Lung cancer remains the leading cause of cancer-related deaths in the world. At present, the only high rate of cure therapy is surgical resection at early stage of disease. Early detection could potentially decrease lung cancer mortality suggesting that this cancer should be a good candidate for screening. Results of trials involving chest X-ray, sputum cytology and low-dose computed tomography (CT) are discussed here. The latter tool offers advantages over chest X-ray, but final results from controlled well conducted trials are necessary before the real utility of CT mass screening can be determined. Further approaches to secondary prevention such as screening with positron emission tomography (PET), autofluorescence bronchoscopy and biomarkers hold great promise for the future.

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Keywords: Lung cancer; Screening

1. Introduction

Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Europe and in other Western countries. The annual number of newly diagnosed patients in Europe exceeds 200,000, accounting for about 20% of all cancer deaths, and on average 25% of male cancer deaths across the continent. In females, lung cancer accounts for 10% of deaths. Five-year survival is 9.6%, ranging from 5.9% in Denmark to 16.2% in Switzerland [1,2]. More than 150,000 patients die in the United States (U.S.) each year from this disease, and the overall mortality has not significantly changed in decades [3–5]. Lung cancer treatment and survival are functions of disease stage at presentation. Most patients at diagnosis have advanced disease, as stages I and II rarely cause symptoms becoming difficult to be detected. The overall 5-year survival rates remain at approximately 15%, with 22–67% for stages I and II lung cancer and 1–25% for advanced stages (Table 1) [6]. At present, the only chance of cure is surgical resection at early stage of disease with better prognosis for small tumours as compared to larger ones. Early detection could potentially decrease lung cancer mortality everywhere by diagnosing the
disease at an earlier and potentially more curable stage. These data suggest that lung cancer should be a good candidate for screening.

Lung cancer is clinically divided into two categories: non-small cell lung cancer (NSCLC), including squamous carcinoma, adenocarcinoma and large cell carcinoma, representing approximately 80% of all lung cancers and small cell lung cancer (SCLC). The latter is known to metastasize early and is generally not considered amenable for surgery [7].

An important issue regards the population to be enrolled into screening trials. About 85% of lung cancers is caused by smoking and the risk for developing the disease is higher in current smokers than in former smokers or non-smokers. An increased risk for lung cancer remains even many years after cessation of smoking [8]. It has been estimated that 80% of lung cancer deaths among men and 75% among women are attributable to smoking [7]. Therefore, primary prevention is to reduce smoking habits for a minor exposure to inhaled carcinogens from cigarette smoke. Screening trials for early detection of lung cancer are considered secondary prevention. These are less efficient and more costly than primary prevention but can be made available for people who have already been exposed to carcinogen-enrolling individuals with at least 10–20 pack-years smoking [8].

Age is another risk factor for developing lung cancer, with the incidence rising up to the reaching of the eighth decade in men and the seventh in women [8]. The aim of screening is the detection of early stage disease to be operated on, but the old age could contraindicate the surgery. Therefore, many screening studies defined the low and high limits of age for participants, and/or criterion for thoracic surgery fit patients in case a malignancy was found [9–17].

A screening test must be capable of detecting the lung cancer at a point in which the course of its natural history can be altered through treatment. Moreover, the screening test should be non-dangerous nor should it have too many false-positive results [18]. Therefore, the prevalence, specificity, sensitivity, accessibility, cost and associated morbidity of the screening test must be reasonable [19].

In the last decades, several tools were adopted for lung cancer screening reflecting the progress in imaging techniques and improvements in trial designing [8]. We reviewed the most remarkable trials performed, looking at the new screening approaches in perspective.

2. Screening biases

The most important outcome measure of the effectiveness of a screening is the demonstration that the mortality rate from the disease is significantly lower in the total screened population when compared with the cancer mortality rate in an equivalent population or unscreened people. Individuals with cancer identified by screening will have longer survival times than those diagnosed with usual clinical detection. These apparent increased survival times are not always equivalent to reduction in mortality from cancer. Survival from the time of diagnosis is not an appropriate measure of screening and can be misleading because of the effects of certain biases [20].

One major potential source of bias is known as the volunteer bias in which those individuals who participate in screening programs differ from general population in some manner that may be relevant to overall disease specific mortality [8,20]. Lead-time bias is the interval between the time of diagnosis of a disease as identified with a screening procedure and the time of usual clinical detection subsequent to symptoms development. Therefore, despite the apparent increase in survival time, the natural history of the disease and the time of death remain unchanged [8,20].

Length-time bias is an over-representation of more indolent cancer cases detected by screening compared to the unscreened population. If the outcomes of individuals with screening-detected cancers in uncontrolled clinical screening trial are compared with a general population of clinically detected cancers, the screened group may show an artificially higher survival rate due to length-time bias. A controlled trial obviates this bias [8,20].

Overdiagnosis bias is defined as finding lung cancers that are not life threatening (including neoplasms that would regress, remain stable or progress slowly), and thus, lead to unnecessary resection. New screening strategy detects less aggressive tumours, some cases of benign conditions artificially elevating the apparent survival benefit. Controlled trials, with standardized pathologic review, offset the effects of this bias [20–24].

Stage-migration bias may occur when outcomes of a screening strategy are compared with historical controls. Any new clinical investigation includes more accurate cancer staging data than previous data; this results in an apparent increase in survival rates by age. Comparison of screening outcomes to outcomes from a contemporaneous similar unscreened control group allows more equivalent staging techniques and criteria in both groups and obviates stage-migration bias [20]. Therefore, all these abovementioned biases should be considered in designing a controlled screening trial and also in evaluating the reported results.
3. Past

The first screening test for lung cancer used in the past was the two-dimensional chest X-ray. In 1968, were published the data of a trial performed in London, in which 55,034 men were randomised to chest X-ray every 6 months for 3 years or chest X-rayed at the beginning and the end of the 3-year period (control group). A total of 132 versus 96 cases of lung cancer were identified in the intervention and control group, respectively. Lung cancer mortality was similar, with 62 deaths in the frequently screened group and 59 in the control group [25,26].

The following four randomised trials integrated chest X-ray with sputum cytology. Three studies were performed by the U.S. National Cancer Institute (NCI), two of which (the Johns Hopkins Lung Project and the Memorial Sloan-Kettering Cancer Center Lung Cancer Screening Program), randomised individuals to annual chest X-ray alone (control arm) or plus sputum cytology analysis every 4 months. The Memorial Sloan-Kettering study, conducted over an 8-year period from 1974, enrolled a total of 10,040 subjects detecting 144 lung cancers per arm. No differences in terms of stage distribution, resectability, survival or disease specific mortality between groups were reported [10,27]. The third NCI trial, the Mayo Lung Project, over a period of 6 years from 1971, randomised 10,933 subjects to chest X-ray and sputum cytology every 4 months versus chest X-ray and sputum cytology annually. In this study no differences in survival or lung cancer-related mortality were reported [11,29,30].

The last trial, started in 1975 in Czechoslovakia, randomised 6364 male smokers to chest X-ray and sputum cytology every 6 months for 3 years or at the beginning and after 3 years screening. After 3 years, both groups entered a follow-up period during which they received annual chest X-ray. A greater number of lung cancers (206 versus 160) were reported with significantly earlier stage of malignancy at diagnosis and improved 5-year survival. Unfortunately, the trial reported no reduced mortality from lung cancer even with follow-up extended to over 20 years [12,31].

In Table 2, the five screening randomised trials for lung cancer of two-dimensional chest X-ray with or without sputum cytology are reported. Considering the results reported by these five studies, chest X-ray with or without sputum cytology failed to reduce the mortality from lung cancer. However, several critiques have been provided. International Union Against Cancer observed that many of these trials may be invalid due to the absence of an unscreened study arm and thus no determination of true efficacy could have been made [32]. Moreover, no women

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>Scheme</th>
<th>Age</th>
<th>Cigarette smoking exposure</th>
<th>No. Participants</th>
<th>Detected lung cancer (%</th>
<th>Survival Lung cancer mortality</th>
<th>Surv</th>
<th>No.</th>
<th>Screening arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>London [25,26]</td>
<td>CXR every 6 mo for 3 yr bx</td>
<td>≥ 45</td>
<td>100% – PY = NS</td>
<td>20,723</td>
<td>132</td>
<td>NR</td>
<td>2.1</td>
<td>3</td>
<td>CXR every 6 mo for 3 yr b 25,311</td>
</tr>
<tr>
<td>MSKCC [10,27]</td>
<td>Annual CXR + sputum cytology every 4 mo</td>
<td>≥ 45</td>
<td>100% – PY = NS</td>
<td>4,968</td>
<td>144</td>
<td>35 (5-yr)</td>
<td>2.7</td>
<td>2</td>
<td>Annual CXR b 5,072</td>
</tr>
<tr>
<td>Johns Hopkins [9,28]</td>
<td>Annual CXR + sputum cytology every 4 mo</td>
<td>≥ 45</td>
<td>100% – PY = NS</td>
<td>5,226</td>
<td>202</td>
<td>20 (8-yr)</td>
<td>3.4</td>
<td>2</td>
<td>Annual CXR b 5,161</td>
</tr>
<tr>
<td>Mayo [11,29,30]</td>
<td>CXR + sputum cytology every 4 mo for 6 yr</td>
<td>≥ 45</td>
<td>100% – PY = NS</td>
<td>4,618</td>
<td>206</td>
<td>10 (15-yr)</td>
<td>3.9</td>
<td>2</td>
<td>Recommended annual CXR + sputum cytology b 4,593</td>
</tr>
<tr>
<td>Czechoslovakia [12,31]</td>
<td>CXR + sputum cytology every 6 mo</td>
<td>≥ 45</td>
<td>100% – PY = NS</td>
<td>3,172</td>
<td>140</td>
<td>30</td>
<td>5.4</td>
<td>2</td>
<td>CXR + sputum cytology at end of 3 yr b 3,174</td>
</tr>
</tbody>
</table>

CXR: two-dimensional chest X-ray; mo: months; yr: year; PY: pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked); NS: not specified; NR: not reported.

a Per 1000 person-years.

b Control arm.
were included in any of these trials despite the fact they are believed to be of higher susceptibility than men to lung cancer and whose incidence has risen. People enrolled in these studies were not at high-risk for lung cancer due to smoking history, because the inclusion criteria in some cases allowed to randomise subjects with only one pack-year of smoking [8]. Another criticism concerned the sample size of these trials, which was considered inadequate [18]. Based on these biases, it is impossible to draw any conclusion from these studies. In order to further determine the role of chest X-ray in screening for lung cancer, a large randomised, controlled, NCI-sponsored trial (the Prostate, Lung, Colorectal and Ovarian – PLCO – Cancer Screening Trial) is ongoing. For lung cancer, the smokers receive annual chest X-ray for 3 years, whereas non-smokers will undergo only two annual repeat screenings. This study planned to randomise 148,000 men and women aged 55–74, it has an 89% power to detect a 10% reduction in lung cancer mortality, but the results are not expected to be published before 2010 [16,33].

4. Present

Low-dose computed tomography (LDCT) used as a screening tool for lung cancer allows a low-resolution image of the entire thorax to be obtained in a single breath-holding with low radiation exposure [34]. LDCT, when compared with chest X-ray, was able to detect approximately three to five times as many lung cancers with a difference in the average size of the tumour (12 mm for LDCT and 30 mm for chest X-ray) [14,15]. In addition, data obtained through LDCT and standard CT scans can be used to reconstruct three-dimensional images that can be assessed sequentially for evidence of growth patterns prior to invasive diagnostic tests [35]. For these reasons, LDCT emerged as a new and promising screening test for early detection of lung cancer.

A non-randomised historical comparison between the outcomes of about 18 years of screening with chest X-ray and sputum cytology and a following period of 5 years of the same screening plus LDCT was reported. In the first period, 43 patients with primary lung cancer were found, compared to 36 patients of the second period. The percentage of stage I disease diagnosis increased from 42 to 81%, and the 5-year survival from 48 to 82%, respectively. These results suggest that the screening with LDCT can increase the diagnosis of early stage lung cancer but does not constitute a strong evidence of a mortality benefit [36].

At the moment few trials have been published as full reports, reporting the prevalence results and in less studies also incidence results. All of them enrolled both men and women and, prevalently current or former smokers. The Early Lung Cancer Action Program (ELCAP) enrolled 1000 symptom-free volunteers, aged 60 years or more, with at least 10 pack-year history of smoking who were fit to undergo surgery. They received yearly LDCT and chest X-ray in a single arm study. A total of 233 non-calculated nodules on spiral CT scan were detected and 183 underwent a high-resolution CT. Of these, 27 were diagnosed to be lung cancer (23 at stage I). The lung cancer detection rate was 2.7%. Among these, 27 malignant nodules, 20 nodules were not found on standard chest X-ray; but no malignant nodules were detected by chest X-ray that were also not seen by LDCT. In the second year of screening (incidence), seven cancers were diagnosed and six were stage I [15,37]. The study by Mayo Clinic enrolled 1520 subjects, aged 50 years or more, who underwent annual sputum cytology and DNA analysis, too. Non-calculated nodules were identified in 1000 subjects 1-year after baseline screening. A total of 25 lung cancers (22 NSCLC and 3 SCLC) were diagnosed, of which 2 were detected by sputum cytology only. Stage I disease was reported in 14 patients and the lung cancer detection was 1.38%. Two years after baseline LDCT scanning, further 588 non-calculated nodules were identified (incidence), of which 10 were lung cancer (9 stage I) [17,38].

Sone et al. screened, in a mobile unit, 5483 persons aged 40–74 years, most of which underwent to chest X-ray and sputum cytology, while 3967 subjects received chest X-ray concurrently with LDCT. Only 953 (24%) individuals were smokers and underwent sputum cytology. This trial enrolled subjects from the same geographic area and represents the only true population-based screening. Nineteen lung cancers were diagnosed and 16 of them were in stage I. Only 1 of 17 lung cancers that were ≤2 cm was seen on chest X-ray. One lung cancer not seen on LDCT was diagnosed by sputum cytology. Lung cancer detection rate was 0.48%, significantly higher than the rate of 0.03–0.05% reported in the same area prior to LDCT screening. Moreover, the difference in prevalence of lung cancer between smokers and non-smokers was non-significant (0.52% versus 0.46%, respectively), probably due to a small sample size of smokers [14].

Sobue et al. conducted a one-arm longitudinal screening project. A total of 1611 asymptomatic patients aged 40–79 years, 86% with smoking history, were screened by LDCT, chest X-ray and sputum cytology with a 6-month interval. Fourteen cases of lung cancer were detected with 77% being stage I. At repeated screening, in 7821 examinations, 22 lung cancers were diagnosed of which 82% were at stage I [39].

Titiola et al., in another small trial, screened 602 persons with evidence for asbestos-related lung disease. The participants had also a median cigarette consumption of 24 pack-years. Five lung cancers were found out of 111 identified non-calculated nodules. The lung cancer detection rate was 0.40% despite the added risk of asbestos exposure but, probably, for this reason no stage I disease was reported [40].

Nawa et al. reported results of baseline and 1-year follow-up, non-randomised screening study that enrolled 7956 subjects. Of those participants, 5568 were screened again 1 year later. During the baseline screening, 2865 solitary pulmonary nodules were detected and primary lung cancer was histologically confirmed in 41 cases (35 were stage I). The prevalence was 0.44% of all participants from the baseline, and 0.07% from the repeated screening [41].
Table 3

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>No. of participants</th>
<th>Sex</th>
<th>Age</th>
<th>Risk factors exposure</th>
<th>No. of non-calcified nodules</th>
<th>No. of lung cancers</th>
<th>Stage I (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henschke [15,37]</td>
<td>1000</td>
<td>M = 540</td>
<td>≥60</td>
<td>Smokers 100%/PY ≥10 Asbestos 14%</td>
<td>235/63 (incidence)</td>
<td>27/7 (incidence)</td>
<td>25/6 (incidence)</td>
</tr>
<tr>
<td>Sone [14]</td>
<td>5483</td>
<td>M = 2971</td>
<td>≥40</td>
<td>Smokers 46.1%/PY ≥1</td>
<td>279</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Swensen [17,38]</td>
<td>1520</td>
<td>M = 765</td>
<td>≥50</td>
<td>Smokers 100%/PY ≥20</td>
<td>2244/588 (incidence)</td>
<td>25/10 (incidence)</td>
<td>14/9 (incidence)</td>
</tr>
<tr>
<td>Sobue [39]</td>
<td>1611</td>
<td>M = 1415</td>
<td>≥40</td>
<td>Smokers 86%/PY = NS</td>
<td>186/721 (incidence)</td>
<td>14/8 (incidence)</td>
<td>10/7 (incidence)</td>
</tr>
<tr>
<td>Tiitola [40]</td>
<td>602</td>
<td>M = 591</td>
<td>Mean 63</td>
<td></td>
<td>111</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nawa [41]</td>
<td>7956</td>
<td>M = 6319</td>
<td>≥50</td>
<td>Smokers 62.1%/PY = NS</td>
<td>2865</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>Diederich [43,44]</td>
<td>817</td>
<td>M = 588</td>
<td>≥40</td>
<td>Smokers 100%/PY ≥20 Asbestos 2.4%</td>
<td>858/174 (incidence)</td>
<td>12/10 (incidence)</td>
<td>7/6 (incidence)</td>
</tr>
<tr>
<td>McRedmond [42]</td>
<td>449</td>
<td>M = 224</td>
<td>≥50</td>
<td>Smokers 100%/PY ≥10 Asbestos 7.6%</td>
<td>155</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

M: male; F: female; PY: pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked); NS: not specified.

McRedmond et al. reported data about 449 subjects, aged ≥50 years, smokers, screened with LDCT and finding 155 non-calcified nodules of which 2 were detected to be lung cancers with a prevalence of 0.46% [42].

Diederich et al. screened, with annual LDCT, 817 subjects, aged ≥40 years, smokers detecting in 43% (350 of 817) of individuals 858 non-calcified nodules of which 12 were lung cancers (7 in stage I). Follow-up of non-calcified nodules present at baseline LDCT demonstrated growth in 11 cases and 7 were lung cancers. At rescreening test, further 174 new nodules were found of which 3 were lung cancers. Six of the 10 screen-detected lung cancers were at stage I. In this trial, the incidence of lung cancer was lower than prevalence [43,44]. Table 3 summarises the main LDCT screening trials for lung cancer.

Further preliminary data are available in literature about the use of LDCT in lung cancer screening. Considering the non-definitive results, final comments should not be made but few considerations are mandatory. LDCT detects more lung cancers than chest X-ray and mainly in stage I. The finding of early stage disease does not relate to an improvement in life expectancy. In fact, LDCT may detect neoplastic nodules that could be indolent in their behaviour, so treating these patients cannot increase life expectancy. The detection of small lesions that do not grow has been referred to as overdiagnosis. Moreover, surgery can alter the natural history of the disease. LDCT detects many more non-cancerous than cancerous nodules but three-dimensional reconstructions with serial CT scans seem to reduce the number of invasive procedures performed on subjects with abnormality, but which do not have lung cancer. Obviously, these persons experience overdiagnosis.

In Japan, 50% of lung cancers in non-smokers were slow-growing adenocarcinomas appearing as faint ground-glass opacities on CT, whereas rapidly growing cancers appearing as solid nodules were more commonly seen in smokers. The prevalence of well-differentiated adenocarcinomas was greater in non-smokers (88%) than in smokers (29%) (p < 0.001). The prevalence and incidence of pathologic stage IA disease were greater in non-smokers than in smokers (92% versus 58% and 100% versus 70%, respectively) (both p < 0.05) [46]. The same authors were also the first to show that lung cancers were missed at LDCT screening in a Japanese general population. All missed cancers were intrapulmonary, and 28%
were very subtle and appeared as small faint nodules, overlapping normal structures or opacities in a complex background of other disease, such as tuberculosis, emphysema or lung fibrosis [47].

At present, several large observational and randomised trials are ongoing or planned. Recently, Million et al. reported preliminary results of a randomised screening trial of LDCT versus chest X-ray that planned to enrol 40,000 asymptomatic subjects, aged 50–75 years, current or former smokers (more than 15 cigarettes/day during 20 years at least). On the first 353 randomised individuals, LDCT detected 89/180 (49.5%) non-calcified nodules of which 6 were lung cancers and chest X-ray revealed 12/173 (7%) nodules of which 1 was diagnosed as lung cancer [48]. U.S. National Lung Screening Trial randomised nearly 50,000 current or former smokers to annual screening with LDCT or chest X-ray for 3 years. The accrual, lasting 18 months, ended in February 2004 but the trial should be completed in 2009. It is designed to have a 90% power to detect a mortality reduction of 20% [49].

5. Future

Waiting for the ongoing above-mentioned screening trials on chest X-ray, sputum cytology and LDCT results, the developments in imaging and biological research provide new tools for lung cancer screening.

LDCT trials showed an higher cumulative frequency of non-calcified nodules, raising the questions about the challenge of differential diagnosis, efficacy and costs of screening. Positron emission tomography (PET) with the glucose analogue 18-fluorodeoxyglucose (FDG) identifies malignant tumours on the basis of their increased metabolic rate [50,51]. Pastorino et al. investigated the efficacy of repeated yearly LDCT and selective use of PET (non-calcified nodules of size ≥7 mm) in 1035 volunteers, for 5 years. The subjects, aged ≥50 years, had smoked for 20 pack-years or more. By year 2, a total of 411 (284 at baseline and 127 at 2 years) non-calcified nodules were identified of which 22 (11 in prevalence and 11 in incidence) were lung cancers (17 stage I). PET scans were positive in 18 identified lung cancers but it was the main reasons for biopsy in three of five benign lesions. The authors found selective use of PET to be helpful in replacing fine-needle aspiration biopsy for differential diagnosis [52]. Gould et al. evaluated the cost-effectiveness of strategies for pulmonary nodule diagnosis comparing, specifically, the strategies that did and did not include FDG–PET. The authors, based on their analysis, concluded that, at the moment, FDG–PET should be used selectively when pre-test probability and CT findings are discordant or in patients with intermediate pre-test probability who are at high-risk for surgical complications. CT-based strategies resulted in similar quality-adjusted life-years and lower costs [53].

Mucosal dysplasia, angiogenic squamous dysplasia and carcinoma in situ are considered premalignant conditions and to be early stages of invasive lung cancer [54]. These lesions originate from the mucosal surface and are too small to be detected by any radiographic techniques but can be visualized by flexible bronchoscopy (FB). FB has not been used in screening trials for lung cancer for its invasiveness. Autofluorescence spectra of normal bronchial tissue differs from those of premalignant conditions [55]. Light-induced fluorescence endoscopy (LIFE) employs a blue light rather than a white light for illumination and premalignant and malignant tissue is distinguished by a change in colour from normal tissue [56]. Whereas normal bronchial mucosa appears green, premalignant and malignant tissue appears brown-red [57]. Conflicting results were reported about the real advantage of LIFE in detecting abnormal bronchial tissue [58–60]. Lam et al. reported the results of a multicenter North American trial of 173 patients that showed the relative sensitivity of white-light FB plus LIFE versus white-light FB alone to be 6.3 for intraepithelial lesions and 2.71 if invasive cancers were included [59]. Further trials need to define the role of LIFE in the surveillance of patients with a history of lung cancer or with dysplastic cells in their sputum or screened because at high-risk for lung cancer.

Sputum immunocytology promises much greater sensitivity than conventional sputum cytology. There are a series of both genetic and molecular alterations found in lung cancers and preneoplastic lesions. Polymerase chain reaction (PCR) and microarray analysis have enabled rapid analysis of deoxyribonucleic acid (DNA) isolated from sputum cells to detect genetic changes. The presence of these genetic and molecular changes may be clinically useful in identifying patients with cancer or those at high-risk of developing cancer. Identified changes in lung cancer include the detection of loss of heterozygosity (LOH), microsatellite alterations or instability (MIN), mutations in specific genes, cancer-specific methylation changes and the detection of mutant gene products [61–63]. This suggests that chromosomal analysis may allow for the detection of premalignant changes in the airway epithelium long before it would be apparent on CT.
and may serve as a high-risk marker for lung cancer. Experiments with the monoclonal antibody 703D4 have shown that overexpression of heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1, an ribonucleic acid (RNA)-binding protein, is a powerful predictor of early subclinical cancer in high-risk groups [64]. University of Colorado Specialized Program Of Research Excellence (SPORE trial) is conducting a cohort study to assess sputum cytological and molecular biomarkers in subjects at high-risk for lung cancer (≥30 pack-years and chronic obstructive pulmonary disease defined by spirometry). Preliminary results showed that severe atypia or worse cytological changes in the sputum represent a high-risk for developing lung cancer within a short time [65]. Analysis of circulating DNA in plasma can provide a useful marker for early lung cancer detection. In a study assessing the sensitivity and specificity of a quantitative molecular assay of circulating DNA to identify patients with lung cancer and to monitor their disease, the median concentration of circulating DNA in patients was almost eight times the value detected in controls [66]. This suggests that plasma DNA elevation is a strong risk factor for lung cancer [67]. At the moment, no marker has been tested in a wider population-based trial and none of them is recommended for lung cancer screening (Table 4) [68].

From the first screening trials, conducted in 1950s, that failed to show any benefit by the use of chest X-ray [69,70], passing through the progresses in imaging techniques, the molecular biology knowledge and increasing sophistication in trial design, we will have promising tools for future lung cancer screening program (Table 5).

### Table 5

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<tr>
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<tbody>
<tr>
<td>Chest X-ray</td>
<td>→</td>
<td>Chest X-ray</td>
<td>→</td>
<td>Chest X-ray</td>
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<tr>
<td>Sputum cytology</td>
<td>→</td>
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<tr>
<td>Low-dose computed tomography (LDCT)</td>
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<td>Positron emission tomography (PET)</td>
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<td>Bronchoscopy (LIFE)</td>
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<td>Biomolecular markers</td>
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6. Screening for elderly population

Lung cancer may be considered typical of advanced age. More than 50% of lung cancer patients are diagnosed over the age of 65 and about 30% over the age of 70 [71,72]. Age-adjusted incidence rates for 1990–1994 reported by the National Cancer Institute Surveillance Epidemiology End Results (SEER) program are 26.7 per 100,000 inhabitants under the age of 65, whilst the rate grows to 345.9 among people aged 65 years or more. More than two-thirds of patients dying of lung cancer in the U.S. are over 65 years old [73].

Important issues to be addressed in the elderly are co-morbidity and frailty. It has been reported that among individuals aged 65–74 years, the mean number of chronic diseases is six. The prevalence of these co-morbid conditions is about twice as high as in the general population [74]. The most important co-existing pathologies in lung cancer patients are cardiovascular and pulmonary diseases, common among heavy cigarettes smokers [75]. In fact, there is a clear evidence for a dose–response relation between smoking and lung cancer. The risk of lung cancer increases with the number of cigarettes smoked, years of smoking duration, earlier age at onset of smoking, degree of inhalation, tar and nicotine content, the use of unfiltered cigarettes, and passive smoking, and it decreases in proportion to the number of years after smoking cessation [76]. The frailty is a condition in which most functional reserve is exhausted. Frail patients are those who depend on others for daily routine activities prevalently because of physical and cognitive dysfunctions [77].

Based on these considerations, smokers and lung cancer are more frequent in elderly populations. Earlier stage of disease at diagnosis has been previously described in elderly lung cancer patients [78]. So, lung cancer screening should lead to earlier detection of disease, in a stage susceptible of surgery in order to change its natural history. Considering that co-morbidity, being a predictor of outcome [77], influences treatment choices, and that the inherent risk of thoracic surgical procedures, it is mandatory, for lung cancer screening, to enroll persons which are elderly but can be considered fit for potential surgery. To the best of our knowledge, at present no retrospective or prospective data about the elderly screened persons in the previous trials are available.

7. Discussion

The most effective treatment for lung cancer remains surgical resection of early stage disease. However, only 15–20% of lung cancer is diagnosed in its earliest stages and can be radically resected. The main outcome of screening trials is to provide benefit to persons who have the illness through increasing life expectancy without being dangerous or painful. Lung cancer screening is able to increase the percentage of early stage disease diagnosis. About 70–90% of tumours detected by screening trials, in particular, LDCT screening studies are in clinical stage I. This suggests that the
majority of them might be cured through surgery. However, none of these trials reported a change in lung cancer mortality. This could mean that some of the screened detected cancers are overdiagnosed [18]. Overdiagnosis represents a subclinical condition that would not have produced signs or symptoms before the individual died to other causes. It may cause the person being screened to worry for months or years about having cancer [80].

Unfortunately, false positive and false negative tests will occur due to the fact that no tests have complete reliability. False positive results on a screening test lead to unnecessary diagnostic and therapeutic interventions that may lead to the added cost, morbidity and even mortality (for lung cancer screening due to the risk of thoracic surgery). False positive is also associated to the psychological stress in a patient who believes to have a malignant disease. In patients who have an indolent tumour that would otherwise be undiagnosed and clinically silent, a screening intervention could lead to psychological distress unnecessarily. Finally, finding a cancer may have serious consequences on patient’s and patient’s family insurability [8,81].

Despite a lack of evidence about whether LDCT screening for lung cancer saves lives, direct-to-consumer marketing has increased demand for the procedure. For this reason, the issue of cost-effectiveness of screening with LDCT had been addressed in several reports. Based on the results of ELCAP trial, the estimated cost was lower than US$ 10,000 per life-year saved [82]. Using the same data and evaluating the cost-effectiveness based on risk, it was US$ 5940 and US$ 23,100 per life-year saved for very high-risk and low-risk cohort, respectively [83]. Recently, ELCAP data were incorporated into a decision analysis model comparing LDCT scan screening of high-risk persons (≥60 years old, at least 10 pack-years of cigarette smoking) to observation without screening. The cost-effectiveness ratio of single baseline LDCT scan was US$ 2500 per life-year saved. In the base-case analysis, screening would be expected to increase survival by 0.1 year at an incremental cost of US$ 230. The conclusion was that a baseline LDCT scan for lung cancer screening is potentially highly cost-effective [84]. By contrast, Mahadevia et al. recently reported a cost-effectiveness analysis of lung cancer screening with helical CT in older adult smokers. They compared annual helical CT screening with no screening for hypothetical cohorts of 100,000 current, quitting and former heavy smokers, aged 60 years, of whom 55% were men. The estimated incremental cost-effectiveness for current, quitting and former smokers was US$ 116,300, US$ 558,600 and US$ 2,322,700 per quality-adjusted year of life (QALY) gained, respectively. In multivariate sensitivity analyses, a program screening current smokers was US$ 42,500 per QALY gained if extremely favourable estimates were used for all of the influential parameters simultaneously. They concluded that given the current uncertainty of benefits, the harms from invasive testing, and the high costs associated with screening, direct-to-consumer marketing of helical CT is not advisable [85]. Tsushima et al. used a decision-tree analysis model, based on Japanese health care costs, to assess the accuracy and cost-effectiveness of four strategies for diagnosis and management of solitary pulmonary nodules (SNPs): CT alone strategy, CT plus FDG–PET strategy, CT plus FDG–PET plus CT-guided needle biopsy strategy, and CT plus CT-guided needle biopsy strategy. The Authors concluded that the introduction of CT-guided needle biopsy and FDG–PET for the evaluation of SNPs, which are discovered on screening chest X-ray, is potentially cost-effective in Japan with high accuracy [86]. Based on the cost-effectiveness analysis, screening for lung cancer is too expensive. In this analysis, should be done only when a screening that works will be found.

U.S. Preventive Services Task Force (USPSTF) outlines a recommendation statement for lung cancer screening, concluding that the current evidence do not support screening for lung cancer with any method. However, these data are also insufficient to conclude that screening does not work. Further data from ongoing and planned trials need to better inform lung cancer screening decision [87,88].

In conclusion, screening for lung cancer: new horizons?

Yes, at present, as from the preliminary screening trials results employing LDCT, this technique has emerged as being a very promising tool. At the moment, the screening has to be performed only in well-conducted trial. In the future, of particular interest will be the use of FDG-PET and the analysis of biomolecular markers of lung cancer to be detected in serum, sputum and exhaled air. While waiting and hoping for current and future improved lung cancer screening results, it is best to increase the primary prevention, promoting smoking cessation.

**References**


Biographies

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