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Lung cancer screening has the potential to save lives, but shall we do it?

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Summary

Almost three decades ago several controlled studies failed to show that lung cancer screening by chest x-ray (CXR) and sputum cytology improves survival in a screened population. A number of subsequent studies using chest computed tomography (CT) in smokers revealed lesions suspect for cancer in around 20% and had a lung cancer detection rate of approx. 1%. Since these trials lacked a control arm, the question whether screening has an impact on lung cancer mortality remained unproven. Recently, the preliminary results of the randomised controlled National Lung Screening Trial (NLST), a study organised by the US National Cancer Institute, confirmed for the first time that lung cancer screening by CT is associated with a reduction in lung cancer mortality (20.3%) and in all-cause mortality (7%) compared with a control group undergoing CXR at the same time intervals. However, before lung cancer CT screening can be recommended, many open questions need to be answered with respect to costs and reimbursement, duration of an appropriate screening programme and its psychological impact.

Key words: *low dose chest CT; lung cancer screening; early detection; lung cancer mortality*

Until the First World War lung cancer was a rare disease and fewer than 400 cases had been reported in the medical literature up to 1912 [1]. Thirty years later, Richard Doll and Bradford Hill were the first to demonstrate a close association between an extraordinary increase in mortality attributable to lung cancer and cigarette smoking [2]. Although the findings of this case-control survey were confirmed by others [3] and by prospective studies by the same investigators [4, 5], it took another two decades to become common knowledge in the medical community and the general public that cigarette smoking is the one major risk factor for lung cancer.

Lung cancer is the leading cause of death due to cancer worldwide. In Switzerland, this type of cancer is number one in cancer deaths among men (2000 deaths per year; 23% of all cancer deaths) and second after breast cancer in women, with 900 deaths (13%) [6]. The most effective way to lower the incidence of lung cancer is to reduce cigarette smoking. Recent changes in smoking habits in Switzerland were followed by a slight decrease in lung cancer mortality between the observation periods 1998–2002 and 2003–2007 in men. In women the incidence and mortality of lung cancer increased slightly within the same time period, most probably due to unchanged smoking habits [7]. However, even after smoking cessation individuals with a long-term smoking history continue to be at increased risk of contracting lung cancer. By the time symptoms develop, lung cancer is often at an advanced stage and the prognosis is dismal. Treatment of a less advanced and asymptomatic stage by surgical resection has been shown to be associated with substantially reduced mortality (e.g., in stage IA: 5-year survival >70%) compared with an approximate 15% overall 5-year mortality at all lung cancer stages. Hence screening for lung cancer might have a significant impact on lung cancer mortality.

Early detection trials with chest x-rays (CXR) and sputum cytology in the 1970s were futile in reducing lung cancer mortality, despite the higher proportion of early-stage cancer identified in the screened arm [8-12]. The advent of low-dose spiral chest computed tomography (LDCT) opened up new perspectives. In 1999 the Early Lung Cancer Action Project (ELCAP) of New York's Cornell University showed that spiral CT scans were sensitive enough to detect very small lung tumours (<1 cm), a sensitivity six times higher than that of CXR [13]. Several observational single-arm studies evaluating LDCT, including a population of almost 65 000 subjects, showed an average frequency of suspicious non-calcified solid lesions of 20% (range 7–53%). The average lung cancer detection rate was 1% (range 0.4–2.7%) with a proportion of stage I lung cancer of 81% (range 50–100%). The lung cancer detection rate depended on the proportion of non-smokers and heavy smokers over the age of 60 included in the studies. These observations were significant and readdressed the issue of early lung cancer detection. However, in the absence of control groups, the relevant question whether LDCT does have an impact on lung cancer mortality remained unresolved.

On November 4, 2010 the National Cancer Institute announced that the National Lung Screening Trial (NLST), launched in 2002, was ending. Independent experts who reviewed annual interim ana-lyses came to the conclusion that the study's primary objective, benefit for the group screened by LDCT, was proven [14]. An overview on the topic of lung cancer screening and a description of the methodological design of this landmark study were published online in November 2010 and as a full paper in January 2011 [15]. The NLST participants were randomised to either LDCT or CXR at baseline and at two annual follow-up examinations. The primary endpoint was lung cancer mortality, and secondary endpoints comprised overall mortality, lung cancer incidence and screening- and treatment-related morbidity. The target accrual was 25 000 persons in each arm and the recruitment goal was already reached after one and a half years with 53 456 participants at 33 screening centres across the US. The NLST included a very specific population of men and women, aged 55–74 years, who had a smoking history of at least 30 pack-years and had not stopped smoking more than 15 years ago. During the eight years' follow-up a total of 354 deaths from lung cancer had occurred among participants in the CT arm of the study, whereas a significantly larger number of 442 cancer deaths had occurred among those in the CXR group. This difference of 88 deaths implied a statistically significant 20.3% reduction in lung cancer mortality and was the reason for ending the study early. An additional finding, which was not the main endpoint of the trial's design, was that all-cause mortality was 7% lower in those screened with LDCT than in those screened with CXR. Approximately one quarter of deaths in the NLST were due to lung cancer, while other deaths were due to other conditions such as cardiovascular diseases. After a more comprehensive ana-lysis of the data it can be expected that more related details will be published in peer reviewed journals in due course.

Other screening trials are currently being performed worldwide, and in Europe six randomised studies are under way [16]. The NELSON trial involving individuals in the Netherlands and Belgium was designed to detect a 25% reduction in lung cancer mortality in subjects aged between 50 and 74 years who had smoked more then 15 cigarettes per day for over 25 years, or more than 10 cigarettes per day for over 30 years. LDCTs are performed at years 1, 2, and 4 in the screening arm, whereas those in the control arm undergo no tests while they remain asymptomatic. Initial results have shown a 0.9% lung cancer detection rate at baseline and a 27.2% proportion of invasive procedures which revealed benign disease. The Danish Lung Cancer Screening Trial comprises a similar risk population (50–70 years, ≥20 pack-years smoking history) and includes annual CT screening for five years. The baseline lung cancer detection rate was similar to that of the NELSON trial (0.8%). I assume that these and other similar controlled trials in Germany and Italy will eventually confirm the NLST findings. From a methodological point of view it is obvious that only a randomised controlled trial with mortality as the outcome has the potential to prove a causal relationship between screening and reduced mortality. The NLST complies with these ambitious standards and represents a historic landmark in the field of cancer screening. For the first time in thirty years of research this remarkable study demonstrates that screening by LDCT has a positive impact on lung cancer death and overall mortality in a high risk population.

The purpose of screening is early detection of disease with the potential for improved treatment and reduced mortality. Everyone would agree that this is a magnificent goal. However, it is not self-evident that screening does more good than harm [17]. To avoid cancer screening being initiated prematurely and without sound evidence of its cost-effectiveness and utility, the Swiss healthcare system needs a nationwide screening commission mandated to evaluate the evidence of the impact of screening interventions, to make recommendations and monitor the performance of ongoing screening regimens [18].

Only a minor proportion of lung lesions detected by LDCT will finally turn out to represent early lung cancer. The costs and side effects linked to the work-up of cases which eventually turn out to have no lung cancer have to be considered and include not only repeated LDCTs at shorter intervals but also PET scans and transthoracic, bronchoscopic and video-assisted thoracic biopsies. The NLST will, it is hoped, answer the question as to the costs per gained quality-adjusted years of life. An issue which cannot be adequately assessed by costs is the psychological impact of indeterminate findings on screened individuals who are awaiting the results of a follow-up LDCT or an invasive diagnostic procedure. In addition, the question remains whether health insurance should bear the cost of screening individuals who are not willing to stop smoking. It is well known that ex-smokers' risk of developing lung cancer declines considerably after smoking cessation, but never approaches the risk in never-smokers [19]. The last LDCT in NLST was performed two years after study inclusion. Thus, the question of an optimal time horizon for screening and optimal screening intervals will remain unanswered until the results are available of trials with a longer screening duration, such as the NELSON and other European trials with 5 years [16, 20] or the MILD trial with 5 screening rounds at 2-year intervals [16]. Patients screened by LDCT are exposed to a much lower radiation dose than from a regular diagnostic CT. Nevertheless, an increased lifetime risk of cancer due to exposure to ionising radiation will remain. The NLST will address the question whether the benefit of potentially finding a treatable cancer by repeated LDCTs outweighs the risk from exposure to a low dose of radiation, but a definite answer will not be forthcoming for the next decade.

Potential competing interests

No financial support and no other potential conflict of interest relevant to this article was reported.

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