Lung Cancer Screening Overdiagnosis:

Reports of Overdiagnosis in Screening for Lung Cancer Are Grossly Exaggerated

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The National Lung Cancer Screening Trial (NLST) demonstrated a mortality reduction benefit associated with low-dose computed tomography (LDCT) screening for lung cancer. There has been considerable debate regarding the benefits and harms of LDCT lung cancer screening, including the challenges related to its practical implementation. One of the controversies regards overdiagnosis, which conceptually denotes diagnosing a cancer that, either because of its indolent, low-aggressiveness biologic behavior or because of limited life expectancy, is unlikely to result in significant morbidity during the patient's remainder lifetime. In theory, diagnosing and treating these cancers offer no measurable benefit while incurring costs and risks. Therefore, if a screening test detects a substantial number of overdiagnosed cancers, it is less likely to be effective. It has been argued that LDCT screening for lung cancer results in an unacceptably high rate of overdiagnosis. This article aims to defend the opposite stance. Overdiagnosis does exist and to a certain extent is inherent to any cancer-screening test. Nonetheless, the concept is less dualistic and more nuanced than it has been suggested. Furthermore, the average estimates of overdiagnosis in LDCT lung cancer screening based on the totality of published data are likely much lower than the highest published estimates, if a careful definition of a positive screening test reflecting our current understanding of lung cancer biology is utilized. This article presents evidence on why reports of overdiagnosis in lung cancer screening have been exaggerated.

Key Words: Lung cancer CT screening; randomized trials; overdiagnosis; cost effectiveness; risks; harms.

WHY LUNG CANCER SCREENING MATTERS? THE CLINICAL CHALLENGE

Lung cancer is the leading cause of cancer-related deaths worldwide. In the United States, it causes more deaths than the next three most common cancers combined (colon, breast, and pancreatic). It kills nearly 160,000 Americans yearly, comprising 13% of all cancer diagnosis but 27% of all cancer deaths, denoting a substantially higher lethality than most other cancers (1–4). Among American women, although breast cancer affects circa 233,000 and lung cancer 108,000 annually, lung cancer kills 72,000 versus breast cancer 40,000 (1). Cigarette smoking is the single most important causative factor in lung cancer, with approximately 90% of lung cancers attributable to smoking and an average 20-fold increase in relative risk of lung cancer in smokers versus never smokers. [The lifetime risk of developing lung cancer ranges from 0.2–1.4% in never smokers to 18.5–24.4% in "heavy" smokers (1,3,5,6)]. There are estimated 1.1 billion active smokers in the world, and about 50% of them will die from the health consequences of their smoking habit. The cumulative risk of developing lung cancer in former smokers markedly decreases over time but never reaches that of a lifetime nonsmoker (5,6).

Once diagnosed, lung cancer requires multimodality therapy that is complex, potentially morbid, and very expensive. The National Institutes of Health estimate that direct costs related to lung cancer treatment reached over $12 billion and indirect costs related to lost productivity and years of life reached over $36 billion, making it the costliest cancer to society (7). Nonetheless, in spite of all the advances in surgery, radiation therapy, and chemotherapy, the overall 5-year survival rate of lung cancer patients remains an average dismal 16.8% in the United States (<10% in the United Kingdom), in comparison to 89% for breast, 91% for melanoma, and 65% for colon and rectum. More importantly, the survival likelihood drops precipitously once the neoplasm has spread to regional lymph nodes or distant sites (eg, metastasized). Local lung cancer carries a 5-year survival of 54%, whereas it drops to 26% once it has spread to regional lymph nodes or neighboring tissues and to a dismal 4% once it has metastasized to distant sites (1,3,4,6).

These numbers demonstrate that lung cancer is a major global health care problem accounting for substantial suffering and premature deaths. To make a meaningful impact in reducing lung cancer deaths, society has to aim primarily at prevention, not just at treating manifested lung cancers. A concerted effort must involve both primary and secondary prevention strategies.

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Primary prevention relies on smoking control and cessation, and several countries have introduced smoking bans, educational programs, and heavy taxation, with varied degree of success. Secondary prevention involves detection of cancers in the preclinical phase, also called screening. Given that the statistics show that the chances of cure are only significant when lung cancer is detected at an early stage (eg, has not spread regionally or to distant sites), there is a strong conceptual argument that screening for lung cancer may allow a greater detection of early-stage cancers, and this may lead to increased long-term survival and increased rates of cure.

LUNG CANCER IS A HETEROGENEOUS DISEASE: INSIGHTS FROM CANCER BIOLOGY

When lung cancer is discussed, especially in the lay press, there is a common misconception that it is a single, well-defined entity. This could not be farther from the truth. Cancer comprises a large heterogeneous group of diseases, which are related by the presence of uncontrolled, progressive growth and spread of abnormal cells that if unchecked for a long enough period of time will ultimately lead to morbidity and may lead to death. It is known that for a cell to become cancerous, it must acquire several changes in its genome and proteome. Rarely will a single mutation suffice. Several genes that control cell cycle regulation, cell-to-cell and cell-to-matrix interactions, and angiogenesis must be altered for a single cell to become cancerous, denoting a multistep route for cancer induction, which is different for each cancer. Furthermore, the cancerous cell must evade immune surveillance to be allowed to proliferate. These interactions are complex and happen over the course of years or decades, amidst continued exposure to environmental and internal carcinogenic factors. The myriad of possible pathways and different types of cells involved accounts for the range of variation of biologic behavior, from very indolent cancers that are highly unlikely to cause clinically significant harm in one end of the spectrum to aggressive cancers that are typically lethal within months on the other, with an entire spectrum of cancers lying in between. There is no binary distinction of "indolent" versus "aggressive" cancers as those are just opposite ends of a continuum spectrum of biologic aggressiveness.

Therefore, a more accurate picture emerges of lung cancer as a set of heterogeneous but related diseases that generally develop nonlinearly over a long span of time, with wide variation of biologic resilience and aggressiveness. These concepts will be crucial when discussing overdiagnosis (8,9).

LUNG CANCER SCREENING TRIALS AND RESULTS: BENEFITS OF LUNG CANCER SCREENING

Given that lung cancer is a major global public health problem, there have been multiple research efforts to prove whether screening for lung cancer is effective. Several multi-institutional trials have taken place in the United States and Europe in the past two decades, involving chest radiography, sputum samples, and low-dose computed tomography (LDCT). The largest trial ever performed was the National Lung Screening Trial in the United States. In the NLST, 53,454 high-risk patients (based on age 55–74 years and smoking history >30 pack-years) were randomized to either LDCT or radiography and screened annually between 2002 and 2009. The trial demonstrated a 20.0% relative reduction in mortality from lung cancer in the LDCT arm, statistically significant (relative risk [RR], 0.80; 95% confidence interval [CI], 0.70–0.92, $P = .002$), after 6.5 years of follow-up. The absolute risk reduction was approximately 0.4% (17 of 1000 deaths in the chest x-ray arm vs. 13 of 1000 deaths in the LDCT arm). For each lung cancer death avoided, 320 individuals underwent LDCT screening, which compares favorably with the number needed to screen of diagnostic mammography in the age range of 50–59 years, which is 1339 (ie, number of women who need to undergo screening to avert one breast cancer–related death). Using the NLST definition of a positive screen, the sensitivity of LDCT was 93.1% and the specificity of LDCT was 76.5% (10–12).

Among those screened with LDCT after two rounds of screening, 227 of 24,102 (cumulative incidence of 0.94%) had confirmed lung cancers, of which 211 (93%) were detected by LDCT, whereas in the control x-ray arm, 122 of 23,346 (cumulative incidence of 0.52%) had confirmed lung cancers, of which 78 (64%) were detected by chest x-ray. The number of false positives, defined as a positive screening study in which further confirmatory tests fail to demonstrate the presence of lung cancer (ie, the finding that prompted the screening study to be called positive was found not to be a lung cancer), was high, varying between 95% and 98% for the LDCT arm. Because of the large number of false positives, the positive predictive value of a positive screening study is low, varying between 5.2% and 6.7%. The first two incidence screenings of the NLST (round T1 and T2) demonstrated a stage shift in comparison to the radiography arm, as most LDCT detected cancers were stage IA (47.5%), whereas most radiography detected cancers were stage III or IV (59.1%). This stage shift is the most likely reason the trial was able to demonstrate diminished lung cancer–specific mortality in the LDCT arm (13,14).

Other trials that tested the efficacy of chest radiography screening alone have failed to demonstrate a survival benefit in the screened arm, such as the National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian trial (RR, 0.98; 95% CI, 0.96–1.01) (15,16). The International Early Lung Cancer Action Project (ELCAP) trial results suggest a similar stage shift as demonstrated by the National Lung Screening Trial (NSLT), with 85%–92% of LDCT screen detected cancers found not to be associated with metastatic disease, and hence potentially curable. Smaller European trials have not replicated the NSLT results but were not sufficiently statistically powered. Several European trials are currently underway, the largest of which being the