

Lung Cancer Screening, Radiation, Risks, Benefits, and Uncertainty

George T. O'Connor, MD, MS

Hiroto Hatabu, MD, PhD

COMPUTED TOMOGRAPHY (CT) SCANNING, WHICH WAS introduced for imaging the head in 1972 and became widely available for imaging the rest of the body by the early 1980s, has revolutionized the practice of medicine and surgery. This technology, for which the Nobel Prize was awarded in 1979, has been used to diagnose and guide the management of diseases affecting every part of the body, improving quality of life and saving countless lives. Two articles in this issue of *JAMA*,^{1,2} however, point out the complexities involved in deciding whether to extend the use of CT scanning from diagnosis to screening and in determining whether the current use of CT scanning is appropriate or excessive.

As the value of CT scanning as a diagnostic tool became clear, it was natural to consider a potential role for this technology to screen for subclinical disease amenable to early intervention. The potential benefits of such screening must, of course, be weighed against the risks and costs. The risk that the ionizing radiation exposure from medical diagnostic tests will cause cancer appears to be small but not zero. Ionizing radiation causes DNA double-strand breaks that are repaired imperfectly, potentially leading to mutations and consequent cancers. An analysis of data from 15 countries has led to the estimate that from 0.6% to 3.2% of cancer diagnosed to age 75 years may be attributable to diagnostic x-rays, including CT scans, although these calculations involved assumptions subject to considerable uncertainty.³ Another risk of screening is the occurrence of false-positive findings that may lead to adverse psychological effects on patients as well as physical harm caused by diagnostic procedures undertaken to investigate the findings. Moreover, CT scans are expensive, as are the diagnostic procedures performed to evaluate abnormalities detected.

In this issue of *JAMA*, Bach and colleagues¹ report the results of their systematic review of randomized clinical trials (RCTs) and cohort studies addressing the benefits and risks of screening for early-stage lung cancer using low-dose CT (LDCT) scans. The authors focus on lung cancer-specific and all-cause mortality outcomes in RCTs, avoiding the mis-

taken inferences that can result from lead-time bias, length-biased sampling, and overdiagnosis with other outcomes and designs.⁴ Their review yielded only 3 RCTs from which valid inferences can be drawn concerning the effect of LDCT screening for lung cancer among current or former smokers aged 50 years or older. Of these 3 studies, the National Cancer Institute's National Lung Screening Trial (NLST)⁵ was by far the largest and most persuasive, driving the authors' conclusion that lung cancer mortality is reduced by LDCT screening of adults meeting the NLST entry criteria: age 55 to 74 years, current or former smokers, 30 or more pack-years, and still smoking or having done so within the past 15 years.

The good news of a mortality benefit is tempered by some of the specifics. In the NLST, the number needed to screen to prevent 1 lung cancer death was 320 persons undergoing 3 annual LDCTs. Across all studies reviewed, the average rate of detecting nodules per round of screening was 20%, and more than 90% of these nodules turned out to be benign, leading to substantial follow-up testing including invasive procedures. Combining screening and follow-up diagnostic scans, the estimated mean 3-year radiation exposure of NLST participants in the screening group was 8 mSv, which Bach et al¹ estimate would cause 1 cancer death per 2500 persons screened, although this death would likely occur many years later. The heterogeneity in nodule detection rate both among NLST sites and among the other studies reviewed by Bach et al,¹ and the inconsistent mortality results of the 2 smaller RCTs, add a measure of uncertainty to the estimated benefit that would be obtained from broad application of LDCT screening. Nevertheless, the estimates of the benefits and risks of LDCT screening for lung cancer derived from the NLST are the best information currently available.

The American College of Chest Physicians, the American Society of Clinical Oncology, and the American Thoracic Society have endorsed an evidence-based practice guideline, included as an online appendix to the article by Bach et al,¹ rec-

Author Affiliations: Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts (Dr O'Connor); and Department of Radiology and Center for Pulmonary Functional Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Dr Hatabu). Dr O'Connor is also Contributing Editor, *JAMA*.

Corresponding Author: George T. O'Connor, MD, MS, Pulmonary Center, Boston University School of Medicine, 72 E Concord St, Room R304, Boston, MA 02118 (goconnor@bu.edu).

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ommending that LDCT screening “should be offered” to persons meeting the NLST entry criteria, assuming this offer is made with counseling about risks and benefits and assuming the screening and follow-up are done at an institution with the resources for managing the findings of screening. The National Comprehensive Cancer Network has also recently issued a clinical practice guideline recommending LDCT screening for lung cancer in persons meeting NLST entry criteria as well as smokers older than 50 years with other lung cancer risk factors, including a history of chronic obstructive pulmonary disease or family history of lung cancer.⁶ These recommendations have been made with recognition that the cost-effectiveness of such screening has not been assessed and that the psychological effects on screened patients found to have a nodule⁷ are not well understood. Rigorous evaluation of these aspects of lung cancer screening—and the finding of a reasonable degree of cost-effectiveness—may be needed before the Centers for Medicare & Medicaid Services and other payers are willing to cover LDCT lung cancer screening.

Even without a new application of CT scans for lung cancer screening, the use of diagnostic CT and other advanced imaging modalities involving radiation exposure is frequent and increasing in the United States, as revealed by the report of Smith-Bindman and colleagues² in this issue of *JAMA*. In their analysis of data from 6 large health maintenance organizations (HMOs), the use of CT scans increased from 52 per 1000 enrollees in 1996 to 149 per 1000 enrollees in 2010, an average annual increase of 7.8%, although the increase appears to have flattened after 2007. During this 15-year interval, there was an approximate doubling of the mean per capita radiation dose and of the percentages of enrollees who received a high or very high dose of radiation in a given year.

This report of HMO data and another recent report in a fee-for-service population⁸ both indicate that a nontrivial number of patients in the United States receive a high (20–50 mSv) or very high (>50 mSv) annual exposure to ionizing radiation from imaging studies in a given year. However, these data are not linked to clinical outcomes and do not reveal whether the radiation risks from these imaging studies are outweighed by the health benefits provided by the diagnostic information obtained. The data also cannot address how much of this testing is driven by defensive practice styles due to concerns about malpractice. They do, however, suggest that clinicians need to consider—and discuss with their patients—radiation risks when ordering diagnostic tests, possibly taking into account the cumulative radiation exposure a patient has received in recent months or years. Furthermore, the radiation risks and financial costs of advanced diagnostic imaging clearly warrant more research, including studies using informatics infrastructures such as that used by Smith-Bindman et al,² to enhance decision support to guide the use of these technologies.

It is encouraging that advancing CT technology has permitted the reduction of ionizing radiation exposure,^{9,10} and in the

near future, it may be possible to further decrease radiation exposure by an order of magnitude by combining modern scintillation materials for x-ray detectors, iterative physical model-based reconstruction algorithms, and more personalized image-acquisition protocols. Diagnostic modalities without radiation exposure, such as magnetic resonance imaging and ultrasonography, may be able to be substituted for some CT scans. For lung cancer screening, more selective patient targeting on the basis of genotype,¹¹ gene expression profile,¹² or plasma biomarkers¹³ may in the future reduce the number needed to screen and thereby reduce risk relative to benefit.

One of the authors of this Editorial recently had an office visit with a patient in her late 50s regarding obstructive lung disease. She reported difficulty quitting smoking in part due to stress related to her sibling's recent diagnosis of lung cancer, and she asked whether there was a test available to see whether she might have lung cancer herself. After a brief discussion of some of the major findings of the NLST—including the likelihood of discovering 1 or more small nodules that would need to be followed up over time, perhaps adding to her anxiety—the patient and physician together decided to pursue an LDCT scan. This seems like a reasonable decision based on available information in 2012, but it is important to recognize, as do Bach et al¹ in the final sentence of their abstract, that “uncertainty exists.”

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