

Lung cancer screening: history, current perspectives, and future directions

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Abstract

Lung cancer has remained the leading cause of death worldwide among all cancers. The dismal 5-year survival rate of 16% is in part due to the lack of symptoms during early stages and lack of an effective screening test until recently. Chest X-ray and sputum cytology were studied extensively as potential screening tests for lung cancer and were conclusively proven to be of no value. Subsequently, a number of studies compared computed tomography (CT) with the chest X-ray. These studies did identify lung cancer in earlier stages. However, they were not designed to prove a reduction in mortality. Later trials have focused on low-dose CT (LDCT) as a screening tool. The largest US trial – the National Lung Screening Trial (NLST) – enrolled approximately 54,000 patients and revealed a 20% reduction in mortality. While a role for LDCT in lung cancer screening has been established, the issues of high false positive rates, radiation risk, and cost effectiveness still need to be addressed. The guidelines of the international organizations that now include LDCT in lung cancer screening are reviewed. Other methods that may improve earlier detection such as positron emission tomography, autofluorescence bronchoscopy, and molecular biomarkers are also discussed.

Key words: lung cancer screening, low-dose computed tomography scan.

Introduction

Screening is the testing of an individual who is at risk for a disease, but who does not exhibit signs or symptoms of the disease. The goal of screening is to detect disease at a stage when cure is possible, and thus reduce the mortality attributable to the disease in the screened population. The history of lung cancer screening with current and promising modalities will be discussed in this article with a focus on the role of low-dose computed tomography (LDCT) scan as the lung cancer screening tool.

Before the turn of the twentieth century, lung cancer was considered an extremely rare malignancy [1]. Now, lung cancer is the leading cause of cancer death worldwide [2]. In the United States, it is the leading cause of cancer death in both men and women and accounts for 28% of all

cancer deaths [2]. The relative lack of symptoms during the early stages of lung cancer frequently results in delayed diagnosis. More than half of patients already have metastatic disease by the time of diagnosis [3]. The 5-year overall survival rate of 16% is low in comparison with 5-year survivals of 88% for breast cancer, 65% for colon cancer, and 100% for prostate cancer [4]. The 5-year survival rate for lung cancer with localized stage I disease is 52%, whereas for metastatic stage IV disease it is less than 5%, which shows that if detected early enough, lung cancer is curable. Lack of an effective screening test is one of the major reasons for this dismal survival rate for lung cancer.

Trends in incidence and mortality

The incidence of lung cancer and resulting mortality is fortunately declining in both men and women. In the United States in 2011, there were 115,060 new cases of lung cancer in men and 106,070 new cases in women. The number of deaths in 2011 caused by lung and bronchus cancers was an estimated 156,940: 84,600 in men and 71,340 in women [2]. In men, this represents a continuing decline in incidence and mortality after a peak in the 1980s. This decline is due primarily to the decreased cigarette consumption in men. Since smoking is a factor in approximately 80% of lung cancer deaths, future lung cancer mortality rates will continue to reflect smoking rates from 20 years earlier. Lung cancer incidence rates in women began declining in the late 1990s, more than a decade after the declining trend was seen in men. For the first time, a decline in US female lung cancer mortality rates was observed in 2011 [2].

Histopathology of lung cancer

The major cell types of cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter category comprising several histological subtypes, the major ones being squamous cell cancer, adenocarcinoma, and large cell cancer [5]. The cell types with the strongest association with cigarette smoking are SCLC and squamous cell lung cancer, but there is growing evidence that adenocarcinoma is also strongly associated with smoking [6]. In 1979, squamous cell lung carcinoma was significantly more common than adenocarcinoma, at a ratio of approximately 17 : 1. In the last 30 years, there has been a greater increase in adenocarcinoma relative to squamous cell cancer such that the ratio of the two cell types has become 1.4 : 1 [7].

Screening tests and biases

In 1968, Wilson and Junger established the principles of screening for the World Health Or-

ganization (WHO) [8]. The ideal screening test should pose little risk to the patient, be sensitive for detecting the disease early in its course, give few false-positive results, be acceptable to the patient, and be relatively inexpensive to the health system [8]. The search for an ideal screening test for lung cancer started in the 1960s. Early results were promising, but all the tests used had inherent biases.

The most significant of these biases were lead time, length time, and overdiagnosis bias [9]. Lead time bias occurs when a cancer is detected earlier than it would have been in the absence of screening. However, even with appropriate intervention, the natural history of the disease is not changed. As the measure of time between detection and death is lengthened, apparent survival is lengthened, suggesting a benefit. However, mortality remains unchanged. A patient with cancer would appear to live longer simply because the disease was detected earlier.

Length time bias describes an apparent improvement in survival when that improvement is actually due to selective detection of cancers with a less progressive course while missing cancers that have the most rapidly progressive course. Application of a screening tool at specified time intervals would have a higher likelihood of detecting a cancer with a more indolent course than one with a more rapid course that presents with symptoms between screenings. The result is the demonstration of an apparent improvement in survival. However, the better outcome reflects the fact that more indolent cancers are found with screening. For example, computed tomography (CT) screening is most likely to detect peripheral nodular cancers, and these are more likely to be adenocarcinoma with a more favorable outcome than small cell lung cancers that tend to be central and aggressive, and less likely to be found by periodic CT screening.

Overdiagnosis bias is an extreme form of length time bias in which indolent lung cancers are detected that would not have altered the expected survival when compared with the normal population. Were it not for screening, these lung cancers may have gone undetected. The natural history of these cancers does not need to be altered with detection and treatment as they were not destined to do harm. The patient eventually dies with cancer, but due to some other reason.

In summary, because of these biases inherent in screening, survival would be expected to appear more favorable even if earlier detection and intervention did not alter the course of disease. Mortality reduction, rather than survival improvement, is the ultimate measure of a screening tool's effectiveness and needs to be demonstrated by

performance of randomized control trials (RCTs). An RCT is the best evidence for efficacy of any intervention in medical science [10].

Screening with chest X-ray

Studies on the utility of chest x-ray (CXR) and sputum cytology in detecting asymptomatic lung cancer began in 1960 with the Northwest London Mass Radiography Service. This study randomized 55,000 male workers to receive a biannual CXR for 3 years or a baseline and end-of-study CXR only. At 0.7 and 0.8 per 1000 persons, respectively, mortality from lung cancer was not statistically significantly different between the 2 groups [11]. Subsequently, the National Cancer Institute sponsored 3 large randomized trials in the 1970s – the Memorial Sloan-Kettering study, the Johns Hopkins study, and the Mayo Lung Project. In the Memorial Sloan-Kettering and the Johns Hopkins studies, a combined total of 20,427 men were randomized to either an annual CXR alone or in combination with sputum cytology, and were followed for 5 years. No difference was noted in lung cancer incidence or mortality between the 2 groups [12–14]. The 5-year survival in these two studies was nearly 35%, considerably above the historical average at the time of 13%, but was simply the result of screen bias [13, 14]. Each of these studies demonstrated the lack of benefit from adding sputum cytology to annual CXRs, but did not address the utility of CXRs alone. In the Mayo Lung Project, 10,993 male smokers underwent a baseline screening with CXR and sputum cytology. If results were negative for cancer, the men were randomized to receive CXR and sputum cytology every 4 months or usual care, which was a recommendation for an annual CXR [15, 16]. After 6 years, there were 206 and 160 lung cancers detected in the experimental and the control groups, respectively. The lung cancer mortality rate of 3.2 per 1000 person-years in the screened group was not statistically different from the mortality of 3.0 per 1000 person-years in the control group [16].

In a Czechoslovakian study published in 1986, 6364 male smokers underwent a baseline screening with CXR and sputum cytology and were then randomized to an intervention group that received biannual CXRs and sputum cytology for 3 years or to a control group, which underwent no screening for 3 years [17]. Thereafter, all subjects had annual CXRs for 3 years. More cancers were detected in the intervention group, but there was no difference in cancer mortality between the groups [17, 18]. A Cochrane meta-analysis of the controlled trials of CXR screening found no significant advantage regarding all-cause mortality [19].

Lack of mortality reduction as shown by the above studies somewhat curtailed lung cancer

screening research until interest was renewed in the late 1990s when reexamination of the data from the Mayo Lung Project and other similar trials raised issues regarding their methods and low power [20]. Because of the concern that a positive effect of chest radiographic screening may have been missed because of the small size of the study populations in prior trials, this topic was reexamined in the recently concluded Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [3]. In this population-based study of men and women aged 55 to 74 years, 154,901 participants were randomly assigned to receive either annual CXR for 4 years or standard of care (no CXR) and were followed up for approximately 12 years. Participants in the 2 study groups were similar in terms of smoking status, sex distribution, and age. At the end of the study, the two groups demonstrated similar cumulative lung cancer incidences (20.1 vs. 19.2 per 10 000 person-years), similar cumulative lung cancer mortality ($n = 1213$ vs. $n = 1230$), and similar stage and histologic findings of detected lung cancers.

The PLCO study also included an ancillary analysis that compared annual chest radiographs with standard of care in a subset of 15,183 participants who met entry criteria for the National Lung Screening Trial (NLST) with current (more than 30-pack-year history) or previous heavy smokers (less than 15 years since cessation). Cumulative lung cancer incidence and mortality rates were similar between the two groups in this ancillary analysis, showing no benefit of chest radiographic screening in this high-risk cohort [3].

Computed tomography screening

The interest in CT as a screening tool developed when CT technology evolved and made it possible to get good images in single breath hold time with less radiation exposure. Conventional CT was not ideal for screening as radiation exposure was 7 millisieverts (mSv) and scan time was long [21]. Low-dose CT (LDCT) reduced the radiation exposure to 1.6 mSv in the NLST trial [22]. Low-dose CT delivered images with excellent resolution to detect nodules of 0.5 cm to 1 cm size. Low-dose CT is comparable in sensitivity and specificity of lung nodule detection with the conventional CT mode. Studies from Japan initially suggested the viability of LDCT as a tool for early lung cancer detection. The first report was from Kaneko *et al.*, who screened 1369 high-risk participants with both LDCT and chest radiography [23]. Computed tomography detected 15 cases of peripheral lung cancer, while 11 of these were missed on chest radiography. Of the non-small cell carcinomas identified, 93% were stage I [23]. Sone *et al.* authored the second report in the literature with 3958 par-

ticipants screened with both LDCT and CXR [24]. Only 4 lung cancers were detected by CXR, whereas 19 were seen on CT, of which 84% were stage I at resection [24].

The Early Lung Cancer Action Project (ELCAP) was one of the first trials in the United States and was completed in the late 1990s [25]. One thousand high-risk patients were screened with CXR and an LDCT scan of the chest. More malignant and benign nodules were detected with the LDCT scan when compared with CXR (2.7% vs. 0.7% and 20.6% vs. 6.1%, respectively). Out of the 27 lung cancers detected in the ELCAP trial, 23 (85%) were stage I [25]. The ELCAP trial was then expanded to include 38 centers in 5 countries as the International-ELCAP (I-ELCAP) study [26]. Standard protocols were developed for the trial's screening and subsequent diagnostic interventions. The trial screened 31,567 patients with a baseline LDCT scan, and 27,456 patients underwent an annual LDCT screening [26]. Thirteen percent of the initial scans and 5% of the subsequent annual scans were positive, and lung cancer was identified in 484 patients, of whom 412 (85%) had stage I cancer [26].

The Mayo Clinic LDCT (2005) study was another large prospective study that enrolled 1520 asymptomatic current or former smokers who underwent a baseline LDCT scan of the chest followed by annual LDCT screening [27]. After 5 years, 74% of the patients had noncalcified nodules, and 95% of the nodules were benign on follow-up. Sixty-eight lung cancers were diagnosed, and 61% were stage I [27].

In each of these early studies, LDCT detected about 4 times more lung cancers than did CXR. Several additional single-arm observational studies reported similar results with LDCT in Germany, Italy, and Japan [28–30]. The reported survival results from these studies were promising. However, by design, they were insufficient to show that CT screening saved lives. Bach *et al.* highlighted this point by applying a validated lung cancer prediction model to 3 prospective single-arm observational studies of CT screening combining 3246 participants [31]. Computed tomography screening found 3 times the number of expected cancers, resulted in 10 times the expected number of resections (109 of 144 cancers were resectable), and identified more than the expected number of advanced stage cancers. The 4-year actual survival was 94% for participants with surgical stage I cancers. However, CT screening did not result in a predicted reduction in the expected number of deaths from lung cancer. These results emphasized the need to evaluate the effectiveness of screening by mortality reduction rather than survival improvement.

The need to prove mortality reduction led to the next phase of RCTs using LDCT. Two small

RCTs of LDCT screening reported data on both the screened and the control group [32, 33]. The Lung Screening Study was the pilot study (published in 2004) performed to determine the feasibility of the NLST. A total of 1660 subjects were randomized to the LDCT arm and 1658 to the CXR arm [32]. In the LDCT arm, the rate of cancer detection on the baseline scan was 1.9%, and for year 1 it was 0.57%. In the CXR arm, the rate of cancer detection at baseline was 0.45%, and for year 1 it was 0.68%. No mortality information was presented for the study. However, the finding of a nearly two-fold higher number of advanced stage cancers in the CT arm suggested that there was not likely to be any mortality benefit from CT screening. The Depiscan study (2007) randomized 621 participants between CT and CXR [33]. One or more nodules were seen in 152 (45%) of 336 subjects receiving CT with 8 lung cancers identified, whereas only one cancer was detected in the CXR arm.

The largest trial evaluating LDCT screening for lung cancer is the NLST, in which 53,454 current (more than 30-pack-year history) or previous heavy smokers (less than 15 years since cessation) were randomized to receive either an LDCT scan or CXR annually for 3 years and were then followed for an additional 3.5 years with no screening [34]. Positive results were defined as a noncalcified nodule ≥ 4 mm for the LDCT scan and any noncalcified nodule or mass for CXR. Positive lesions were found in 39.1% of the LDCT scans and in 16% of CXRs over the 3-year period. The most common follow-up procedures undertaken for a positive screening were additional radiologic imaging (conventional CT or positron emission tomography-CT (PET-CT)). Invasive procedures were infrequent. Lung cancer was confirmed in 3.6% and 5.5% of positive screenings in the LDCT scan and CXR groups, respectively, giving false-positive rates of 96.4% for the LDCT scan and 94.5% for CXR. The complication rates from procedures undertaken for a positive screening were low, at 1.4% for the LDCT group and 1.65% for the CXR group. The number of lung cancers detected was 1060 in the LDCT group and 941 in the CXR group at the end of 6 years of observation. However, in the LDCT group, 649 cancers were detected by initial screening, another 44 during the interval screening, and 367 at follow-up. By comparison, in the CXR group, 249 cancers were detected at initial screening, while 137 were detected in the interval studies, and another 525 cancers were detected at follow-up. The difference in number of cancers detected at follow-up supports the likelihood that some cancers were missed by CXR. Although there was not an impressive difference in the number of cancers detected between the 2 groups, the LDCT group had a more favorable stage distribution. In

the LDCT group, 63% of the cancers were stage I, compared with 47.6% seen in the CXR group. There were 356 lung cancer-related deaths in the LDCT group and 443 in the CXR group. This represented a 20% reduction in mortality, which was statistically significant. The number needed to screen with the LDCT scan to prevent one death was calculated to be 320 [34].

NLST collaborators have collected pathology specimens of resected lung tumors. Each specimen has been reviewed by one expert lung cancer pathologist to ensure consistency of cored areas. Tissue microarrays have been constructed and stored for subsequent studies. The tumor data will be linked to clinical and radiological data collected as part of trial-wide operations. These specimens will enable numerous comparisons at the molecular level, including comparisons between persons with a diagnosis of lung cancer and those who remain free of the disease, persons with a diagnosis of lung cancer through screening and those with a diagnosis due to symptoms, and those who die of their disease compared with those who survive it.

The NLST will also provide a unique opportunity to explore and provide early phase validation of emerging molecular technologies in a well-characterized cohort of people at elevated risk of lung cancer, because biospecimens including urine, sputum and blood have been collected in a subset of participants.

Limitations of the NLST are its lack of comparison with standard of care, which is no screening. There were also systematic differences between the 2 study groups. First, adherence to each screening was 3 percentage points lower for the second and third radiography screenings than for the corresponding LDCT screenings. Because more participants in the radiography group missed 1 or 2 screenings, the radiography group had more time in which a lung cancer could metastasize before it was detected. Second, participants in the LDCT group were much less likely than those in the radiography group to have a diagnostic work-up after a positive result in the second and third round of screening, which might have led to fewer screening-related diagnoses of early-stage lung cancer after low-dose CT. The potential effect of these 2 differences in the study conduct seems to be too small to nullify the large effect of low-dose CT screening on lung cancer mortality. Additionally, the high adherence rate of more than 90% may be difficult to replicate in the general population. The trial was conducted at large medical centers with expertise in cancer management, and the results, especially the complication rates from interventions, may not be comparable with those of community hospitals. The reported mortality of surgical resection was 1% in the NLST group versus the previously reported 4%, possibly dimin-

ishing the mortality benefit with widespread implementation. The NLST participants were younger, better educated, and less likely to be current smokers as compared to the general population based on the US Census Survey, a phenomenon also described as the healthy volunteer effect. The average age at diagnosis of lung cancer in the USA is 70 years, and only 8.8% of participants of NLST were in the age group of 70–74 years. The incidence of lung cancer was similar at the 3 low-dose CT screenings, which implies that a negative result of low-dose CT screening did not substantially reduce the probability that the next round would detect cancer. Lung cancer was also diagnosed frequently during the 3 years of follow-up after the third low-dose CT screening. Apparently, every year, there are many lung cancers that first become detectable that year. This observation, together with the overall NLST results, suggests that continuing to screen high-risk individuals annually will provide a net benefit, at least until deaths from coexisting chronic diseases limit the gains in life expectancy from screening.

The NLST results show that 3 annual rounds of low-dose CT screening reduce mortality from lung cancer, and that the rate of death associated with diagnostic procedures is low. Seven million U.S. adults meet the entry criteria for the NLST, and an estimated 94 million U.S. adults are current or former smokers. With either target population, a national screening program of annual low-dose CT would be very expensive. The cost-benefit analysis and the impact on quality of life from the NLST are being analyzed and will be published at a later date.

In the Danish Lung Cancer Screening Trial (DLCST), 4104 men and women, healthy heavy smokers/former smokers were randomized to 5 annual low-dose CT screenings or no screening [35]. The volume doubling time of nodules was measured. Nodules between 5 and 15 mm without benign characteristics were rescanned after 3 months. Growing nodules (> 25% volume increase and/or volume doubling time < 400 days) and nodules > 15 mm were referred for diagnostic work-up. In the control group, lung cancers were diagnosed and treated outside the study by the usual clinical practice. The lung cancer detection rate was 0.83% at baseline, and the mean annual detection rate was 0.67% at incidence rounds. More lung cancers were diagnosed in the screening group (69 vs. 24), and more were low stage (48 vs. 21 stage I–IIb non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC)), whereas frequencies of high-stage lung cancer were the same (21 vs. 16 stage IIIA–IV NSCLC and extensive stage SCLC). At the end of screening, 61 patients died in the screening group and 42 in the control group. Fifteen and 11 died of lung cancer, respec-

tively. The authors concluded that CT screening for lung cancer detects more cancers and early disease, but does not significantly reduce mortality due to lung cancer [35].

Ongoing lung cancer screening trials

The Dutch Belgian Randomized Lung Cancer Screening trial (NELSON) has randomized patients to LDCT scans performed at baseline, and years 1, 2, and 4, or to no screening at all [36]. The study will enroll 15,600 participants and is the only other study except NLST which is powered to detect a 25% reduction in lung cancer mortality in 10 years. It is scheduled to conclude in 2015 [36]. The trial is also different as it has also enrolled lung cancer survivors, has a detailed assessment of smoking cessation in the context of a screening program, and looks into cost effectiveness, quality of life, and volumetric assessment of nodules to reduce false positives [37].

The ITALUNG study from Italy in which 3206 participants were randomized to LDCT versus no screening published their 4-year results [38]. The baseline CT was positive (defined as a pulmonary nodule ≥ 5 mm) in 426 (30.3%) of 1406 subjects. Twenty-one prevalence lung cancers were diagnosed in 20 participants (prevalence 1.5%), of which 10 (47.6%) were stage I [38].

The Randomized Study on Lung Cancer Screening with Low-Dose Spiral Computed Tomography (DANTE) trial is an Italian study that randomized 2472 male smokers to annual LDCT screening for 4 years or no screening [39]. All patients underwent baseline CXR and sputum cytology. The study was designed to assess lung cancer-specific mortality over 10 years. At the end of 3 years, there were 20 deaths related to lung cancer in each group, and the investigators concluded that the mortality benefit from LDCT screening may be smaller than anticipated [39]. However, the final analysis at the conclusion of the 10-year period needs to be evaluated.

Concerns with low-dose computed tomography screening

In lung cancer screening trials using LDCT scans, noncalcified nodules were seen in up to 43% of patients and, of these, up to 96% were false positives [26–30]. Similarly, in the NLST study, only 3.6% of all the nodules detected ultimately proved to be cancerous [34]. Although most nodules are ultimately benign, they require additional interventions such as serial LDCT scans, bronchoscopic procedures, and needle or surgical biopsies, each of which has its own inherent risks. Furthermore, the detection of a nodule is likely to raise a certain level of anxiety among patients and their families. To decrease the high rate of false

positive, many researchers considered any nodule less than 4 mm to 5 mm to be negative. This may inappropriately increase the false negative rate. Of nodules with a size less than 4 mm, 18% were cancer as reported in 1 study [40].

Although exposure to radiation from an LDCT scan is 20% of that from a conventional CT scan, radiation exposure from the annual screening procedures themselves may increase the risk of cancer [41]. Women are estimated to have a higher risk of cancer-related mortality than men with similar levels of exposure [42]. Age at radiation exposure is also a factor. The number of CT scans of the chest that would be required to cause 1 radiation-induced cancer is estimated to be 720 CT scans for 40-year-old women and 1566 CT scans for 40-year-old men. Older age reduces the eventual risk. For 60-year-old persons, 1 cancer would be induced for every 1090 CT scans for women and 2080 CT scans for men [43]. The NLST investigators estimated that the radiation risk from screening 55-year-old smokers results in 1 to 3 lung cancer deaths per 10,000 screened and 0.3 new breast cancers per 10,000 women screened [34]. Estimates of the increase in risk of death range from 0.01% to a few percent, and the increase in cancers is up to 1.8% over a 25-year screening period [41].

Follow-up studies will be needed to look for increased rates of cancer in patients receiving annual screenings. Long-term studies will also help to determine optimal duration and frequency of patient screenings. The LDCT also has only a limited role in screening lesions in central airways.

The cost of screening can be substantial. There are approximately 7 million high-risk individuals in the United States who would meet screening criteria per the NLST, and at approximately \$300 per LDCT scan (Medicare reimbursement rate), the annual cost for screening would be \$2.1 billion [44]. In the NLST, the LDCT screening group received 1471 PET-CT scans and 8807 standard CT scans, compared with 397 PET-CT scans and 3003 standard CT scans in the CXR group, adding significantly to the total screening cost [34]. However, Pyenson *et al.* reported that lung cancer screening with LDCT could be cost effective [44]. Using actuarial models, they estimated the costs and benefits of annual lung cancer screening offered as a commercial insurance benefit in the high-risk US population aged 50–64 years. Assuming current commercial reimbursement rates for treatment, they found that screening would cost only \$0.76 per insured member per month. The calculated cost per life-year saved was \$19,000, an amount that compares favorably with screening for cervical, breast, and colorectal cancers, and is less expensive than screening for cervical or breast cancer (about \$50,000 and \$31,000, re-

spectively). The eagerly awaited NLST cost-effectiveness analysis will provide a more realistic estimate of costs associated with CT screening.

In conclusion, LDCT scan can detect early-stage lung cancers among high-risk patients, and the NLST has shown a significant reduction in lung cancer mortality. Although the other small European trials have not supported this view, the sample size and good design of the NLST strongly support the role of LDCT in lung cancer screening.

Recommendations for lung screening by expert groups

The National Comprehensive Cancer Network (NCCN) issued guidelines for lung cancer screening in October, 2011 [45]. These guidelines recommend annual low-dose CT scan screening for those at high risk and no routine screening for moderate- or low-risk individuals. High risk was defined by the NCCN as age 55 to 74 years with a 30 pack-year history of smoking and, if no longer smoking, smoking cessation within 15 years or a 20 pack-year history of smoking with one additional risk factor other than secondhand smoke exposure. These risk factors include radon or occupational exposure, cancer history, presence of chronic obstructive pulmonary disease or pulmonary fibrosis, or family history of lung cancer. Although the guidelines note that the duration of screening is uncertain, they advise a minimum of 3 scans so that individuals initiating screening at age 74 years would stop screening at age 76 years. The guidelines emphasize that lung cancer screening should be done within the context of a multidisciplinary program that may include radiology, pulmonary medicine, internal medicine, thoracic oncology, and/or thoracic surgery to manage downstream testing.

Similar guidelines, following high-risk criteria from the NLST, were issued by the American College of Chest Physicians [46] and from the American Society of Clinical Oncology [47]. These guidelines were based on a review from Bach *et al.* [31] and were also endorsed by the American Cancer Society in 2013 [48]. These guidelines advise counseling patients about the risks and benefits of screening; the development of a registry to collect data on follow-up testing, smoking behavior, radiation exposure, and patient experience; the development of quality metrics for CT interpretation, similar to quality control for mammography; and also emphasize the importance of smoking cessation. The American Lung Association [49] and the American Association for Thoracic Surgery (AATS) also released guidelines in 2012 that recommend low-dose CT screening for high-risk individuals who meet the NLST criteria. The American Association of Thoracic Surgery recommends increasing

the upper age limit of screening to 79, because the peak incidence of lung cancer is at 70 years in the USA, and while the average life expectancy is 79 years, at least half of Americans are expected to live until the age of 80–89 years [50].

Similar to the US guidelines discussed above, a multidisciplinary expert group from France, representing the intergroup for thoracic oncology and French-speaking oncology (the French Intergroup (IFCT) and the groupe d'Oncologie de langue française (GOLF)), advised screening a target population aged 55 to 74 years who have a 30 pack-year smoking history with a low-dose CT scan after informing individuals about the risks and benefits of screening [51].

The U.S. Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer with LDCT in persons at high risk for lung cancer based on age and smoking history. The guidelines recommend screening healthy persons with a 30 pack-year or more history of smoking who are ages 55 to 79 years (older than the NLST population) and have smoked within the past 15 years. They advise caution in recommending screening to patients with significant comorbidity, particularly those who are toward the upper end of the screening age range. It is still a draft statement, distributed for the purpose of pre-release review [52].

The International Association for the Study of Lung Cancer (IASLC) chartered an advisory committee in 2011, to work with professional societies who are developing guidelines for screening [53]. The IASLC identified several issues that need to be addressed in guideline development and implementation. These issues include defining the optimal population for screening, determining the cost-effectiveness of screening, developing consistent CT screening protocols, defining the optimal work-up for abnormal findings, defining optimal management of screen-detected nodules, determining the optimal screening interval and number of screening rounds, and encouraging data collection and further research to improve screening outcomes and limit complications. There was a consensus that smoking cessation programs need to be integrated into screening programs and that a lung cancer screening program should involve a multidisciplinary team experienced in evaluation and management of early lung cancer.

A concern with current guidelines based on NLST is the low annual detection rate of 1%, based on age and pack-years alone. Only 50% of all those who will develop lung cancer would be eligible for screening by these criteria [34]. The detection rate will increase if other risk factors for lung cancers and validated risk prediction models are included in the selection criteria of patients [54, 55].

Kovalchik *et al.* have developed a more specific risk-prediction model for lung-cancer mortality by taking into account more factors than the NLST entry criteria. By applying this model to the NLST population, they showed that the population at the high end of the risk spectrum had more benefits and less harm. The number needed to screen could be reduced from 320 in the NLST to 161, and false positive screening CT could be cut from more than 100 to around 65 for every prevented lung cancer death. If this model can be validated in the general population, LDCT screening benefits could be improved with reduced harm of false positives [56].

Newer modalities for lung cancer screening

Positron emission tomography is a promising tool. Two studies have evaluated annual low-dose CT followed by positron emission tomography (PET) with fluorodeoxyglucose (FDG) for evaluating patients with noncalcified lesions ≥ 7 mm in diameter, each with similar results [57, 58]. Garcia-Velloso *et al.* enrolled 911 volunteers ≥ 50 years of age who had smoked for ≥ 20 pack-years. Baseline CT identified 11 non-small cell lung cancers (NSCLC) and 1 small cell lung cancer (SCLC) (1.3% prevalence). Two NSCLCs were found in 424 subjects at the annual follow-up study (0.5% incidence). All NSCLCs were stage I. FDG-PET correctly diagnosed 19 of 25 indeterminate nodules. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for the diagnosis of malignancy were 69%, 91%, 90%, and 71%, respectively. When a negative FDG-PET was followed 3 months later with a repeat CT, the negative predictive value was 100%. The results are promising, but incorporation of PET imaging into large-scale screening programs requires validation with more large-scale studies. Cost and widespread availability are also major hindrances.

Non-radiographic technologies have also shown promise in early detection of lung cancer. Detection and treatment of small lung tumors (prior to radiographic visualization) may produce superior outcomes, although the possibility of other biases increased significantly [59].

Technologies under investigation include investigating sputum for molecular markers. Increased concentrations of these markers – promoter hypermethylation of multiple genes, especially p16 ink4a promoter hypermethylation and p53 mutations – have been shown to occur in chronic smokers before there is clinical evidence of neoplasia [60–63]. Assay of telomerase activity in sputa may help differentiate benign from malignant peripheral tumors [64].

Autofluorescence bronchoscopy (AFB) displays areas of epithelial thickness and hypervascularity

as abnormal fluorescence. Autofluorescence bronchoscopy improves the sensitivity for detection of preinvasive lesions in the central airway and increases the diagnostic accuracy for squamous dysplasia, carcinoma *in situ* (CIS), and early lung carcinoma when used simultaneously with conventional white light bronchoscopy (WLB). In addition to single center studies, 3 multicenter and 2 randomized clinical trials have documented the usefulness of AFB as an adjunct to WLB for detecting intraepithelial neoplasia and CIS [65–69]. However, the specificity of AFB for diagnosing preinvasive lesions is low [66]. Distinguishing between preinvasive lesions and other benign epithelial changes such as bronchitis is problematic. To increase the specificity, a new autofluorescence imaging (AFI) bronchovideoscope system has been developed where preinvasive lesions and benign changes may be differentiated by color [70].

Other fields currently being explored are automated image cytometry of sputum and exhaled breath analysis of volatile organic compounds [71–73], genomic and proteomic analysis of bronchoscopic samples [74, 75], and serum protein microarrays for detecting molecular markers [76].

Conclusions

Chest X-ray as a screening tool has been convincingly proven to have no benefit in lung cancer screening [3]. The recently published large trial NLST has shown that screening a high-risk population for lung cancer with low-dose CT scanning leads to mortality reduction. For the first time, we have a tool to screen lung cancer which has the potential to save 12,000 lives per year, if implemented. It is also important that smoking cessation programs become an integrated part of lung cancer screening endeavors. The questions which remain unanswered concern the cost and radiation exposure. The exact group which should be screened is still to be determined. The high sensitivity of LDCT would lead to a large number of false positive results, which needs to be assessed. The screening bronchoscopy and molecular biomarkers are promising tools as well. These modalities may prove to be additive to LDCT in screening programs.

Conflict of interest

The authors declare no conflict of interest.

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