Viewpoint

Tobacco money: up in smoke?

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> "Pioneering technique to screen lung cancer at early, most treatable stage to be tested in large-scale study . . . While other cities and states are using tobacco settlement proceeds to fund projects unrelated to health, New York City is using a significant portion of its tobacco litigation proceeds to directly combat smoking, the leading cause of lung cancer, and in this instance to fund vital research to detect and conquer lung cancer itself."[1]

On Aug 21, 2000, Rudolf Giuliani, the Mayor of New York City, announced a major health initiative—the New York Early Lung Cancer Action Program (NY-ELCAP)—to "help develop the best means for early detection and successful treatment of lung cancer".[2] Under this initiative, financed mainly by New York's Tobacco Settlement fund, 10 000 present or past heavy smokers from New York will undergo a computed tomography (CT) scan of the chest to try and detect lung cancer at its earliest and most treatable stage. NY-ELCAP would seem to be a great step forward in the war against lung cancer and a model for public and private medical research collaboration, but, unfortunately, it is neither. Here, we describe the history of the NY-ELCAP, and argue that New York City has not made good use of public assets in funding the study. NY-ELCAP will not only be unable to determine whether screening for lung cancer with spiral CT will save lives, but could actually make it even harder to learn the answer.

Origins of lung cancer screening with CT

In the USA, the burden of lung cancer is great: it is the leading cause of cancer death for both men and women, and results in more years of potential life lost than all other cancers. At present, treatment for advanced disease is mostly ineffective—less than 20% of patients are alive at 5 years. At least 90% of lung cancers are attributable to smoking. The substantial burden of disease and the existence of an easily identifiable high-risk group (ie, present and past smokers) make lung cancer an appropriate target for screening.

The idea of screening for lung cancer originated in the 1940s, when screening for tuberculosis was also found to detect unsuspected lung cancers. Various observational studies have confirmed the ability of chest radiographs and sputum cytology, two readily available, simple detection methods, to find preclinical disease. Enthusiasm for screening was stimulated by the observation that patients with cancer that had been detected through screening had improved 5-year survival compared with those whose cancer presented clinically. Unfortunately, in randomised trials designed to assess the benefit of screening, improved survival did not reduce mortality from lung cancer.[3] The improved 5-year survival associated with screening is now widely accepted to be the product of two factors: earlier diagnosis with unchanged time of death (lead time bias) and detection of cancers that never produce symptoms in controls (overdiagnosis).[3] At present, no professional medical organisation in the USA advocates screening for lung cancer. Nonetheless, many believe that screening for lung cancer should work. The failure of trials of lung cancer screening has been attributed to the low sensitivity of chest radiographs. That is, by the time lung cancer is large enough to be detected by chest radiograph, micrometastases have probably already developed.

Many experts believe that effective screening programmes need imaging techniques with better resolution. Although CT scans have been available since the 1970s, their ability to detect lung cancer is limited by artifacts created by respiration. A new CT technique, spiral CT (also called helical CT), avoids this difficulty. This technique, which has the advantage of speed, can continuously scan the whole thorax during one breath. Consequently, spiral CT is much more sensitive than either chest radiograph or conventional CT scans in detection of abnormalities.

In individuals who do not have symptoms, spiral CT scanning can detect lung cancers better than chest radiographs,[4] with chest radiographs failing to detect more than three-quarters of lung cancers that were less than 20 mm, and half of those measuring greater than 20 mm that had been discovered using spiral CT.[5] The finding that spiral CT scanning detects much smaller lesions (ie, <1·0 cm) than earlier imaging methods has renewed interest in lung cancer screening.

The pilot study[6] that motivated NY-ELCAP also compared the ability of spiral CT and chest radiographs to detect lung cancer. All participants underwent baseline and yearly chest radiographs and spiral CT screening. At the time of the mayor's announcement, only the diagnostic yield and follow-up testing from the baseline screening had been reported.[6] Of the 1000 smokers screened, radiographs detected non-calcified nodules in about 7%, whereas spiral CT detected non-calcified nodules in 23%. Similarly, chest radiographs detected lung cancers in only seven patients (four of whom had stage I disease), whereas spiral CT detected such cancers in 27 people (23 with stage I disease).

NY-ELCAP

The official objective of the NY-ELCAP programme is to "validate the preliminary results showing the efficacy of CT screening in early detection".[1] To do so, investigators are recruiting 10 000 individuals who are aged 60 years or

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older, have at least a 10 pack-year smoking history (at least one packet a year for 10 years, or two packets for 5 years), report no history of cancer, and are fit to undergo thoracic surgery, to undergo screening with spiral CT. All participants will also be invited to join a smoking cessation programme (the investigators hope that spiral CT scanning will provide further motivation for smokers to quit smoking).

Participants whose initial low-dose spiral CT scans are abnormal will be referred for confirmatory high-resolution CT scans (providing a better quality image) and follow-up medical consultation to ascertain whether or not they have lung cancer. The study design includes a standard follow-up strategy that is intended to keep unnecessary biopsies to a minimum for patients with abnormally high resolution CT scans. If a biopsy is not immediately indicated, patients are rescanned at 3 months and 6 months, and 1 year and 2 years. Specific guidelines have been provided about what follow-up procedure is recommended on the basis of the growth of the nodule. If the nodule does not grow over the 2 years, it will be judged benign.

Funds for NY-ELCAP

Although the pilot study was funded by the National Institutes of Health,[6] NY-ELCAP is not. Funding for NY-ELCAP was obtained with help from the Academic Medicine Development Company (AMDeC), a non-profit corporation supported by public and private funds. AMDeC was created in 1997 by medical schools, academic health centres, and research institutions located throughout New York to help obtain federal funding for medical research, and to establish New York as an international centre for biomedical research and technology.[7] AMDeC does not provide funding; instead, its role is to help secure funding for projects and to promote collaboration between academic medical centres in New York State. AMDeC's governing board decides which projects to sponsor. A member of the governing board, Antonio Gotto, Dean of Cornell Medical School, approached AMDeC about sponsorship of the project. Maria Mitchell, AMDeC's president, felt that NY-ELCAP satisfied its mission and agreed to sponsor it.[2]

Subsequently, AMDeC and the Association of New York Medical Schools' Research Council (organisations with mostly the same membership), approached Mayor Guiliani's office about the project. After hearing the study presentation, Mayor Guiliani decided that NY-ELCAP merited funding and arranged for US$4 million from the Medicaid tobacco settlement money to be allocated to the project. The mayor did not request a scientific review of the study's merits by epidemiologists in the City's Department of Health, or by outside experts. Ironically, although AMDeC was created to bring funds into New York, the mayor's decision redistributed public funds already in New York to support the project. The mayor's office issued a press release[2] describing the goals of NY-ELCAP:

> "To provide immediate availability of CT screening for individuals with a high risk of lung cancer in a structured program; . . . To rapidly evaluate, within two years, the efficacy of annual CT screening for lung cancer; and to provide the rationale for statewide screening recommendations."

Since NY-ELCAP is expected to cost $10 million over the next 2 years, funding was also sought from various other institutions. To date, NY-ELCAP has received $5·5 million ($4 million from New York City, $1 million Empire Blue Cross and Blue Shield, and $520 000 from a philanthropic foundation, the New York Community Trust). The investigators hope that the city will allocate more tobacco settlement money to the project. Most of the funds are used to pay participating institutions for spiral CT scans (which are provided free to participants), support the central storage facility for the images (located at Cornell Medical School), and to reimburse radiologists for reading the films.

What NY-ELCAP can do

By repetition of their pilot study in a ten-fold larger sample (ie, 10 000 *vs* 1000 patients), NY-ELCAP investigators will be able to generate precise estimates of how often spiral CT scans detect abnormalities that could be associated with cancer, how often patients with these abnormalities undergo various follow-up tests, and how often lung cancer is detected.

Preliminary data suggest that many patients will have abnormal scans.[6] NY-ELCAP will help to refine the 23% positivity estimate from the pilot study. It will also provide an opportunity to confirm the usefulness of the procedures designed to keep unnecessary biopsies to a minimum. Of the 1000 people in the original study, 183 (18%) underwent follow-up examinations after their initial scan; 115 (12%) were followed up with high-resolution CT (scans at 3 months, 6 months, 1 year, and 2 years, nodules are declared benign if no growth after 2 years), and 31 (3%) had biopsies (CT guided fine needle aspiration or video-assisted thorascopy) (figure).

Fortunately, on the basis of the 1000 patients in the preliminary study, steps taken to reduce unnecessary biopsies worked well: only 28 biopsies were recommended and, of these, 27 (96%) were positive for lung cancer. However, three patients had off-protocol biopsies (10% of all biopsies taken), all of which were negative. Since it could take up to 2 years to be declared cancer free (ie, if lesions did not progress), that some patients opted for out-of-protocol biopsies is not surprising. NY-ELCAP's conservative follow-up strategy will provide important best-case estimates about how many patients find the idea of watchful waiting for a possible lung cancer unacceptable.

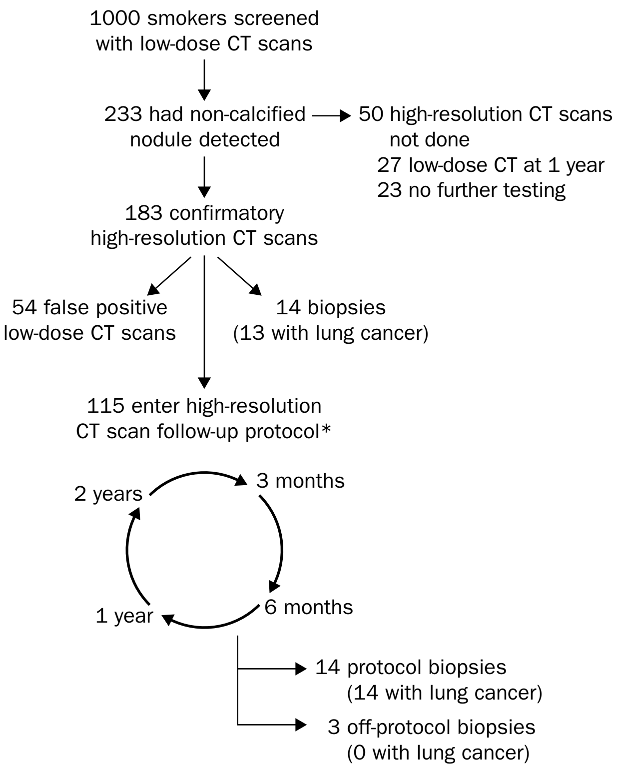
Over time, the study will also provide precise survival statistics (eg, the proportion of patients with cancer detected through screening who are alive 5 years after diagnosis). NY-ELCAP will probably replicate the pilot findings: cancers detected with spiral CT will have an earlier stage distribution than those detected by standard chest radiographic screening or from symptoms. Because of this stage shift, such patients will have improved 5-year survival.

In fact, the promise of NY-ELCAP was presented this way in the New York City press release announcing the study, in the Cornell Medical Center's website, and in statements from the NY-ELCAP investigators. For example, the principal investigator told the *New York Times*:

> "If cancer nodules are detected and removed in their initial phase, the 5-year survival from lung cancer can exceed 70 percent. In contrast, the overall rate of cure for lung cancer is 12 percent. We're saying we could change survival form 12 or 15% to 80% . . . there are 172 000 new cases a year. Think of 12 or 15% compared to 80%."[8]

What NY-ELCAP cannot do

This emphasis on improved 5-year survival, however, is a distraction, and could confuse physicians and potential study participants. As long as scanning advances the time of diagnosis, survival statistics (measured from time of



Protocol and findings of initial observational study of low-dose CT screening

CT=computed tomography. Although confirmatory high-resolution CTs were recommended for all 233 participants with non-calcified nodules, 50 did not have the scan. *Nine patients were only recommended 1 year of follow-up.

diagnosis) always look better, even if treatment is harmful.[3] However, although 5-year survival for lung cancer was substantially improved in the randomised trials of screening with chest radiographs (33% *vs* 15% in the Mayo Lung Project, and 23% *vs* 0% in the Czecheslovakian Study), mortality was not.[9,10] In fact, the trend was for higher mortality in those who had been screened. This finding has persisted after 25 years of follow-up (about 150 000 person years) of the Mayo Lung Project.[11]

Because there is no control group—all participants will undergo screening—NY-ELCAP cannot establish whether or not screening with spiral CT reduces mortality from lung cancer. Although CT screening might ultimately reduce lung cancer mortality, the best that the NY-ELCAP study can do is to show what is already known: that spiral CT is a promising technique that warrants investigation in a randomised trial.

What NY-ELCAP will probably do

Unfortunately, NY-ELCAP could actually result in overdiagnosis, detection of cancers that would never become clinically important during a patient's lifetime (sometimes referred to as pseudodisease).[3,12] Overdiagnosis becomes increasingly relevant with more sensitive techniques for detection. Because it can detect extremely small lesions, spiral CT increases the chance that clinically insignificant cancers—those that progress very slowly or not at all—will be detected. Such detection is harmful because patients diagnosed with such cancers will not benefit from treatment (by definition the cancer would never harm them and would never have been detected without screening); these patients can only be injured by treatment (and by being labelled as having cancer).

Although some have argued that lung cancer cannot be overdiagnosed, many factors suggest that it is. Pseudodisease has been recognised in many cancers including thyroid, prostate, breast, and childhood neuroblastoma.[3,12,13] Why lung cancer is qualitatively different is not clear. Very indolent lung cancers with doubling times of well over 1 year have been documented.[14] In a study[15] of small (<3 cm) surgically resected adenocarcinomas that had been followed up with CT, tumour doubling times ranged from 42 to 1486 days, and half of tumours had doubling times of longer than 1 year. With a doubling time of 1 year, a tumour takes nearly 8 years to increase in size from 5 mm to 3 cm—a time during which many patients (eg, older smokers) are likely to die from other causes such as cardiovascular disease.

Many data lend support to the existence of a potentially large reservoir of unsuspected lung cancer. Almost half of patients assessed for lung reduction surgery had unsuspected lung cancer detected during preoperative examination.[16] In one necropsy series,[17] almost 1% of patients had unsuspected lung cancer. In another necropsy series[18] (specifically looking for lung cancer), 14% of lung cancers identified had not been detected during the person's life. The report[11] on long-term data from the Mayo clinic screening trial also lends support to the existence of pseudodisease. Even after 25 years of follow-up, frequency of lung cancer in the unscreened group has not caught up with that of the screened group.

Spiral CT screening itself provides some of the best evidence for overdiagnosis in lung cancer. Sone's findings[4] of roughly equal numbers of lung cancers detected by CT in smokers and non-smokers in the face of at least a ten to one smoker to non-smoker ratio for lethal lung cancer[19] is strong evidence that overdiagnosis can happen. That is, in addition to usual lung cancers, spiral CT screening must also detect lesions that meet histological criteria for cancer, but do not behave like cancer; some lesions regress, some become dormant, while others progress so slowly that they never become clinically apparent during the patient's lifetime. In Sone's study, the histology of cancers detected by spiral CT screening differed from those detected in practice.[20] Almost all cancers detected by screening were adenocarcinoma: most were well-differentiated adenocarcinomas or bronchioloalveolar cell tumours—cancers with the best prognosis.[21] By contrast, adenocarcinomas comprise less than half of new cases diagnosed clinically.[22]

The future

Lung cancer is a major public health concern. An effective screening programme might save thousands of lives each year. Nonetheless, it is premature, and possibly dangerous, to move forward with spiral CT screening for lung cancer before a randomised trial has confirmed its safety. Unfortunately, NY-ELCAP does just that.

We believe that the underwriting of NY-ELCAP is a poor use of public funds for three reasons. First, the study cannot tell us if screening saves lives. The fundamental design flaw is especially distressing because it could have been corrected if New York City had required a scientific review before allocation of funding. Peer reviewers would probably have insisted on a randomised design. Fortunately, two randomised controlled trials of spiral CT screening are under active consideration, one by the US National Cancer Institute, the other in the UK.

Perhaps even more concerning, NY-ELCAP could harm participants. Some will have false positive scans—data from the pilot study suggests that about 2000 people in New York will have a suspicious initial scan. Although few will undergo (unnecessary) biopsies, most will have to wait for up to 2 years until they are declared free of cancer. The biopsy procedures, via thorascopy or fine needle aspiration, are not trivial. Patients undergoing thorascopy need general anaesthesia and usually need chest tubes. And, although rare, complications such as serious infection or even death can follow either procedure. NY-ELCAP will also harm participants diagnosed with pseudodisease; however, there is no way of knowing how many people will be harmed by such overdiagnosis.

Finally, NY-ELCAP could actually make it harder to ever learn the true effect of spiral CT screening. New York City's optimistic promotion of NY-ELCAP could increase public demand for screening, a demand that is already growing as more health institutions across the country advertise the promise of spiral CT scans.[23] If people accept the assumption of benefit, it will be extremely difficult to recruit patients for the definitive trials needed. A US National Cancer Institute sponsored trial of bone marrow transplant for ovarian cancer, for example, had to be abandoned because eligible patients did not want to participate in the study—they wanted bone marrow transplantation.

The benefits of early detection and the value of screening are intuitively appealing ideas. It would be hard to find a more worthy target for screening efforts than lung cancer. Nonetheless, we must resist the temptation to move too fast, or our efforts could go up in smoke.

Conflict of interest statement
None declared.

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