The changing epidemiology of lung cancer with a focus on screening

Gerard A Silvestri,[1] Anthony J Alberg,[2] James Ravenel[3]

[1]Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston, SC 29425, USA

[2]Hollings Cancer Center and Department of Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina

[3]Department of Radiology, Medical University of South Carolina

Correspondence to: G A Silvestri silvestri@musc.edu

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Lung cancer is a global public health problem of epidemic proportions, and the number of people affected is expected to grow in the near future. Worldwide, in 2002 more than 1.3 million people were newly diagnosed with lung cancer.[1] It is the leading global cause of death from cancer, and it accounts for 18% of all deaths from cancer and more than one million deaths a year since as far back as 1993.[2 3] Lung cancer is the 10th leading overall cause of death, and it is expected to move to fifth place as its incidence rises in developing countries. Lung cancer is a disease that seems to fit the profile for a successful screening programme. However, developing an efficacious screening test that meets the established criteria for screening has proved elusive, despite evidence from many screening trials, and screening remains controversial. This review aims to shed light on the questions surrounding screening for lung cancer.

What are the established causes of lung cancer?

Active cigarette smoking is the main cause—it accounts for 85-90% of all lung cancers.[2 w1-w5] In addition, exposure to secondhand cigarette smoke; pipe and cigar smoking; occupational exposure to agents such as asbestos, nickel, chromium, and arsenic; exposure to radiation, including radon gas in homes; and exposure to air pollution are all established risk factors for lung cancer.[2] There has been longstanding interest in genetic susceptibility to lung cancer, and results of recent genome-wide association studies consistently point to the long arm of chromosome 15 as being linked to increased risk.[4 5 w6-w8]

What is the emerging global picture of lung cancer?

Whereas in the mid-1900s the lung cancer epidemic was largely confined to developed nations, by 2002 the absolute numbers of newly diagnosed lung cancers occurring in developed and developing countries were nearly equal.[1 6]

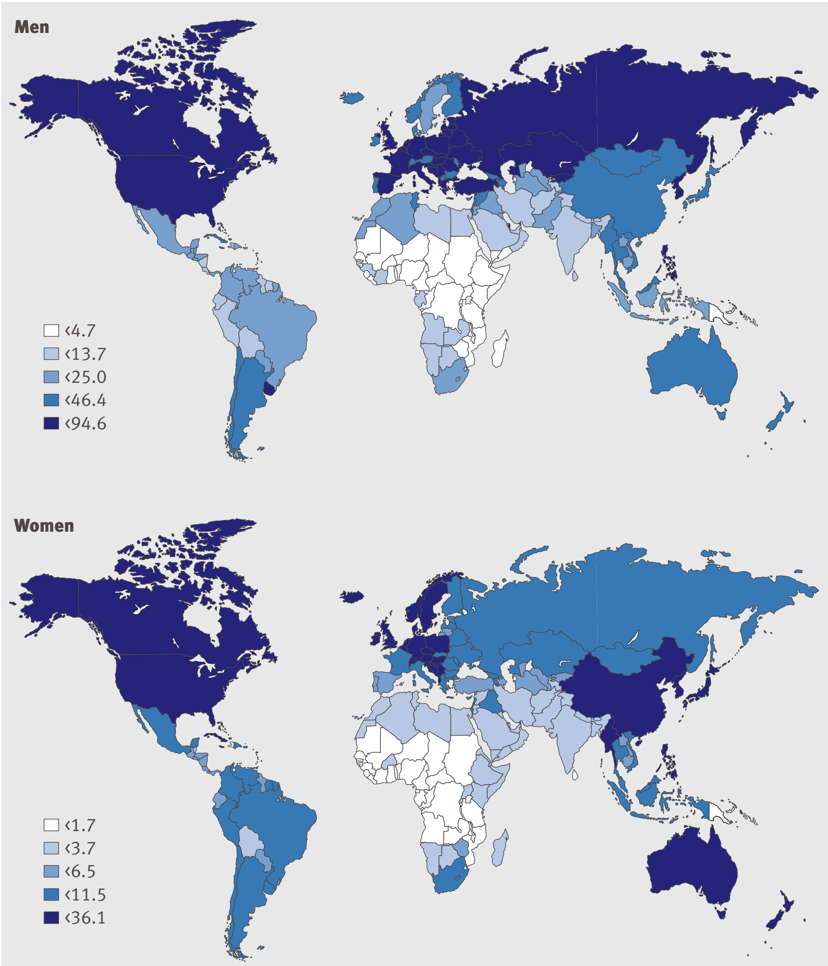
Considerable geographical variation exists, with a greater than 20-fold variation in occurrence across countries (figure).[2 7] As of 2002, the age adjusted annual incidence ranges from a high of 65.7 per 100 000 in Central and Eastern Europe to less than 25 per 100 000 in Africa, with most of that continent at less than five per 100 000 (figure).[1 7] The occurrence of lung cancer is so strongly determined by cigarette smoking that historical and current smoking prevalence data can help reliably forecast the future patterns of occurrence.

Countries where the lung cancer epidemic is in its infancy, or it is in full force without signs of coming under control, are of greatest public health concern. The hallmark characteristics of a country in transition from lower to higher rates of lung cancer are a low current incidence of lung cancer but a high current prevalence of cigarette smoking. The high prevalence of smoking in these countries foretells a future epidemic of lung cancer. Countries in the middle of an uncontrolled epidemic of lung cancer are those with high current mortality from lung cancer coupled with a high current prevalence of cigarette smoking. The populations of such countries are at the highest risk at present and for the foreseeable future. Korea, the Russian Federation, Kazakhstan, Poland, and Hungary fall into this last category as far as men are concerned, whereas in Venezuela, Germany, Norway, the United States, and Denmark women are at the greatest current and future risk.[8]

Populations may avoid the lung cancer epidemic entirely if cigarette smoking never becomes prevalent, as has historically been the case in many African countries. Unfortunately, several African countries have recently experienced a surge in cigarette smoking.[9] Conversely, the high burden of lung cancer currently seen in some countries will decrease because public health efforts have reduced the prevalence of smoking. Risks are now lower for men in Singapore, Canada,

SUMMARY POINTS

- Lung cancer is the most common cancer worldwide
- Incidence varies greatly between countries because of the varying prevalence of cigarette smoking
- The epidemic of lung cancer has just begun in developing countries, although a decrease is being seen in some developed countries
- Screening for lung cancer using low dose computed tomography has not been proved to be efficacious
- Several large randomised controlled trials to assess the efficacy of screening for lung cancer are under way
- Screening for lung cancer cannot be recommended outside a well designed clinical trial



Global annual incidence (per 100 000) of lung cancer in men and women. Adapted, with permission, from GLOBOCAN 2002[7]

Germany, the United Kingdom, the US, the Netherlands, and Belgium, and for women in Malaysia, Korea, Bahrain, the Philippines, Canada, and Belgium.

Chinese men will strongly influence the global burden of lung cancer in the 21st century because they have a high prevalence of cigarette smoking and they form a large proportion of the world's population. Per capita cigarette consumption among Chinese men has risen from one cigarette per day in 1952, to four in 1972, to 10 in 1992.[10] The rate of smoking among Chinese men today is equivalent to the highest rates ever seen in developed countries. The incidence of lung cancer has already risen, with more substantial increases yet to come.[11] Socioeconomic status is inversely associated with the incidence of lung cancer and mortality. A recent study of nearly 400 000 Europeans found a higher risk of lung cancer in the least well educated populations (a proxy for socioeconomic status). Adjustment for smoking reduced the risk of lung cancer by 50% in men and women in all regions and for all histological types.[12]

With a sustained global burden of lung cancer projected for the coming decades, a method of early detection that could effectively reduce mortality from lung cancer would potentially have an enormous public health benefit.

Why consider screening for lung cancer?

Three quarters of patients with lung cancer present with symptoms of advanced incurable disease.[13] Despite advances in treatment, the five year survival rate for all stages combined is around 16%.[14] Outcomes are significantly better in patients diagnosed at earlier stages, with a five year survival for stage I disease of 60-75%.[15 w9-w11] An efficacious screening test that could result in early detection and reduced mortality would thus represent a major advance in combating mortality from lung cancer.

Does screening lead to reduced mortality from lung cancer?

Principles of a screening test

Screening is the process of detecting disease before it becomes symptomatic. For a screening test to be effective, certain criteria must be met regarding the disease, the proposed screening test, and treatment (box).[16] The disease must have serious consequences and be readily detectable in the preclinical phase. The test should have a high accuracy, detect the disease before a critical point, cause little morbidity, be available and affordable, and result in little overdiagnosis. Finally, treatment for the disease must exist, and it must be effective before symptoms occur, with little risk or morbidity. Both chest radiography and computed tomography have been evaluated as screening tests for lung cancer.

Findings from studies evaluating chest radiography

Several randomised trials in the 1960-1980s screened for lung cancer using chest radiography and found no difference in mortality between the screened and unscreened groups, even though more early stage cancers were identified in the screening group.[17] Late stage cancers were not reduced, and deaths from lung cancer were higher in the screened group after 20 years of follow-up, probably because of overdiagnosis.[18 w12-w17]

Findings from studies of screening using chest computed tomography

Low radiation dose computed tomography uses lower doses of radiation than standard techniques to generate an image. Nodules as small as 2-3 mm can be detected, which means that this method detects at least three times as many small lung nodules as a standard chest radiograph.[19] The only evidence on screening for lung cancer

TEN CRITERIA FOR EFFECTIVE SCREENING

- The disease has serious consequences
- The screening population has a high prevalence of detectable preclinical disease
- The screening test detects little pseudodisease (overdiagnosis)
- The screening test has high accuracy for detecting preclinical disease
- The screening test detects disease before the critical point
- The screening test causes little morbidity
- The screening test is affordable and available
- Treatment exists
- Treatment is more effective when applied before symptomatic detection
- Treatment is not too risky or toxic

ONGOING RESEARCH AND UNANSWERED QUESTIONS

- Two large randomised controlled trials of more than 70 000 people assessing the efficacy of screening with low radiation dose computed tomography for lung cancer are under way
- If lung cancer screening is found to be efficacious how would the health system implement mass screening?
- Would it be better to use scarce healthcare resources to prevent people starting to smoke or to provide better tools for smoking cessation?

using this method is from observational cohort studies that provide information on the distribution of disease stage and survival of the screened population but do not measure efficacy of screening in reducing mortality.

Cohort studies conducted in Japan which included 15 050 at risk participants detected 72 lung cancers during prevalence screening (0.5%), 57 of which were stage IA.[20-22] In 21 762 annual incidence screens, 60 (0.3%) new cancers were detected, of which 50 were stage IA.

The Early Lung Cancer Action Project (ELCAP) screened 1000 asymptomatic volunteers with at least a 10 pack year (number of cigarettes smoked each day times number of years smoked) history of smoking with chest radiography and low radiation dose computed tomography.[23] Non-calcified lung nodules were detected in 23% using computed tomography and 7% using chest radiography. Malignant nodules were detected in 2.7% by computed tomography compared with 0.7% by chest radiography. Twenty seven lung cancers were identified and 23 were stage I.

This was followed by a prospective study at the Mayo Clinic of low radiation dose computed tomography screening in 1520 high risk subjects.[19] One year after baseline scanning, a total of 2244 non-calcified lung nodules were identified in 1000 of the 1520 participants (66%). Twenty five cases of lung cancer were diagnosed (22 prevalent cases and three incident cases), and 22 patients underwent surgical resection. Twelve of the 21 non-small cell cancers detected were stage IA at diagnosis. After five years of annual computed tomography scanning,[24] a total of 3356 non-calcified nodules were found in 73.5% of the cohort; about 95% of the nodules were found to be benign with clinical follow-up or surgical biopsy. Sixty eight primary lung tumours were documented in 66 participants, 34 on annual (incidence) studies and three interval lung cancers not detected through annual screening. Of the incident cancers, 21 were stage I and 11 presented at stage III or IV. The large proportion of non-calcified nodules found (5-51%) is problematic because most will turn out to be benign but will require further evaluation, including serial computed tomography scans, biopsy, or in some cases surgical resection, which can carry serious morbidity and a low but real risk of death.

A large multicentre multinational non-randomised trial, the International ELCAP (I-ELCAP) was recently reported.[25] This trial screened 31 567 subjects using low radiation dose computed tomography. Lung cancer was detected in 484 patients (1.3%), 412 of whom had stage I disease. Estimated 10 year survival was 80% for all patients regardless of stage and treatment, and 88% for stage I cancer. This study confirmed earlier observations that lung cancers detected by computed tomography screening are at an early stage and are highly treatable.

This study provides a basis for optimism, but it cannot confirm the efficacy of screening for lung cancer with low radiation dose computed tomography because, although survival was higher in people diagnosed with early stage lung cancer, the study was not designed to assess whether screening reduces overall mortality in patients with lung cancer. A comment on the study gave four reasons why the findings did not make a persuasive case for screening.[26] Firstly, the lack of a control group precluded the study from investigating what would happen to a similar group of patients in the absence of screening. Secondly, lack of an unbiased outcome measure meant that the confounding features of lead time, length time, and overdiagnosis bias were not controlled for. Thirdly, the study did not take into account what is already known about lung cancer screening, particularly the evidence for overdiagnosis bias arising in single arm studies from Japan.[22] Finally, although the study emphasised the positive aspects of screening, it did not discuss potential harms, especially the unnecessary investigation or treatment of benign disease.

The positive findings of the I-ELCAP trial contrast with those from a longitudinal study that examined three populations of current or former smokers, one in Italy and two in the US. The study screened 3246 people annually with computed tomography and had a median follow-up of 3.9 years.[27] The numbers of observed new cases of lung cancer, resections for lung cancer, cases of advanced lung cancer, and deaths from lung cancer were compared with the numbers predicted using two validated models. One hundred and forty four people were diagnosed with lung cancer compared with 44.5 expected cases (relative risk 3.2, 95% confidence interval 2.7 to 3.8; $P<0.001$). The rate of lung cancer resection was 10 times higher than expected—109 compared with the 10.9 predicted for that cohort (10.0, 8.2 to 11.9; $P<0.001$). There were 42 cases of advanced lung cancer compared with 33.4 expected cases and 38 deaths, which is the number predicted for that cohort (1.0, 0.7 to 1.3; $P=0.90$). This study showed that screening with low radiation dose computed tomography increased the detection of lung cancers and the numbers of tumours resected, but it did not reduce the risk of advanced lung cancer or of overall mortality from lung cancer. The survival of patients with stage I tumours that were resected was similar to that seen by the I-ELCAP investigators.

TIPS FOR NON-SPECIALISTS

- Counselling patients about smoking cessation is the most effective way to reduce the risk of lung cancer
- Screening for lung cancer using chest radiography or low dose computed tomography of the chest is not currently recommended
- At risk patients who are interested in screening should be counselled about the potential harms of screening, including further unnecessary testing and complications associated with the evaluation of screen detected findings

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Manser R, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D. Screening for lung cancer. *Cochrane Database Syst Rev* 2004;(1):CD001991.

Bach BP, Silvestri GA, Hanger M, Jett JR. Screening for lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). *Chest* 2007;132 (supp):69S-77S.

These two references provide an evidenced based review of screening for lung cancer

Resources for patients

Welch HG. Should I be tested for cancer? Maybe not and here's why. Berkeley: University of California Press, 2004

What can we conclude?

Results from observational computed tomography studies show that low radiation dose computed tomography can detect early lung cancer in asymptomatic people. However, we still do not know whether early detection reduces mortality from lung cancer or is cost effective.[28] For this reason, the National Cancer Institute has instituted the National Lung Screening Trial (NLST; www.cancer.gov/nlst). The NLST is a randomised controlled trial that by 2004 recruited nearly 50000 current or former smokers and randomised them to screening with chest radiography (the control group) or helical computed tomography. Subjects were screened for three years and are now being followed up. The NLST is powered to detect a 20% reduction in mortality from lung cancer by screening with spiral computed tomography compared with chest radiography.

The NELSON trial is a European computed tomography based screening trial being conducted in the Netherlands and Denmark.[29] Almost 20000 at risk participants have been randomised to computed tomography screening versus no screening. It is designed to have 80% power to show at least a 25% reduction in mortality from lung cancer 10 years after randomisation.

Evidence based reviews have concluded that current evidence does not support computed tomography screening for lung cancer outside the auspices of a well designed clinical trial.[30 31 w18] The upsurge in smoking in developing countries has thwarted the tremendous strides in tobacco control that have been made in many developed countries. The net result is that global mortality from lung cancer will rise in the short term.

Even if screening is found to be efficacious and new treatments are developed, global reductions in smoking initiation combined with effective smoking cessation strategies in those who currently smoke will have the biggest effect on mortality from lung cancer.

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