EDITORIAL

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Perhaps it is time for a change in policy on lung cancer screening

IN THIS ISSUE of the *Cleveland Clinic Journal of Medicine*, Mazzone and colleagues[1] pose the question "Lung cancer screening: Is it time for a change in policy?" and conclude that it is not. I respectfully differ: perhaps it *is* time to think seriously about using computed tomography as a screening test for lung cancer.

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Policy on screening is not always based on randomized controlled trials

In reaching their conclusion, Mazzone et al review the results of the International Early Lung Cancer Action Program (I-ELCAP, in which I was an investigator, and which found that screening was beneficial)[2] and a more recent study by Bach et al (who concluded that it may not meaningfully reduce the risk of advanced lung cancer or death from lung cancer).[3] They assert that the best measure of the usefulness of computed tomographic screening is a reduction in the lung cancer-specific mortality rate, they discuss the various biases in screening studies, and they express the hope that ongoing randomized controlled trials will settle the debate once and for all.

To this I would reply that new information has been presented about the study by Bach et al[4] that places lung cancer screening in a more favorable light. Furthermore, in many ways the current debate about lung cancer screening echoes the debate we went through about breast cancer screening, in which consensus eventually emerged that screening is beneficial even without evidence of a reduction in the mortality rate found in randomized controlled trials. In addition, I do not think that lead-time bias, length bias, or overdiagnosis bias affected the I-ELCAP findings.

NEW INFORMATION

Although the original paper by Bach et al stated that the patients in their study were "asymptomatic current or former smokers screened for lung cancer,"[3] this was incorrectly reported. In fact, some of the patients at one of the three sites in their study (the Moffitt Cancer Center) did present with symptoms suggestive of lung cancer.[4]

In this study, if only five deaths had been excluded from the analysis because the subjects were ineligible for enrollment in a screening program due to symptoms suggestive of late-stage lung cancer, the results would have shown a statistically significant benefit from screening. And in fact, at least five such deaths were included[4]; thus, their main conclusion that screening does not prevent deaths is invalid.

LESSONS FROM THE DEBATE ON BREAST CANCER SCREENING

Mazzone et al suggest that a reduction in the mortality rate must be demonstrated, preferably in a randomized controlled trial, before we can consider changing public policy on lung cancer screening. This type of evidence would surely be helpful in making that type of decision. However, when decisions about screening were made in the past, results from randomized controlled trials were not always pivotal.

This topic was recently reviewed in the context of updating the guidelines for breast

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cancer screening.[5] In 2002, congressional hearings were held after a controversy erupted when a Cochrane review of seven randomized controlled trials of mammography concluded "there is no reliable evidence that screening for breast cancer reduces mortality."[6] This conclusion was supported by the editor of *Lancet*, as well as by the screening and prevention board of the US National Cancer Institute's expert advisory board, the Physician Data Query.[7]

At the congressional hearings, the statisticians were divided in their interpretation of the evidence. However, the clinicians affirmed their support for mammography even if a reduction in the mortality rate could not clearly be demonstrated in randomized controlled trials. The clinicians clearly recognized that mammography led to early diagnosis of breast cancer and that treating it earlier rather than later has many benefits (an argument that can equally applied to lung cancer screening). Senator Barbara A. Mikulski, chairwoman of the hearings, concluded[8]:

"First of all, what we see is that the biostatisticians disagree. That is clear. And they will continue to look at data and analyze it. Clinicians, those who have the lives of patients in their hands, do not disagree . . . and recommend in the most enthusiastic, unabashed, and unqualified way that we follow the existing guidelines that have been established by the National Cancer Institute, recently reaffirmed by the Preventive Services Task Force at HHS, and have also been the longstanding recommendations of the American Cancer Society."[8]

Another issue raised at that congressional hearing, and one that has been recognized as a turning point in the mammography controversy, was why those mammography trials failed to show a benefit even though mammography detected early-stage breast cancer that was curable.[7] In a research letter published in *Lancet*,[9] we explained that two conditions need to be met for a randomized controlled trial of screening to produce meaningful results: the screening must continue long enough for the reduction in deaths to become fully manifest, and so must the follow-up (focusing on a suitably delayed time interval after the screening's initiation), as the deaths averted as a result of the early treatment associated with screening are well in the future. When these principles were applied to the data from the Malmö study, one of the randomized controlled trials of breast cancer screening that had initially been interpreted as showing no reduction in the mortality rate, that study gave evidence of a dramatic benefit.[9]

Nevertheless, those exact design errors are currently present in the National Lung Screening Trial (NLST). It is limited to three rounds of screening and short-term follow-up. Therefore, I predict that the NLST will also produce a misleading result. With few rounds of screening, the full reduction in deaths will not become fully manifest.

DID BIASES AFFECT I-ELCAP'S FINDINGS?

No one would argue that the use of survival data can produce misleading results when one compares relatively short-term survival rates to assess the effectiveness of treatment with lead time relative to treatment without lead time.

However, this was not done in the I-ELCAP. Ten-year survival was used only as a means to determine the cure rate, a very different concept. When early treatment cures the patient's lung cancer, the patient becomes free of the cancer and thus cannot die from that (case of the) cancer. Patients whose cancer is not cured die of it, unless the cancer's malignant course is interrupted by the patient's death from some other cause. The I-ELCAP used Kaplan-Meier survival, with only cancer considered as a possible cause of death, that is, conditionally on not dying from a "competing" cause. With increasing time from diagnosis, the survival rate declines until it reaches a plateau, the asymptote, representing the proportion of the cases that were cured, the cure rate. There is no lead-time bias involved in estimates of cure rates.

Screening and follow-up must continue long enough and focus on the relevant time interval to show a reduction in deaths

Cancers that are diagnosed at baseline tend to grow more slowly than do cancers of the same type in general. They also grow more slowly than do tumors that are diagnosed in repeated screenings. This fact does not introduce a length bias, but it may call for making a distinction between baseline screening and repeated screening. As for those slow-growing

cancers, the main challenge is to learn to identify them so as to avoid overtreatment.

As to whether overdiagnosis introduced a bias in the I-ELCAP survival rates, the diagnoses reported were confirmed by an expert panel of pulmonary pathologists; 95% of the surgical specimens obtained from patients with clinical stage I tumors were classified by the panel as invasive. All patients with untreated stage I disease died of lung cancer. In addition, cancers identified on repeat screening all had to demonstrate growth before they were resected.

PERHAPS IT IS TIME FOR A CHANGE

The whole topic of lung cancer screening has been quite controversial and indeed confusing. In 2004 the United States Preventive Services changed their recommendation regarding lung cancer screening from a "D" (meaning fair evidence against its usefulness) to an "I," (meaning that they "could not determine the balance between the benefits and harms of screening for lung cancer").[10] The reason for the change was based primarily on conflicting results from multiple randomized controlled trials and case-controlled studies. It is also interesting to note that this agency rates the quality of the studies that it reviews on a three-point scale: good, fair, and poor. Not a single study of lung cancer screening received a "good" rating.[11]

Looking beyond this evidence, the I-ELCAP has clearly demonstrated that lung cancer can be diagnosed early, that early lung cancer is curable, and that various screening biases have been accounted for and controlled. Therefore, it can be concluded that screening serves to save lives. In the I-ELCAP study, it was estimated that some 80% of lung cancer deaths could be averted, whereas currently in the United States, 95% of people diagnosed with lung cancer die of it.

Given the confusion to date regarding expert interpretation of available evidence and the subsequent confusion being played out in the lay press, along with the appropriate concern that the ongoing randomized controlled trials will produce misleading results, it would seem that, as with breast cancer screening, it is time to have more open discussions that include members of society beyond the scientific community to help in making decisions regarding policy. Perhaps it is time for a change. ■

Perhaps it is time to open the screening debate beyond the scientific community

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