screening rounds and differences in baseline lung cancer risk [7]. The number of screening rounds per participant would be much higher in a continuous population screening program. On the other hand, the background lung cancer risk (and screening eligibility) in the population has been shown to decrease over time, as younger birth-cohorts smoke less [8]. Finally, while all randomized trial estimates used the cumulative excess-incidence approach, this approach should not be used in a continuous screening program in the general population [9]. Using other methods may also lead to different estimates [10]. Consequently, it remains uncertain whether the published estimates of lung cancer overdiagnosis are generalizable to a continuous screening program in the general population. Therefore, we used three distinct methods to estimate the degree of lung cancer overdiagnosis in the general US population when fully implementing a continuous lung cancer screening program in 2018.

2. Material and methods

2.1. MISCAN-Lung model

Although the United States Preventive Task Force (USPSTF) has recommended lung cancer screening in the United States since 2013 [11], current uptake is limited [12]. Consequently, comprehensive data on lung cancer incidence and overdiagnosis in a continuous screening program are currently not available. Therefore, we used the Microsimulation Screening Analysis Lung (MISCAN-Lung) model to project future lung cancer incidence and overdiagnosis in the presence and absence of screening.

MISCAN-Lung uses the National Cancer Institute's Smoking History Generator [8] to generate sex and birth-cohort specific life histories, including smoking histories and non-lung cancer specific causes of death (corrected for smoking behavior). The generated smoking histories determine the chance of developing preclinical lung cancer. When preclinical lung cancer develops, it can progress to more advanced preclinical stages. At each of these stages, the preclinical cancer can be either clinically detected or screen-detected. For each individual, full life histories are generated in the presence and absence of screening. Key model parameters, such as the mean histology and sex-specific duration in each stage (i.e. the natural history), and the stage and histology-specific screening test sensitivity, have been calibrated to data from the National Lung Screening Trial and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Details of model calibration have been described in previous publications [13,14]. The model was previously used to inform the USPSTF on the lung cancer screening policy with the optimal ratio of benefits and harms [11,15].

2.2. Projecting incidence

We used MISCAN-Lung to project lung cancer incidence in the US population in the absence and presence of screening. First, we simulated histology, stage, age, and sex-specific lung cancer incidence rates for each individual birth-cohort from 1916 to 2005 (i.e. persons aged 35–99 in years 2015–2040). Thereby, we account for different smoking trends and life-expectancies in the evaluated population. Next, we used the age and sex-specific Census population projections [16] to convert the annual incidence rates for each birth-cohort to cohort-specific Census-adjusted annual incidence counts. Finally, we aggregated these Census-adjusted annual incidence counts across all cohorts, forming the Census-adjusted annual incidence count for the general US population. In the screening scenario, we assumed perfect adherence to the USPSTF recommendations between 2018–2040 (i.e. annual screening of those

aged 55–80 with a smoking history of at least 30 pack-years, that currently smoke or quit less than 15 years ago).

2.3. Estimating overdiagnosis

We used three distinct methods to estimate overdiagnosis: the cumulative excess-incidence approach, the annual excess-incidence approach, and the microsimulation approach. The cumulative excess-incidence approach subtracts the cumulative incidence in the absence of screening after a certain period of follow-up from the cumulative incidence in the presence of screening, and attributes this difference to overdiagnosis. This approach provides an unbiased estimate of overdiagnosis in a closed cohort with a limited number of screens and sufficient follow-up [3,9]. We assume that the effect of radiation exposure due to LDCT screening on lung cancer incidence was negligible [15,17]. Therefore, we used this approach to estimate overdiagnosis in several separate US birth-cohorts with a lifetime follow-up. As the number of individuals differs per birth-cohort, overdiagnosis using the cumulative excess-incidence approach was expressed as the rate of overdiagnosed cases per 100,000 persons in the cohort alive in 2015. Also, we expressed overdiagnosis as the lifetime percentage of screen-detected cases that would be overdiagnosed, calculated by dividing the rate of overdiagnosed cases by the rate of screen-detected cases. Finally, we expressed overdiagnosis as the lifetime percentage of all lung cancer cases that would be overdiagnosed, calculated by dividing the rate of overdiagnosed cases by the cumulative incidence rate in the presence of screening.

In a continuous screening program in the general population, the annual excess-incidence should be used instead of the cumulative excess-incidence [9]. The underlying principle is that in a continuous screening program in the general population, new persons will receive their first screening at the end of a chosen follow-up period, which would bias the cumulative excess-incidence approach. In each calendar year, an increased incidence due to early detection is partly compensated by a drop in incidence among individuals that are no longer eligible. In the annual excess-incidence approach, incidence in the absence of screening is therefore subtracted from incidence in the presence of screening for each calendar year, and this difference is attributed to overdiagnosis. This approach should provide an unbiased overdiagnosis estimate after waiting until screening uptake stabilizes plus the longest preclinical duration [9,18]. A recent analysis suggests that the lead time of screen-detected lung cancers in the National Lung Screening Trial can be as long as 9 years [19]. Therefore, we used the annual excess-incidence approach to estimate the Census-adjusted annual number of overdiagnosed cases between 2027 (i.e. 2018 plus 9 years of lead time) and 2040 in the general US population. Overdiagnosis was also expressed as the annual percentage of screen-detected cases that would be overdiagnosed, calculated by dividing the Census-adjusted excess-incidence count by the Census-adjusted number of screen-detected cases in each year. Finally, we expressed overdiagnosis as the annual percentage of all lung cancer cases that would be overdiagnosed, calculated by dividing the Census-adjusted excess-incidence count by the Census-adjusted overall incidence count in the presence of screening in each year.

In the microsimulation approach, we used the identical individually simulated life histories in the presence and absence of screening to determine the Census-adjusted annual number of overdiagnosed cases in the general US population between 2018–2040. The percentage of overdiagnosis among screen-detected cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted number of screen-detected cases in each year. The percentage of overdiagnosis among all cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted overall incidence count in the presence of screening in each year.

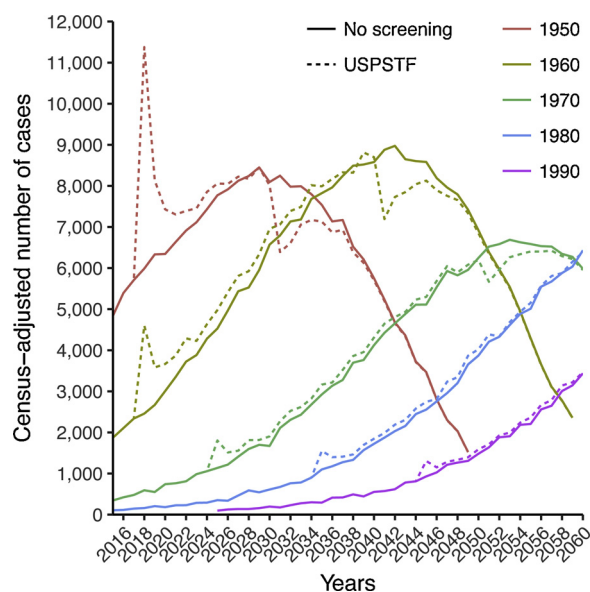


Fig. 1. Census-adjusted annual lung cancer incidence count between 2015–2060 for several US birth-cohorts when implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. Results are presented through 2060 to show the lifetime effect of screening on incidence for several birth-cohorts.

2.4. Sensitivity analyses

A previous study found that the degree of lung cancer overdiagnosis varies across histologies [4]. As the MISCAN-lung model incorporates sex and histology-specific natural history parameters, our estimates account for these differences. To provide insight into these differences, we stratified our lifetime cumulative excess-incidence estimates of the percentage of screen-detected cancers that are overdiagnosed for several separate birth-cohorts by histology and sex.

Furthermore, smoking trends in the general population are different for men and women [8]. Therefore, we also stratified our estimates of overdiagnosis in the general US population using the annual excess-incidence approach and the microsimulation approaches by sex.

3. Results

3.1. Projecting incidence

For each separate birth-cohort, the Census-adjusted annual lung cancer incidence count would increase when individuals first become eligible for screening (see Fig. 1). As individuals reach the upper age limit for screening eligibility, there would be a compensatory drop in incidence. Both these peaks and drops in the Census-adjusted annual incidence count would be higher for older birth-cohorts than for younger birth-cohorts. For example, the peak difference in the Census-adjusted annual incidence count between screening and no screening would be +5389 cases for the 1950 cohort compared to +374 cases for the 1990 cohort.

In the aggregated general US population, the full-scale (i.e. 100% adherence) introduction of lung cancer screening in 2018 would increase the Census-adjusted annual incidence count in that year from 197,348 to 309,327 (+ 56.7 %). Subsequently, incidence in the presence of screening would gradually decrease (Fig. 2A). By 2028, the Census-adjusted annual incidence count in the presence of screening (212,810 cases in 2028) would approach incidence in the absence of screening (212,050 cases in 2028). Fig. 2B shows that the projected Census-adjusted annual incidence count in the presence of screening would even be lower than in the absence of screening from 2029

onwards (up to -1.0 % in 2036).

3.2. Overdiagnosis estimate using the cumulative excess-incidence approach

As shown in Table 1, the cumulative background incidence rate in the absence of screening would be higher in older birth-cohorts than in younger birth-cohorts (1950 cohort: 6206 per 100,000; 1990 cohort: 4157 per 100,000). Also, the percentage of persons ever screened would be higher in older birth-cohorts (1950 cohort: 15.5 %; 1990 cohort: 2.9 %). Consequently, the rate of screen-detected cases and the rate of overdiagnosed cases would also be lower in younger birth-cohorts (1950 cohort: 1414 screen-detected cases and 148 overdiagnosed cases per 100,000; 1990 cohort: 287 screen-detected cases and 17 overdiagnosed cases per 100,000). With lifetime follow-up, 10.5 % of screen-detected cases would be overdiagnosed in the 1950 birth-cohort compared to 5.9 % in the 1990 birth-cohort. Finally, 2.3 % of all lung cancer cases would be overdiagnosed in the 1950 birth-cohort compared to 0.4 % of the 1990 birth-cohort.

3.3. Overdiagnosis estimate using the annual excess-incidence approach

In the general US population, the Census-adjusted annual excess-incidence count would be 2579 cases in 2027 (4.3 % of screen-detected cases and 1.2 % of all lung cancer cases). By 2028, the Census-adjusted annual excess-incidence count would have decreased to 760 cases (1.4 % of screen-detected cases and 0.4 % of all lung cancer cases). From 2029 onwards, incidence in the presence of screening would be lower than incidence in the absence of screening (see Fig. 2B). Therefore, there would be no annual excess-incidence from 2029 onwards, suggesting that no overdiagnosis would occur between 2029–2040.

3.4. Overdiagnosis using the microsimulation approach

Using the individually simulated life histories in the presence and absence of screening, the Census-adjusted annual number of overdiagnosed cases in the general US population in 2018 would be 11,429 (see Fig. 3A). After that, overdiagnosis would gradually decrease to 2851 cases in 2040. Fig. 3B shows the components necessary to express overdiagnosis as a percentage of screen-detected cases and as a percentage of all cases. Similar to the Census-adjusted annual number of overdiagnosed cases, the Census-adjusted annual number of screen-detected cases would also decrease, although at a faster rate (see Fig. 3B). Consequently, the proportion of screen-detected cases that are overdiagnosed would initially increase from 7.1 % in 2018 to 9.5 % in 2035 (see Fig. 4).

In contrast to the decreasing Census-adjusted annual number of screen-detected cases, the Census-adjusted overall annual incidence count in the general population would remain relatively stable after the initial incidence peak. Combined with the declining Census-adjusted number of overdiagnosed cases, the percentage of all lung cancer cases that are overdiagnosed would decrease from 3.7 % of all lung cancer cases in 2018 to 1.4 % in 2040 (see Fig. 4).

3.5. Sensitivity analyses

Using the cumulative excess-incidence approach, the percentage of screen-detected cancers that were overdiagnosed was higher for women (range: 5.7 % in the 1990 cohort to 11.2 % in the 1950 cohort) than for men (range: 6.1 % in the 1990 cohort to 9.8 % in the 1950 cohort) in each evaluated birth-cohort except the 1990 cohort (see Supplementary Fig. 1). This was also the case for the percentage of screen-detected adenocarcinomas that were overdiagnosed (range across women: 6.3 % in the 1990 cohort to 12.7 % in the 1950 cohort; range across men: 6.8 % in the 1990 cohort to 10.9 % in the 1950 cohort). Across histologies, screen-detected adenocarcinomas were most likely to be overdiagnosed (range: 6.6 % in the 1990 cohort to 11.9 % in the 1950 cohort).

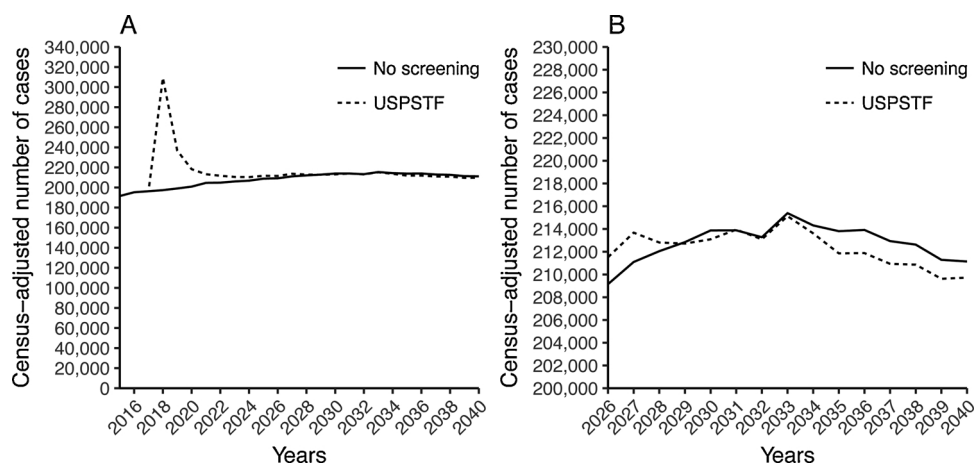


Fig. 2. A) Census-adjusted annual lung cancer incidence count in the general United States population between 2015–2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. B) Detail of panel A for years.2026–2040.

Table 1

Lung cancer incidence rates, screening eligibility, and overdiagnosis for several separate US birth-cohorts when fully implementing lung cancer screening in 2018 using the United States Preventive Task Force recommendations.

Birth-cohort	Cumulative incidence in the absence of screening ^a	Percentage of the cohort ever screened ^b	Number of screen-detected cases ^a	Cumulative incidence in the presence of screening ^a	Number of over-diagnosed cases ^{a,c}	Percentage of screen-detected cases that would be overdiagnosed ^d	Percentage of all cases that would be overdiagnosed ^e
1950	6206	15.5 %	1414	6354	148	10.5 %	2.3 %
1960	5791	13.8 %	1307	5899	108	8.2 %	1.8 %
1970	4665	7.1 %	660	4712	47	7.1 %	1.0 %
1980	4635	5.1 %	492	4666	31	6.2 %	0.7 %
1990	4157	2.9 %	287	4174	17	5.9 %	0.4 %

^a Because the absolute size of each birth-cohort is different, numbers are expressed as rates per 100,000 persons of the cohort that were alive in 2015.

^b For cohorts 1950 and 1960, it is assumed that individuals who would have been eligible before the implementation of screening in 2018 did not receive screening before 2018.

^c Calculated by subtracting the cumulative incidence in the absence of screening from the cumulative incidence in the presence of screening.

^d Calculated by dividing the rate of overdiagnosed cases by the rate of screen-detected cases.

^e Calculated by dividing the rate of overdiagnosed cases by the cumulative incidence rate in the presence of screening.

The proportion of screen-detected squamous cell carcinomas that were overdiagnosed was higher for men (range: 7.1 % in the 1990 cohort to 10.4 % in the 1950 cohort) than for women (range: 6.4 % in the 1990 cohort to 9.9 % in the 1950 cohort). The percentage of overdiagnosed screen-detected small cell lung cancers was low for both sexes (range: 1.7 % in the 1990 cohort to 2.8 % in the 1950 cohort).

Using the annual excess-incidence approach, the Census-adjusted number of overdiagnosed cases would still approach zero in 2029 in both men and women (see Supplementary Fig. 2). Using the micro-simulation approach, overdiagnosis among screen-detected cases and

all cases was more common among women than men (see Supplementary Fig. 3). However, time trends were similar to the base-case analysis.

4. Discussion

4.1. Modeling incidence

To our knowledge, we are the first to project the impact of continuous lung cancer screening on incidence and overdiagnosis for a

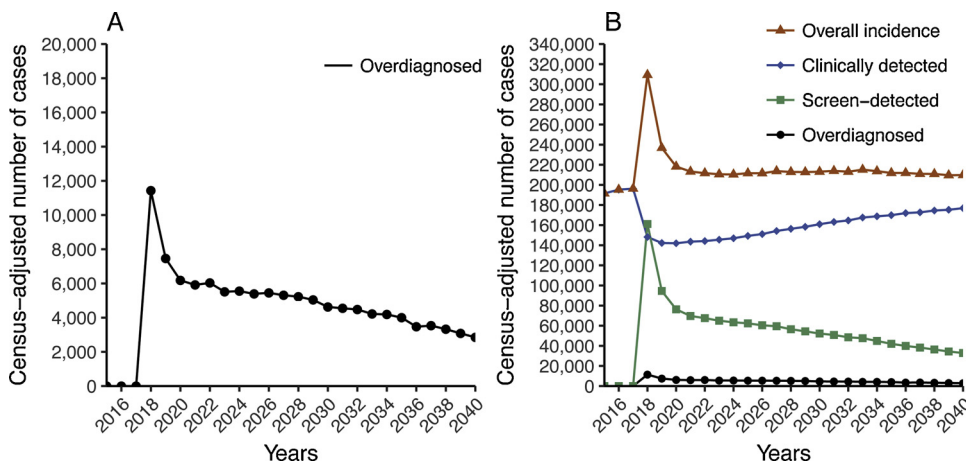


Fig. 3. A) Census-adjusted annual number of overdiagnosed lung cancer cases in the general US population between 2015–2040 when fully implementing screening using the United States Preventive Task Force recommendations in 2018. Perfect screening adherence was assumed. B) Census-adjusted annual lung cancer incidence count in the general US population between 2015–2040 when fully implementing screening using the United States Preventive Task Force recommendations in 2018, stratified by mode of detection, and the Census-adjusted annual number of overdiagnosed cases.

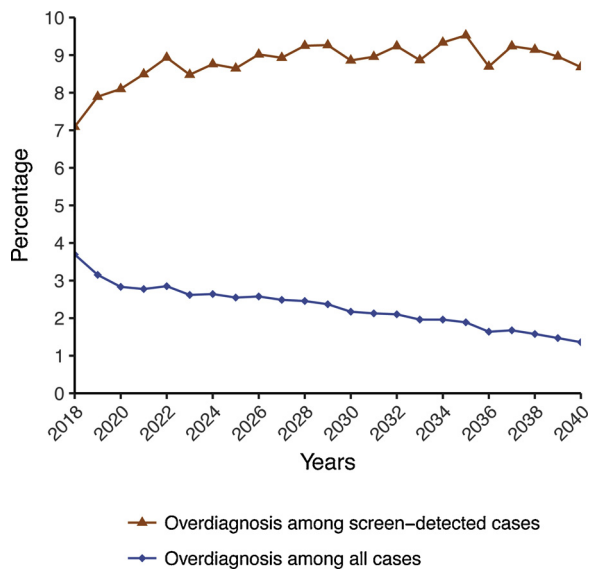


Fig. 4. Annual percentage of overdiagnosed lung cancer cases in the United States between 2018–2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. The percentage of overdiagnosis among screen-detected cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted number of screen-detected cases in each year. The percentage of overdiagnosis among all cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted overall incidence count in the presence of screening in each year.

multitude of US birth-cohorts as well as for the general US population, using three different methods. Stratified by birth-cohort, incidence would increase once individuals reach the lower age threshold for screening (55 years). This increase is due to the early detection of prevalent and incident preclinical cases. As individuals within each cohort pass the upper age threshold for screening (80 years), there would be a compensatory drop in incidence. To fully account for this compensatory drop in incidence, the follow-up after screening stops should be at least as long as the longest lead-time [3]. As we used lifetime follow-up, we fulfill this criterion. We found that the effect of screening on lung cancer incidence (i.e. both the peak and drop) would be much larger for older cohorts than for younger cohorts. This can be explained by reductions in smoking trends [8], due to which younger birth-cohorts 1) have a lower background risk of getting lung cancer, and 2) are less often eligible for screening [20,21].

In the aggregated general US population, we projected a large incidence peak upon the implementation of screening in 2018, which occurs because several cohorts would become eligible for screening in that year (i.e. cohorts 1938–1963). In most other cancer screening programs, incidence with screening remains higher than incidence without screening [22]. However, we found that as lung cancer screening in the general population stabilizes, annual incidence with screening would become lower than without screening. This happens because annual incidence in the general population consists of overlapping incidence peaks and drops from different birth-cohorts. Eventually, the larger incidence drops from older cohorts start to overlap with the smaller incidence peaks from younger birth-cohorts.

4.2. Estimating overdiagnosis

Using the cumulative excess-incidence approach, we found that overdiagnosis was much more common in older birth-cohorts than in younger birth-cohorts. These differences are also driven by declining background lung cancer risk and screening eligibility. Due to these trends, cumulative excess-incidence estimates from closed cohorts are

not generalizable to a broader population. Therefore, existing lung cancer overdiagnosis estimates from randomized controlled trials are not representative for a continuous lung cancer screening program in the general US population. In the general US population, the lack of annual excess-incidence as a result of these declining smoking trends would suggest that no overdiagnosis occurs after 2029. However, we used the microsimulation modeling approach to show that overdiagnosis would be present in the general US population in each year since the implementation of screening.

Using the microsimulation approach, the percentage of screen-detected lung cancers in the general US population that would be overdiagnosed increased between 2018–2040, while the percentage of all lung cancer cases that would be overdiagnosed decreased in the same period. The increasing percentage of overdiagnosis among screen-detected cases can be explained by the average age of the pool of screening-eligible individuals. Over time, this pool will increasingly consist of elderly individuals because fewer individuals from younger birth-cohorts become eligible for screening. As overdiagnosis is more common among elderly individuals (due to limited life expectancy), the Census-adjusted annual number of overdiagnosed cases decreases at a slower rate than the Census-adjusted annual number of screen-detected cases. Therefore, the percentage of screen-detected cases that is overdiagnosed will increase over time. In contrast, the total Census-adjusted annual incidence count will remain relatively constant over time due to growth and aging of the population. Therefore, the percentage of all lung cancer cases that is overdiagnosed will decrease. These findings confirm previous work stating that overdiagnosis estimates across different studies can only be compared when the same denominator is used (i.e. among screen-detected cases or among all cases) [23]. We add that using different denominators can lead to different conclusions regarding possible time trends in overdiagnosis.

Our sensitivity analyses show that overdiagnosis estimates differ by sex and histology. Overdiagnosis was generally most common among adenocarcinomas and among women. These findings may be explained by the preclinical duration of disease, which has been estimated to be longer for women and for adenocarcinomas. [14]. With a longer pre-clinical duration, the likelihood of overdiagnosis increases. Conversely, small cell carcinomas are known to progress quickly, which explains the lower likelihood of overdiagnosis. Among cases with squamous cell histology, overdiagnosis was more common in men than in women. This can be explained by the fact that while the preclinical duration is similar between men and women, the overall life expectancy for men is lower [14]. The small differences between men and women in the 1990 cohort can be explained by the small numbers due to the low background risk of lung cancer. Differences in population smoking trends between men and women did not affect our conclusions regarding the appropriateness of the annual excess-incidence approach and regarding time trends in overdiagnosis using the microsimulation approach.

4.3. Considerations for other screening programs

Compared to other cancer screening programs, lung cancer screening is unique because the main risk factor for lung cancer (i.e. smoking) reduces over time, which affects not only the background risk, but also screening eligibility. In most other cancer screening programs, screening eligibility is only determined by age. Nevertheless, screening participation rates can still vary over time. Also, background risk may change over time due to changes in behavioral, lifestyle, and medical factors. For example, the risk of breast cancer has been related to body mass index, reproductive behavior, and the use of hormone replacement therapy [24], all of which may change over time. An earlier theoretical study found that, if breast cancer risk and breast screening participation rates increase over time, the excess-incidence approach would overestimate overdiagnosis [25]. Indeed, the background risk of breast cancer seems to increase over time [23]. Therefore, previous studies that have applied the excess-incidence approach to a population

setting may have overestimated breast cancer overdiagnosis [26].

4.4. Strengths and limitations

A major strength of our study is the use of the MISCAN-Lung model, which allows for a comparison of identical full life histories in the absence and presence of screening. Also, our model can take smoking trends across birth-cohorts into account. Finally, microsimulation modeling can assess the effects of many different screening strategies. For example, Han et al. showed that lung cancer overdiagnosis estimates (within a fixed cohort) are sensitive to the eligibility criteria used, such as screening starting and stopping age, and different pack-years criteria [27]. Nevertheless, using microsimulation modeling to estimate overdiagnosis can have limitations. Most importantly, constructing a model implies making underlying assumptions. Also, some parameters of microsimulation models, such as the natural history, must be calibrated. This should be done with great care, as different combinations of parameters can fit the same data [28]. For MISCAN-Lung, details on calibration and validation have been published previously [13,14].

4.5. Conclusion

We conclude that it is crucial to use appropriate methods to account for trends in background cancer risk and screening eligibility when estimating overdiagnosis in the general population. Lung cancer overdiagnosis estimates from randomized trials, which are based on the cumulative excess-incidence approach in a closed cohort with a limited number of screens, are not generalizable to a screening program in the general population. Using the annual excess-incidence approach in the general US population suggests that no overdiagnosis will occur between 2029–2040. However, this estimate is biased as differences in background risk and screening eligibility across cohorts are not taken into account. Using the microsimulation method, we show that lung cancer overdiagnosis in the general US population between 2018–2040 will be limited but not nil. Due to trends in background risk and screening eligibility, overdiagnosis among screen-detected cases will increase between 2018–2040, while overdiagnosis among all cancer cases will decrease.

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HJdK, KtH and EFB are members of the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung working group (grant 1U01CA199284-01 from the National Cancer Institute). HJdK is the principal investigator of the Dutch-Belgian Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings onderzoek; the NELSON trial). KtH and EFB are researchers affiliated with the NELSON trial. HJdK and KtH received a grant from the University of Zurich to assess the cost-effectiveness of CT lung cancer screening in Switzerland. HJdK and KtH were involved in the Cancer Care Ontario Health Technology Assessment Study for CT Lung Cancer Screening in Canada. KtH is involved in the Selection of Eligible People for Lung Cancer Screening using Electronic Primary Care DaTa (SELECT) study. KtH was an invited speaker at the 17th, 19th, and 20th World Conferences on Lung Cancer, as well as the 5th Russian Society of Clinical Oncology conference, for which travel expenses were paid in part.

CRedit authorship contribution statement

Erik F. Blom: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Kevin ten Haaf:** Conceptualization, Methodology, Software, Supervision, Writing - review & editing. **Harry J. de Koning:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

HJdK, KtH and EFB are members of the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung working group (grant 1U01CA199284-01 from the National Cancer Institute). HJdK is the principal investigator of the Dutch-Belgian Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings onderzoek; the NELSON trial). KtH and EFB are researchers affiliated with the NELSON trial. HJdK and KtH received a grant from the University of Zurich to assess the cost-effectiveness of CT lung cancer screening in Switzerland. HJdK and KtH were involved in the Cancer Care Ontario Health Technology Assessment Study for CT Lung Cancer Screening in Canada. KtH is involved in the Selection of Eligible People for Lung Cancer Screening using Electronic Primary Care DaTa (SELECT) study. KtH was an invited speaker at the 17th, 19th, and 20th World Conferences on Lung Cancer, as well as the 5th Russian Society of Clinical Oncology conference, for which travel expenses were paid in part.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.11.024>.

References

- [1] L. Davies, D.B. Petitti, L. Martin, M. Woo, J.S. Lin, Defining, estimating, and communicating overdiagnosis in cancer screening, *Ann. Intern. Med.* 169 (1) (2018) 36–43.
- [2] K. Ten Haaf, M. Bastani, P. Cao, et al., A comparative modeling analysis of risk-based lung cancer screening strategies, *J. Natl. Cancer Inst.* (2019).
- [3] T.M. Ripping, K. Ten Haaf, A.L.M. Verbeek, N.T. van Ravesteyn, M.J.M. Broeders, Quantifying overdiagnosis in cancer screening: a systematic review to evaluate the methodology, *J. Natl. Cancer Inst.* 109 (10) (2017).
- [4] E.F. Patz Jr, P. Pinsky, C. Gatsonis, et al., Overdiagnosis in low-dose computed tomography screening for lung cancer, *JAMA Intern. Med.* 174 (2) (2014) 269–274.
- [5] B. Heleno, V. Siersma, J. Brodersen, Estimation of overdiagnosis of lung cancer in low-dose computed tomography screening, *JAMA Intern. Med.* 178 (10) (2018) 1420–1422.
- [6] E. Paci, D. Puliti, A. Lopes Pegna, et al., Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial, *Thorax* 72 (9) (2017) 825–831.
- [7] M.H. Ebell, K.W. Lin, Accounting for the harms of lung cancer screening, *JAMA Intern. Med.* 178 (10) (2018) 1422–1423.
- [8] T.R. Holford, D.T. Levy, L.A. McKay, et al., Patterns of birth cohort-specific smoking histories, 1965–2009, *Am. J. Prev. Med.* 46 (2) (2014) e31–37.
- [9] R. Gulati, E.J. Feuer, R. Etzioni, Conditions for valid empirical estimates of cancer overdiagnosis in randomized trials and population studies, *Am. J. Epidemiol.* 184 (2) (2016) 140–147.
- [10] R. Etzioni, R. Gulati, L. Mallinger, J. Mandelblatt, Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening, *Ann. Intern. Med.* 158 (11) (2013) 831–838.
- [11] V.A. Moyer, Screening for lung cancer: U.S. Preventive services task force recommendation statement, *Ann. Intern. Med.* 160 (5) (2014) 330–338.
- [12] A. Jemal, S.A. Fedewa, Lung cancer screening with low-dose computed tomography in the United States–2010 to 2015, *JAMA Oncol.* 3 (9) (2017) 1278–1281.
- [13] R. Meza, K. ten Haaf, C.Y. Kong, et al., Comparative analysis of 5 lung cancer natural history and screening models that reproduce outcomes of the NLST and PLCO trials, *Cancer* 120 (11) (2014) 1713–1724.
- [14] K. ten Haaf, J. van Rosmalen, H.J. de Koning, Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials, *Cancer Epidemiol. Biomarkers Prev.* 24 (1) (2015) 154–161.
- [15] H.J. de Koning, R. Meza, S.K. Plevritis, et al., Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force, *Ann. Intern. Med.* 160 (5) (2014) 311–320.
- [16] United States Census Bureau, 2014 National Population Projections Tables, Released December, 2014. Accessed January 1, 2018 <https://www.census.gov/data/tables/>

- 2014/demo/popproj/2014-summary-tables.html.
- [17] A. Berrington de Gonzalez, K.P. Kim, C.D. Berg, Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk, *J. Med. Screen.* 15 (3) (2008) 153–158.
- [18] R. Etzioni, R. Gulati, Recognizing the limitations of cancer overdiagnosis studies: a first step towards overcoming them, *J. Natl. Cancer Inst.* 108 (3) (2016).
- [19] K. ten Haaf, H.J. de Koning, Overdiagnosis in lung cancer screening: why modelling is essential, *J. Epidemiol. Commun. Health* 69 (11) (2015) 1035–1039.
- [20] S.D. Criss, D.F. Sheehan, L. Palazzo, C.Y. Kong, Population impact of lung cancer screening in the United States: projections from a microsimulation model, *PLoS Med.* 15 (2) (2018) e1002506.
- [21] E.F. Blom, K. ten Haaf, D.A. Arenberg, H.J. de Koning, Treatment capacity required for full-scale implementation of lung cancer screening in the United States, *Cancer* 125 (12) (2019) 2039–2048.
- [22] M. Kalager, H.O. Adami, M. Bretthauer, R.M. Tamimi, Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program, *Ann. Intern. Med.* 156 (7) (2012) 491–499.
- [23] R. de Gelder, E.A. Heijnsdijk, N.T. van Ravesteyn, J. Fracheboud, G. Draisma, H.J. de Koning, Interpreting overdiagnosis estimates in population-based mammography screening, *Epidemiol. Rev.* 33 (2011) 111–121.
- [24] W.Y. Chen, Factors That Modify Breast Cancer Risk in Women, (2019) UpToDate Website. https://www.uptodate.com/contents/factors-that-modify-breast-cancer-risk-in-women?search=Factors%20that%20modify%20breast%20cancer%20risk%20in%20women&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed June 12, 2019.
- [25] A. Seigneurin, J. Labarere, S.W. Duffy, M. Colonna, Overdiagnosis associated with breast cancer screening: a simulation study to compare lead-time adjustment methods, *Cancer Epidemiol.* 39 (6) (2015) 1128–1135.
- [26] A. Bleyer, H.G. Welch, Effect of three decades of screening mammography on breast-cancer incidence, *N. Engl. J. Med.* 367 (21) (2012) 1998–2005.
- [27] S.S. Han, K. ten Haaf, W.D. Hazelton, et al., The impact of overdiagnosis on the selection of efficient lung cancer screening strategies, *Int. J. Cancer* 140 (11) (2017) 2436–2443.
- [28] M. van Ballegooijen, C.M. Rutter, A.B. Knudsen, et al., Clarifying differences in natural history between models of screening: the case of colorectal cancer, *Med. Decis. Making* 31 (4) (2011) 540–549.