Lung cancer screening: current situation and perspective

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Summary

Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality with 1,04 million new cases per year and 921 000 deaths, with the highest rates currently observed in Europe and North America. Once diagnosed, the 5-year survival rate for lung cancer in Europe fluctuates between 8% and 12%. Smoking is found in 90% of lung cancer cases. A successful, straightforward preventive strategy to reduce the incidence of the disease is a sustained prevention of tobacco consumption. However, because of the persistent risk among former smokers, early treatment following early diagnosis is still considered as potential development. There is currently no recommended screening strategy for lung cancer, reflecting the negative results of trials showing no mortality reduction following screening programs using chest X-ray and sputum examination. Low dose computed tomography has been recently assessed as a screening tool in observational studies suggesting better impact than the one obtained with chest X-ray. Five RCTs are currently under way to evaluate low dose computed tomography as a screening tool for lung cancer, with a total of 133,000 subjects. First results are expected for 2007. Until the completion of these studies, wild screening intervention should be avoided.

Key words: lung cancer; lung cancer screening; smoking cessation; X-ray; low dose CT

Introduction

Lung cancer is the major cause of cancer-related mortality in both men and women in industrialised countries and causes more deaths than colorectal, breast and prostate cancer combined [1, 2]. No screening strategy is currently recommended for lung cancer, as a result of the negative outcome of trials performed in the 1970s showing no impact on mortality following screening programs using chest x-ray and sputum examination. However, the theme is back because of recent advances in imaging procedures such as computed tomography, showing better performance to identify small neoplastic lesions. We will review the earlier lung cancer screening trials and we will discuss the new methods of screening, especially the CT scans. We will also compare the ongoing and planned experimental studies assessing the efficacy of low dose computed tomography (LDCT) as a screening tool for lung cancer and finally, we will list clinical recommendations provided by various health organisations.

Methods

This review is based on the published literature available in 2005. The Cochrane database was searched using the terms "screening" and "lung cancer" with no restriction. Among the 257 citations identified, 154 relevant articles were selected for full text review. Reference lists were also searched in "Chest", "New England Journal of Medicine", "Cancer", "Lancet" and "Radiology". An additional source of information includes direct contact with researchers involved in evaluation of screening strategies.

Relevance of screening for lung cancer

A remarkable feature of lung cancer is that it is the most avoidable among the frequent diseases. Non smoking is an effective preventive tool, since 90% of lung cancer is attributable to smoking in the general population [3]. There is a decreasing but persistent risk among former smokers [4].

To be screened in the general adult population, a condition has to be frequent (with some exception as for phenylketonury screening) [5]. Lung cancer is the most common fatal cancer in terms of both incidence and mortality with 1,04 million new cases per year and 921000 deaths in the world, with the highest rates currently observed in Europe and North America [6, 7]. The incidence and mortality rates are higher for men than for women. However, lung cancer mortality has increased markedly among women since 1960, following increased prevalence of smoking [8]: in the European Union, the mortality increased from 8,9 to 10,5/100,000 with peaking rates expected in the next decade [9, 10]. Meanwhile, the male mortality declined from 52,4/100,000 in 1985–89 to 49,8 in 1990–94. Any differences of rates between European countries reflect a time-lag in smoking habit [11, 12].

Several procedures to provide lung tissue are currently available: CT-guided fine-needle aspiration, transthoracic core-needle biopsy and video assisted thoracoscopy. Complication rates of these procedures are low [13, 14].

Another prerequisit for screening is that the disease must be severe, with a prognosis related to the stage of the disease. Once diagnosed, the overall survival rate for lung cancer in Europe varies between 8% and 12%. The overall survival rate for colorectal and breast cancer are respectively 41% and 67% [7]. The 5-year survival following resection of stage I lung cancer (TNM classification) is 60–70%, versus 8–13% following treatment of stage III–IV [15–17].

Screening methods

Chest radiography
(combined or not with sputum cytology)

Chest radiography (CXR), with or without sputum cytology (SC), was the first screening tool to be considered. Since the 1950s, six non-randomised screening studies and four randomised trials (RCTs) have been performed. Overall, the non-randomised screening studies suggested a lower case fatality rate, but no clear reduction in mortality from lung cancer [18]. The RCTs, including a total of 35,983 subjects, suggested no effect of CXR screening, with or without sputum cytological examination, on lung cancer mortality as recently confirmed by a meta-analysis [27]. Results are summarised in table 1 [19–26]. Interestingly, analysis using data from extended follow-up of two of these studies showed that subjects undergoing more frequent CXR screening presented higher lung cancer mortality than those receiving less frequent screening [28, 29]. A result that might be explained by a misclassification bias; deaths due to other causes might be more likely to be attributed to lung cancer in the screening group [27].

Sputum cytology and biomarkers

Several RCTs used sputum cytology in combination with CXR [23–25], looking for dysplastic change as the preclinical marker for carcinoma in situ and invasive cancer [30]. The recent development of automated quantitative cytometry and molecular biomarkers has renewed the interest in sputum collection for lung cancer screening [31, 32]. The use of serum markers based on proteomic patterns is under evaluation to identify ovarian and

Table 1

RCTs evaluating chest radiography and sputum cytology as a screening tool.

Study	Intervention	Control	Lung cancer related mortality relative risk (95% CI)
Johns Hopkins Lung Project [19, 20]	Annual CXR + 4 monthly SC	annual CXR	0.80 (0.65–1.00)
Memorial-Sloan Kettering Lung Project [21, 22]	Annual CXR + 4 monthly SC	annual CXR	0.98 (0.76–1.26)
Mayo Lung Project [23, 24]	4 monthly CXR/SC	advised to have CXR/SC annually	1.03 (0.93–1.14)
Czechoslovak Lung Study [25, 26]	6 monthly CXR/SC the 3 first years + annual CXR for 3 more years	CXR at baseline + CXR/SC after 3 years + annual CXR for 3 more years	1.16 (1.00–1.35)

CXR: chest radiography; SC: sputum cytology; CXR/SC: both

Table 2

Observational studies evaluating LDCT as a screening tool [NR: not reported].

Study, Year, Location	Number of participants	Sex	Age (Median)	Exposure (Median) [Former smokers proportion]	Non-calcified pulmonary nodule N(%)	Lung cancer N(%)	Stage I disease N(%)
Henschke, 1999, USA [37, 38] (ELCAP)	1,000	M = 540 F = 460	≥60 (67)	Only smokers ≥10 pack-yr (45)	233(23.3%)	27(2.7%)	23 (85%)
Sone, 2001, Japan [39]	5,483	M = 2,971 F = 2,512	≥40 (64)	Smokers or former smokers [46.1%] ≥1 pack-yr (NR)	279 (5.1%)	22(0.4%)	22 (100%)
Diederich, 2002, Germany [40]	817	M = 588 F = 229	≥40 (53)	Only smokers ≥20 pack-yr (45)	409 (50.1%)	11 (1.35%)	6 (58%)
Nawa, 2002, Japan [41]	7,956	M = 6,319 F = 1,637	≥50 (NR)	Smokers or former smokers [62.1%] (NR)	2,099 (26.4%)	36 (0.45%)	31 (86%)
Sobue, 2002, Japan [42] (ALCA)	1,611	M = 1,415 F = 196	≥40 (NR)	Smokers or former smokers [86%]	186 (11.5%)	13 (0.81%)	10 (77%)
Swenson, 2002, USA [43,44] (Mayo Clinic)	1,520	M = 785 F = 735	≥50 (59)	Only smokers ≥20 pack-yr (45)	782 (51.4%)	21 (1.38%)	14 (66%)

prostate cancer [33, 34]. However, application of proteomics for lung cancer needs further investigations.

Low dose computed tomography

The development of fast, high resolution CT scans (spiral or helical CT) allows the acquisition of multiple slice images within a single breath hold by the patient. With multiple images, the 3-dimensional shape of small nodules can be characterised [35]. Diagnostic CT scan examination uses 200 milliampere seconds (mAs), but lower dose (around 60 mAs) can be used for screening purpose. Imaging with this low-dose computed tomography (LDCT) is of lower quality than with the full dose CT, but is better than the one provided by CXR [36].

First evaluations of LDCT as a screening tool were done in observational (ie non-experimental) studies [37–44]. Results are presented in table 2. No mortality rates have been reported because of the absence of a comparison group and lead time issue.

However, significant observations have been made [45]. LDCT detects a larger number of lung cancers than CXR; for example, Henschke et al. reported 27 lung cancers by LDCT versus 7 by CXR [37]. Furthermore, the majority of lung cancers detected by LDCT are at stage I; eg 85% in the ELCAP study [37, 38]. Expectedly, the number of non-cancerous lesions detected by LDCT largely exceeds the number of cancerous nodules, reflecting a low positive predictive value of LDCT. However the proportion of patients finally undergoing a biopsy is low and the proportion of cancers among those undergoing a biopsy is high, because non-invasive examination carried out among positive screenees (such as high-resolution CT, serial CT scans and 3-D reconstruction) strongly reduces the false positive rates. Overall, the biopsy rates after LDCT ranges between 4,8 and 14,5% among patients undergoing high-resolution CT, and 63 to 90% of them are diagnosed with a cancer [17]. It should be remembered that biopsies are associated with risks and that mortality and morbidity vary depending on the type of biopsy performed, with increase morbidity and length of stay after open lung biopsy compared to percutaneous transthoracic lung biopsy [46].

Overall, these evaluations have reopened the question of early detection. The least biased way to evaluate a screening tool is to do RCTs, using lung cancer mortality as the primary end-point.

Pilot randomised trials evaluating low dose computed tomography as a screening tool

In the perspective of large scale screening trials (ie to assess feasibility of enrolment, randomisation and follow-up), several pilot RCTs have been conducted. Included are the Lung Screening Study (LSS) [1], the Garg et al. Study [47] and the French Depiscan [48]. An Israeli RCT has been reported by others, however with unpublished (or untraced) results [36].

The Lung Screening Study (LSS) [1] is a 1-year sub-project of the US Prostate, Lung, Colorectal and Ovarian Cancer Screening trial. 3,318 participants were randomised into a LDCT arm (N = 1,660) and a CXR arm (N = 1,658). One single screening wave was evaluated, thus the evaluation is related to prevalent cases (and not to incident cases when several screening waves are taken

into account). The proportion of screenees with a positive test was 20,5% in the LDCT arm and 9,8% in the CXR arm. The detection rate of cancer was 1,9% for LDCT and 0,45% for CXR.

The study conducted by Garg et al. [47] is a small single wave study with a LDCT arm (N = 92) compared to a no-screen group (N = 98) arm. 33% of screenees in the LDCT arm presented a positive test, defined as the presence of one to six non-calcified nodules.

DEPISCAN [48] is a RCT which has been conducted in the perspective of the GRANDE-PISCAN. Among the 744 participants recruited, 678 were finally included for randomisation. 70% of them were male, mean age was 57 (47–77) and proportion of ex-smokers was 32.5%. CXR was used as screening tool in the control group (N = 339) and LDCT in the experimental group (N = 339). During intermediary analysis, among LDCT screenees (N = 216), nodules (one or more) were detected in 51,8% of them; six were diagnosed as cancer. Among the CXR screenees (N = 209), nodules (one or more) were detected in 7.4% of them; one was diagnosed as cancer.

Ongoing randomised trials evaluating low dose computed tomography as a screening tool

Table 3 presents the three ongoing RCTs [49–51]. The National Lung Screening Trial (NLST) [49] combines several initiatives coming from the US National Cancer Institute and the American College of Radiology Imaging Network. 50,000 participants are randomised into a LDCT arm (N = 25,000) and a CXR arm (N = 25,000). The study is designed to give a statistical power of 90% to detect a 21% mortality reduction. The end of follow-up is expected in 2009.

The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial is a Dutch-Belgian study which started in April 2003. 16,000 participants are expected in the trial (with 12,000 already enrolled) [50].

The Danish Lung Cancer Group (DLCG) trial started in November 2004, in close collaboration with the Danish Institute of data security and the Danish national cancer central registries (for the annual follow-up). A quarter of the planned number of participants (4,000) has been already enrolled. Danish data are expected to be pooled with those of the Nelson trial [51].

Both the NELSON and the DLCG trials compare LDCT to usual care (ie exclude a CXR or any other screening in the control group as it is done in the NLST trial).

Planned studies evaluating low dose computed tomography as a screening tool

Table 3 describes the characteristics of planned RCTs [52, 53]. Two large RCTs for lung cancer screening with LDCT (the LUCAS project in the UK and a German project) were unable to get the needed funding [54, 55].

Finally, there are also other observational, one-armed ongoing and planned studies [56–59].

Current practice for lung cancer screening

Table 4 lists the clinical recommendations provided by various organisations [17, 45, 60]. None of them recommend screening lung cancer. Even though we did not find any data on the use of LDCT among smokers for routine clinical care screening purpose, this might not reflect the actual practice of physicians. A survey performed in 1996 among 1,271 Australian family physicians showed that 20% of the physicians indicated that an annual CXR was an effective screening test, and 25% of them reported that they recommend an annual CXR as a screening test for asymptomatic heavy smokers [61]. Partly due to the recent media attention (whole body screening), primary care physi-cians have to face patients' interests for early lung cancer diagnosis. Given the lack of data on evidence of lung cancer screening, advising patients is difficult [62]. The 2004 U.S. Preventive Service Task Force recommendations on shared decision-making for interventions for which evidences are insufficient (eg lung cancer screening) are helpful. They proposed techniques to facilitate the decision-making process, including a 5As framework (assess, advise, agree, assist, arrange), during which benefits and harms are balanced [63]. Other organisations proposed, in addition to a shared decision-making process, to include, whenever possible, high-risk individuals in ongoing trials [64]. But,

Table 3

Ongoing and planned RCTs for lung cancer screening with LDCT.

LDCT	Ongoing RCTs			Planned RCTs	
Trial name	NLST [49]	Nelson [50]	DLCG [51]	Grandepiscan [52]	Norway [53]
Country	USA	Netherlands + Belgium	Denmark	France	Norway
Start	2002	2003	2004	2006	Not reported
Number of years of screening	3	3	5	5	5
Frequency of screening	Annual	Years 1, 2, 4	Annual	Annual	Annual
Total duration (screening + follow-up)	5	7	National registry	10	7
Cancer-related mortality endpoint	Yes	Yes	Yes	Yes	Yes
Age inclusion criteria	55–74	50–75	50–65	50–70	57–71
Pack-year inclusion criteria	≥30	≥20	≥20	≥22.5	≥20
Ex-smokers included	Yes	Yes	Yes	Yes	No
Number of participants	50,000	16,000 (already 12,000 in mid-2005)	4,000 (already 1,200 in mid-2005)	40,000	23,000
Randomisation	1:1	1:1	1:1	1:1	1:1
Multicentre	Yes	Yes	Yes	Yes	Yes
Screening procedures in control group	CXR	None	None	Chest x-ray	None
Smoking cessation program	No	Yes	Yes	No	Yes

Table 4

Selected recommendations from health organisations.

Organisation	Recommendation
American Cancer Society, 2001 [57]	Recommends against routine screening of asymptomatic persons. Individuals interested in early detection should be encouraged to participate in trials.
American College of Chest Physicians, 2003 [45]	Recommends that individuals should only be screened in the context of well-designed clinical trials.
US Preventive Services Task Force, 2005 [17]	Evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer.

once again, the authors highlighted the need to discuss smoking cessation and assistance, to present the high false positive rate of imaging procedures and the potential harms of nodule investigations.

Discussion

Worldwide, lung cancer is the most common fatal cancer in terms of both incidence and mortality with 1,04 million new cases per year and 921000 deaths, with the highest rates currently observed in Europe and North America. A key feature of lung cancer is the availability of a primary prevention and that smoking cessation intervention programs have recently been showed to reduce overall mortality [65]. Thus, all possible efforts should be made to reduce the incidence of the disease through a sustained strategy of prevention of tobacco consumption, including reduced accessibility (eg tax increase) and appropriate information (ie advertising ban). However, because there is a decreasing but persistent risk among former smokers, early treatment following early diagnosis is still considered as potential development. Adopting a new screening is a significant decision in public health, especially when this technology is costly (LDCT) and is likely to be applied to a large fraction of the population (smokers and recent ex-smokers). Such a decision must be based on good evidence and sound arguments.

There is no scientific evidence for recommending early diagnosis or systematic screening of lung cancer using LDCT. Such good evidence will be provided from RCTs, using mortality from the diseased targeted by the screening as primary endpoint. Five RCTs are currently under way to evaluate LDCT as a screening tool for lung cancer, with a total of 133,000 subjects.

Another point is how many RCTs are needed to provide conclusive evidence for a sound decision? As a matter of fact, effectiveness of mammography among women older than 50 years has been recognised after the completion of eight RCTs (N = 212,000) [66]. Effectiveness of faecal occult blood testing has been recognised after four RCTs

(N = 330,000) [67]. This question is related to two different aspects, one related to the power of the studies, the second on the variety of the situation investigated.

Studies power

Eliciting the power of a comparative study (ie the probability of detecting a difference between two interventions when a difference does exist [68]) is a controversial matter after the negative results of RCTs on CXR screening. Several authors consider that the targeted reduction of mortality (30%) is too large, and that more modest gains (eg 15%) should be considered as sufficient. For example, two widely accepted screening strategies achieve mortality reduction between 22 to 28% for breast cancer, and between 16 to 23% in colorectal cancer. However, decreasing the targeted reduction of mortality means a substantial increase in the study population.

Another way to increase the power of a comparative study is to select study population at higher risk for the disease, ie to increase the number of events in each arm available for the analysis. There is of course a trade-off between the increasing power of the study and the decreasing generalisability of the results when population at extremely high risks are considered.

Van Klaveren et al. [68] have listed useful recommendations on the way study population should be selected for evaluation of lung cancer screening: smokers with a smoking history of at least 30 years, average consumption of at least 20 cigarettes a day (≥30 pack-yr), and ex-smokers within 5 years of quitting. Considering the current trend of increasing smoking among teenagers, people should be invited once they have reached 30 pack-yr, regardless of age. For the upper age cut-off level, Van Klaveren et al. recommend the age at which the life-expectancy of the population drops below 10 years, ie 70 and 75 years for males and females respectively [69]. Identification of other risk factors that might guide screening is ongoing, including the use of spirometry, family history, occupational history, and possibly genetic biomarkers [70].

Studies variety

A major point is related to the heterogeneity between the different trials, such as inclusion criteria, therapeutic procedures and control group. This reflects different practicalities and availabilities between countries, but these circumstances may limit the pooling of data.

Most of the large RCTs protocols are based on the International Early Lung Cancer Action Project (I-ELCAP) [71]. This project provides practical recommendations, related for example to the production and reading of images, or to the screen-

ing frequency. However, despite this coordination effort, there are differences among RCTs, both planned and ongoing, in terms of age of participants, definition of target population (eg number of pack-yr), screening frequency, duration of follow-up, etc.

A major difference between the trials is the presence or absence of screening in the control group. The most appropriate control should be a no-screen group because there is currently no evidence based strategy with an impact on lung cancer mortality. This is the choice made by the NELSON and Danish RCTs. At the contrary, the NLST and the GRANDEPISCAN use a CXR screened group as control. The argument is that the efficacy of CXR screening is still under evaluation within the framework of the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial [72]. The baseline results of lung cancer detection rate of this study have been recently published but data on lung cancer mortality are not available yet [73]. This two-arms projects (2 x 74,000 subjects) is running now, offering to the intervention arm a CXR screening (one at entry and then annually for 5 years) and to the control arm no screening: thus, if the result is positive (lung cancer mortality reduction), CXR would become the new standard against which LDCT should be evaluated. The argument against the use of CXR is that its efficacy has not been proven until now, resulting in an unnecessary irradiation in the control group.

Finally, a crucial question is to know how far screening programs detect "sleeping" cancers, ie overdiagnoses lesions which do not affect survival. Data are still conflicting. In an autopsy study, 28% of lung cancers identified were not diagnosed during life [74]. Similarly, a retrospective study using DNA flow cytometry showed that screen-detected tumours were less aggressive than symptom-detected tumours [75]. On the other hand, there are data showing that patient with screen-detected, early-stage cancers suffered a high lethality if left untreated (because of personal choice) [16]. Moreover, the type of lung cancer detected by screening programs may differ from those detected by routine clinical care. Indeed, the adenocarcinoma-squamous ratio of lung cancer is frequently higher in screening trial than in clinical care practice. This difference might be due to the fact that adenocarcinomas are typically peripherally located, and thus more easily detectable by lung imaging techniques.

Finally, another concern is the need for further costly evaluations and the anxiety created by the identification of non-malignant lesions. In this context, European studies and particularly the French Grandepiscan study would offer the opportunity to gather interesting data for a national screening program perspective.

Conclusions

Taking care of lung cancer patients will remain a daily task for decades. This is true worldwide (because of the grim prevision in the developing countries [76]), but also in the middle course in the developed world: incidence of lung cancer is increasing among women, and is only starting to decrease among men. Furthermore, there are worrying signs of increasing consumption among adolescents. In this perspective, the careful evaluation of early diagnosis tools is a sound project.

There might be five RCTs evaluating LDCT as a screening tool for lung cancer, with a total of 133,000 subjects. The total number of enrolled subjects in mid-2005 was already 63,200. The control group include either non-screen or chest X-ray screen participants and all trials except one include ex-smokers as participants. First results are expected for 2007. Until the completion of these studies, individual-based screening intervention should be avoided.

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