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Study concept and design: Redberg, Dhruva.
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LESS IS MORE

Estimation of Overdiagnosis of Lung Cancer in Low-Dose Computed Tomography Screening: A Secondary Analysis of the Danish Lung Cancer Screening Trial

There is uncertainty about the extent of overdiagnosis in lung cancer screening with computed tomography (CT). The National Lung Cancer Screening Trial (NLST) estimated that 18.5% of the cancers detected by CT are overdiagnosed, whereas the Italian Lung Cancer Screening Trial (ITALUNG) found no evidence of overdiagnosis. This study aimed to estimate overdiagnosis of lung cancer by screening CT in the Danish Lung Cancer Screening Trial (DLCST).

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Methods | This was an unplanned, post hoc analysis of the DLCST (NCT00496977).[1-3] In brief, 4104 current or former smokers (≥20 pack-years; former smokers must have quit <10 years before enrollment) aged 50 to 70 years were randomized (1:1) to 5 annual low-dose CT screenings or no screening. The absolute difference in the cumulative incidence of lung cancer in the screened and control groups was assessed 5 years after the last screening round. Overdiagnosis was calculated as the ratio between this difference and the cumulative incidence of screen-detected cancers.[4] Bootstrapping (4999 repetitions) was used to estimate the 95% CI. Participants and practitioners could not be masked to the intervention. Cancer status and chest CT use was documented from national registries. Patients were enrolled from October 1, 2004, to March 31, 2006, and the present analysis was performed on follow-up until April 7, 2015. Participant consent was not obtained, but the presented data are deidentified. Statistical analyses were performed using R, version 3.3.1 (R Foundation for Statistical Computing). The DLCST has been approved by the Danish Scientific Ethics Committee and the Danish Data Protection Agency.

Results | A total of 4104 current or former smokers (mean [SD] age, 57.3 [4.8] years; 55.3% male) participated in the study. Participants were comparable at baseline, adherence to screening was high, and there were few losses to follow-up.[1,2] From randomization until the end of follow-up, 416 participants (20.3%) in the control group had at least 1 off-protocol chest CT: 152 participants (7.4%; 357 scans) during the trial period and 264 participants (12.9%; 807 scans) during the follow-up period. In the screened group, 338 participants (16.5%; 955 scans) had at least 1 chest CT performed during the follow-up period.

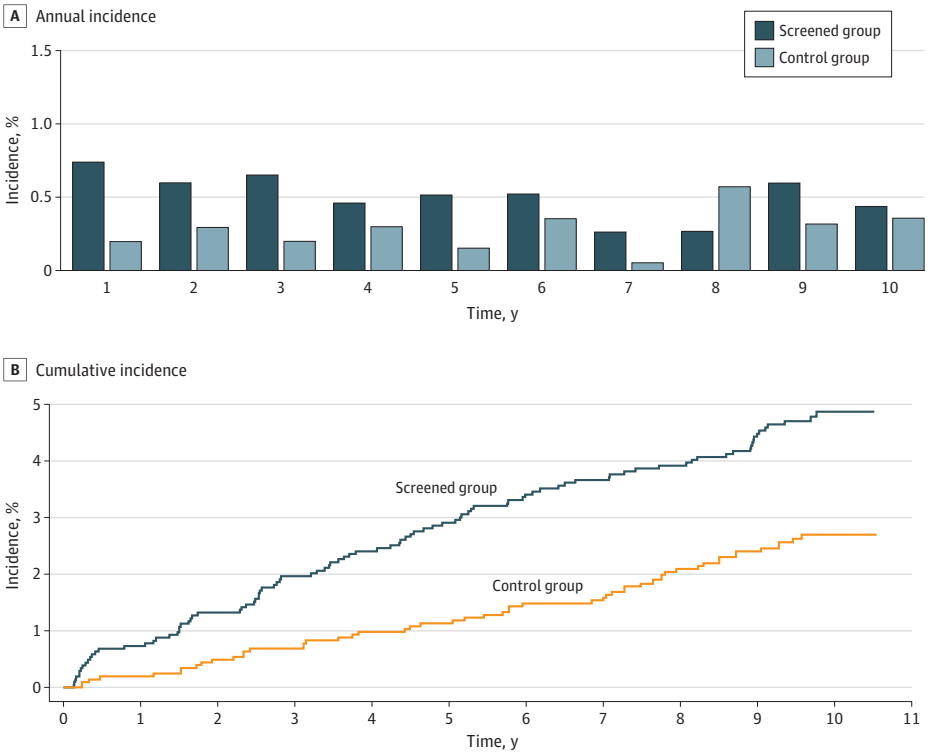
The annual lung cancer incidence rate from randomization until the end of follow-up is presented in **Figure**, A. At the end of follow-up, 96 participants were diagnosed with lung cancer in the screened group (64 cancers were detected by screening) vs 53 participants in the control group. There was a 2.10–percentage point (95% CI, 1.0-3.2 percentage points) increase in the absolute risk of lung cancer with low-dose CT (Figure, B). Overdiagnosis was estimated at 67.2% (95% CI, 37.1%-95.4%) of the cancers detected by screening CT.

Discussion | The estimate of overdiagnosis in the DLCST (67.2%) was different from the estimate in the NLST (18.5%; 95% CI, 5.4%-30.6%),[5] and there was no overdiagnosis in the ITALUNG.[6] The contamination of the control group was low: 7.4% until the end of screening and 20.3% at 5-year follow-up.

All estimates of overdiagnosis were calculated with similar methods and duration of follow-up. The most extreme estimates were found in the ITALUNG and the DLCST, which shared similar eligibility criteria and study design.[1,6] Thus, the differences among the trials' results are not adequately explained by differences in participants, interventions, or comparators.

Limitations. The main limitation of the study is the possibility of higher baseline risk of lung cancer in the screened group of

Figure. Lung Cancer Incidence in the Danish Lung Cancer Screening Trial



the DLCST. There are 2 findings that suggest this. First, in post hoc baseline comparisons, the screened group had a 3.1-percentage point higher rate of heavy smokers and a 1-percentage point lower mean ratio of forced expiratory volume in 1 second to forced vital capacity compared with the control group.[3] Second, the annual lung cancer incidence in the screened group was persistently higher. After screening stops, it takes time for the cancers that were undetectable in the last screening round to grow large enough to cause symptoms. During this time, the annual cancer incidence should be lower in the formerly screened group compared with the control group.

Conclusions | The estimate of overdiagnosis in the DLCST was larger than what has been previously reported,[5,6] but the screened group could have started with a higher baseline risk of lung cancer. However, the small differences in heavy smokers and ratio of forced expiratory volume in 1 second to forced vital capacity cannot explain the 67% overdiagnosis rate. Practice should not be changed immediately; however, it is crucial that the remaining trials report their estimates of overdiagnosis because this is a critical outcome for screening participants.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Heleno.
Critical revision of the manuscript for important intellectual content: Siersma, Brodersen.
Statistical analysis: Heleno, Siersma.
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Invited Commentary

Accounting for the Harms of Lung Cancer Screening

Overdiagnosis is an often underappreciated harm of screening. In the context of cancer screening, it refers to the detection of cancers that appear histopathologically to be invasive malignant tumors but grow so slowly that they never would have become clinically evident during a usual lifetime or occur in a person who dies of another cause before the cancer symptoms appear.[1,2] The causes of overdiagnosis include more sensitive screening tests, increasing biopsy rates, and lower thresholds for reporting abnormal-appearing cells in biopsy specimens as malignant.[3-5]

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The optimal way to determine the percentage of screen-detected cancers that are overdiagnosed would be to randomize patients to screening or no screening and then follow up these patients until death. The excess number of cancers detected in the screened group represents overdiagnosis because the counterpart malignant tumors in the unscreened group never caused symptoms. The excess cancers divided by the number of screen-detected (or alternately total) cancers provides the prevalence of overdiagnosis.[6] However, such studies do not exist, particularly for lung cancer, for which the duration of follow-up after screening is typically less than 10 years.[7-9]

An alternative is to determine the excess cancers detected in the screened group during the follow-up period. If this follow-up period exceeds the upper bound of the usual lead time of a cancer (the time from screen detection until clinical symptoms occur), this measure should provide a reasonable estimate of overdiagnosis. This approach was applied by Patz and colleagues[7] to the National Lung Screening Trial (NLST) data and produced an overdiagnosis estimate of 18%. After an initial increase in annual incidence because of the detection of prevalent cancers, incidence returned to baseline in the absence of overdiagnosis but remained elevated when it was present.

Another approach is to calculate the volume doubling time based on consecutive imaging studies and classify any cancer with a prolonged volume doubling time (eg, >600 days) as indolent and likely to have been overdiagnosed. In an Italian randomized clinical trial,[8] lung cancer overdiagnosis by this method was estimated to be 10.8%, with an additional 15% labeled as slow growing.

The rate of overdiagnosis in a low-dose computed tomography (LDCT) screening study depends on the age and health status of the population (competing causes of mortality will increase overdiagnosis in older or sicker populations), the distribution of cancer types (bronchoalveolar cancers are more likely to be overdiagnosed), the screening protocol (more frequent screening or longer duration of screening will increase the overdiagnosis rate), and whether LDCT is compared with no screening or with chest radiography (because screening chest radiographs also overdiagnosed some cancers, the latter comparison may underestimate overdiagnosis). An imbalance in the baseline risk of lung cancer between screened and unscreened groups can lead to error in either direction.

Heleno et al[9] analyzed data from the Danish Lung Screening Trial using the approach of Patz et al.[7] They found a 67% rate of overdiagnosis compared with 18% for the NLST. There are several possible explanations for this difference. First, the screened group in the Danish trial had a higher baseline risk of lung cancer than the control group. Second, participants underwent 5 rounds of screening compared with 3 in the NLST. Third, the NLST compared LDCT with chest radiography, whereas the Danish trial compared LDCT with no screening. All 3 of these factors could potentially have contributed to a higher estimate of overdiagnosis in the Danish study.

In fact, Patz and colleagues[7] used modeling to estimate overdiagnosis in the NLST population if there were 5 annual screens with 5 years of follow-up and a comparison to no screening rather than chest radiography, similar to the Danish study. They estimated a 53% overdiagnosis rate in this scenario (95% CI, 48%-56%), similar to the Danish estimate of 67% (95% CI, 37%-95%). However, they estimated a lifetime rate of overdiagnosis under these assumptions of only 12%.[7]

The US Preventive Services Task Force[10] recommends that health care professionals practice shared decision making with selected high-risk patients eligible for annual LDCT screening. Patients can make informed choices about LDCT only if practitioners fully disclose all the potential harms of screening, including the risk of overdiagnosis. It will be important for researchers to continue to refine estimates of lung cancer overdiagnosis, allowing physicians to provide more accurate information to our patients.

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