CT lung cancer screening in China
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Chapter 1

General introduction
**Lung cancer epidemiology**

Globally, lung cancer is the second most commonly diagnosed cancer and the most common cause of cancer deaths\(^1\). The WHO cancer data for 2020 show that lung cancer accounts for 11.4% of new cancer cases and 18.0% of cancer deaths\(^1\). In China, the burden of lung cancer is increasing with the fact that it was the 13\(^{th}\) cause of years of life lost (YLL) in 1990 while the third in 2017, and the age-standardized YLL increased by 12.6%\(^2\). Among all cancers, lung cancer is the most common cancer (20.0%) and the most common cause of cancer deaths (27.0%)\(^3\). The age-standardized incidence of lung cancer is 35.9 per 100 000 people (men: 48.87 per 100 000, women: 23.52 per 100 000), ranging from 30.0 to 41.2 per 100 000 people depending on administrative regions in China\(^4\). The age-standardized mortality of lung cancer is 28.1 per 100 000 people (men: 40.11 per 100 000, women: 16.54 per 100 000), ranging from 23.1 to 34.1 per 100 000 people depending on administrative regions\(^4\) (Figure 1).

![Lung cancer incidence and mortality rate by administrative region in China, 2015](image)

**Figure 1.** Age-standardized lung cancer incidence and mortality rate by world standard population (1/10\(^5\)) in 7 administrative regions of mainland China, 2015 (incidence data were extracted from the publication of Zhang et al\(^4\); Hongkong, Macau, and Taiwan were not included for calculating incidence and mortality)

Lung cancer is one of the most lethal cancers, and the 5-year survival ranges from 10% to 20% in most countries\(^5\). The low survival is mainly due to the diagnosis at advanced stage\(^6\). According to the most recent estimation from the Statistics, Epidemiology, and
End Results (SEER) database, the proportion of stage III/IV lung cancer cases among all diagnosed lung cancer cases is 70%\(^7\). It is reported by the International Association for the Study of Lung Cancer (IASLC) that the 5-year survival for stage I lung cancer is 77%-92%, which is much higher than that for stage III/IV lung cancer (0%-36%)\(^8\). Therefore, early detection of lung cancer is crucial for improving survival outcomes.

**Lung cancer screening and target population**

Data support using computed tomography (CT) for early detection of lung cancer. In a systematic review that summarized the stage distribution of CT screen-detected lung cancers, the proportion of stage I lung cancer was 73%\(^9\). The National Lung Screening Trial (NLST) showed that CT screening yielded 20% lung cancer mortality reduction (8% in men and 27% in women) compared to radiography screening\(^10,11\). The Dutch–Belgian lung-cancer screening trial (NELSON) showed more favorable results that CT screening yielded 24% lung cancer mortality reduction in men and 33% in women compared to no screening\(^12\). A systematic review confirmed the efficiency of lung cancer screening, with an estimated average of 17% mortality reduction in lung cancer as a result of CT screening\(^13\).

After the publication of the NLST study, the United States Preventive Services Taskforce (USPSTF) developed eligibility criteria for lung cancer screening in the US in 2013. It recommended annual CT screening for lung cancer in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (abbreviated as A-55-80-30-15)\(^14\). Since the age criteria are under pressure from different stakeholders, broadened eligibility criteria by lowering the starting age to 50 years and the pack-years of smoking to 20 are advocated and has been recently issued (abbreviated as A-50-80-20-15)\(^15\). A study estimated that, when applying NLST eligibility criteria in the US, 6.2% of the US population (over 40 years old) and 26.7% of lung cancers would be covered by screening\(^16\). With the extended eligibility criteria recommended by USPSTF, more people and more lung cancer cases in the US will be covered.

In China, it is not clear which proportion of adults would be covered if the NLST and USPSTF eligibility criteria will be applied at a national level. But according to a study in a Chinese health checkup population, the 2013 USPSTF eligibility criteria would miss 90.8% of lung cancer cases diagnosed at the yearly health examination\(^17\). Another study evaluated lung cancer screening in a selected high-risk group, defined by one of the following risk factors including smoking, cancer history, occupational exposure, passive smoking, and cooking fume exposure\(^18\). The results from that study show that the NLST eligibility criteria would only cover 7.1% of the included participants and consequently miss 75% of the screen-detected lung cancers in men and 100% of the screen-detected lung cancers in women. Those implicate that lung cancer screening in only heavy smokers in China would yield limited benefits at a population level. Therefore, risk factors beyond smoking should be identified for defining a high-risk group for screening in China.
Chapter 1

There are several published studies on lung cancer screening in Chinese populations. Most of those were conducted in high-risk populations defined by various combinations of risk factors and in a one-arm cohort. By using the data from the Cancer Screening Program in Urban China, Guo et al evaluated the CT screening for lung cancer in a population at an elevated risk assessed by a cancer risk scoring system and compared the results between participants and non-participants. The results suggest that the detection rate of lung cancer at 6-year follow-up was similar in the participants as compared to non-participants (0.35% vs 0.38%). However, the differences in the characteristics of the two groups should be noted as presented in that article. The participants were more likely to have risk factors for lung cancer including pulmonary tuberculosis, chronic bronchitis, emphysema, asthma, and family history of lung cancer, as well as were more likely to have the protective factors for lung cancer including female gender, never smoking and high educational level. In addition, participants received one-time screening instead of a series of sequential screening rounds, the latter allows more lung cancers being early detected. The important message of that study is that the cumulative lung cancer rate is generally lower than in other studies in high-risk populations in Western countries, although the included population was considered as “high-risk” according to the predefined risk scoring system (NLST: 4.0% in the screening group and 3.5% in the control group at 6-year follow-up; NELSON: 5.2% in the screening group and 4.6% in the control group at 10-year follow-up; German Lung cancer Screening Intervention (LUSI): 4.2% in the screening group and 3.3% in the control group after a median follow-up time of 8.8 years). Those findings implicate the necessity of optimizing the target population for lung cancer screening in China.

Risk factors for lung cancer

The well-known modifiable risk factors of lung cancer include smoking, passive smoking, air pollution, and occupational exposure, etc. In Western countries, smoking is the main risk factor for lung cancer. About 80% to 90% of lung cancers in Western countries are attributable to tobacco smoking. In addition to smoking, particulate matter less than 2.5 microns in diameter (PM$_{2.5}$) increases the risk of lung cancer mortality by 13% and is estimated to contribute to 14.1% of all lung cancer deaths globally, second to tobacco smoking. Therefore, PM$_{2.5}$ is advocated to be incorporated into the lung cancer risk prediction model.

In China, according to a well-conducted study estimating the population attributable fraction (PAF) for national and province-specific cancer burden due to modifiable risk factors, the top three risk factors that caused the lung cancer burden in men are smoking (55.1%), low fruit intake (24.6%) and PM$_{2.5}$ (14.4%), and in women are low fruit intake (27.2%), PM$_{2.5}$ (14.4%) and smoking (13.9%). However, the figures show substantial heterogeneity by province. For example, in Chinese men, smoking accounts for 62.1% of lung cancer deaths in Guizhou and 41.9% in Xingjiang, and PM$_{2.5}$ accounts for 22.6%
of lung cancer deaths in Hebei and 2.0% in Hainan. Because the relative risk between those risk factors and lung cancer is unified, the heterogeneity across the provinces can be primarily explained by the variations in the prevalence of those risk factors.

**Passive smoking**
It is estimated that worldwide about one in four lung cancers occurs in never smokers\(^{27}\). The figure varies across countries. In East Asia, nearly one-third of lung cancers are diagnosed in never-smokers\(^{28}\). Passive smoking is considered as one of the contributors to lung cancer in never smokers\(^{27}\). In this thesis, lung cancer occurrence due to passive smoking will be extensively evaluated for the Chinese population.

**Airflow limitation**
Airflow limitation showed to be associated with an increased risk of lung cancer\(^{29}\). That association was reported mainly among smokers or more pronounced among smokers than non-smokers\(^{30}\). Both airflow limitation and lung cancer are smoking-related. Many studies consider that impaired lung function or chronic obstructive pulmonary disease (COPD) itself is an independent risk factor for lung cancer regardless of smoking\(^{29,30}\), whereas some others argue that they are just manifestations of the same exposure\(^{31}\). The evidence from studies in the Chinese population is also inconsistent. A case-control study in a Chinese population suggested that the presence of airflow limitation increased the risk of lung cancer\(^{32}\). In a cohort study of the elderly population in Hongkong, obstructive lung disease did not increase lung cancer mortality in female never-smokers\(^{33}\). In another case-control study, COPD showed to be associated with an increased risk of lung cancer in smokers but not in non-smokers\(^{34}\). The various definitions of COPD might partly explain the inconsistency. In this thesis, the association between spirometry-defined airflow limitation and lung cancer incidence will be evaluated in a large Dutch cohort of individuals representative of the Dutch population.

**NELCIN-B3 study in Chinese population**
CT screening for lung cancer showed to be effective in reducing lung cancer mortality in western populations\(^{13}\). Though no results from trials demonstrated the effectiveness in Asian populations, a retrospective study in an Asian population suggests that CT screening could help to detect early-stage lung cancers more often, which results in better survival as compared to radiography screening\(^{35}\). However, many benign lung nodules are commonly detected at CT scans. According to a systematic review, the average nodule detection rate per CT screening round was 20% ranging from 3% to 51% in studies and over 90% of screen-detected lung nodules in CT screening for lung cancer turn out to be benign\(^{16}\). Therefore, the methodology of lung nodule detection and stratification is of high importance. The NELSON study showed that volume-based management of screen-detected lung nodules reduced the false positive rate in comparison to diameter-based management in a European population\(^{37}\). In China, lung
cancer that is attributed to non-smoking risk factors is probably much more frequent than in Europe\textsuperscript{21}. In addition, the proportion of lung cancers that manifested as sub-solid nodules among all detected lung cancers is much higher in Asia than in Western countries\textsuperscript{38}, although the definition of a sub-solid nodule is not standardized. Despite these differences in lung cancer nodule histology distribution between European and Asian countries, the performance of volume-based management of screen-detected lung nodules in a Chinese population is not less important.

Screening for lung cancer in a high-risk population is recommended in China\textsuperscript{39,40}. In addition to age and smoking, other factors are believed to play an important role in increasing lung cancer risk\textsuperscript{26}. However, there is no clear evidence on which factors should be used to define a high-risk group for lung cancer screening in the Chinese population. Using age and smoking only may be inappropriate. Some researchers proposed screening for lung cancer in a general population within a certain age limit\textsuperscript{41}. In addition to lung cancer, COPD and cardiovascular disease are among the five leading causes of years of life lost in China\textsuperscript{42}. The three diseases share the risk factors such as smoking and ambient particulate matter pollution\textsuperscript{42}. Based on the quantitative emphysema score and coronary artery calcium on CT images of the chest, it is possible to screen COPD and cardiovascular disease in addition to lung cancer, and thus increase the benefits of chest CT screening\textsuperscript{43}.

Through the collaboration between the University Medical Center Groningen/Center for Medical Imaging and the Second Military Medical University, a screening project “Netherlands and China Big 3 diseases (abbreviation: NELCIN-B3)” was initiated in 2017. The project was financially supported by the Royal Academy of Sciences (KNAW) in the Netherlands and the Ministry of Science and Technology (MOST) in China. The primary objective of this project was to improve the early detection of lung cancer, COPD, and cardiovascular disease in asymptomatic (population-based) participants in China and the Netherlands with a new, ultra-low dose CT technique, with the final aim to integrate imaging biomarkers into personalized health strategies in the general population of the Chinese urban and Western population and to provide a one-stop-shop screening solution for the 3 diseases in the chest by ultra-low-dose CT. As a part of this thesis, the study designs of the projects in two general populations in China and interim data analysis of lung cancer screening in China were included.

**Cost-effectiveness of lung cancer screening**

After publishing the results of the NELSON study, it was well established that CT screening reduces lung cancer mortality\textsuperscript{44}. Since the medical resources from the perspective of health policy-makers are limited, the cost-effectiveness of a population-based lung cancer screening program has to be evaluated before implementation\textsuperscript{45}. A model-based health economic evaluation allows to simulate a large group of high-risk
participants, and calculate the costs and health effects in the presence and absence of a screening program. The cost-effectiveness analysis helps to assess the incremental costs and incremental health benefits due to screening and then identify the most cost-effective screening strategy. Many cost-effectiveness analyses of lung cancer screening have been conducted in the population of the US, Canada, the UK, and other Western countries\textsuperscript{46–50} and may not be applicable to Chinese healthcare. Most of the studies concluded that lung cancer screening was cost-effective although the cost per incremental benefit varies across countries, with incremental cost-effectiveness ratios (ICERs) ranging from US$15,000 to 100,000 per quality-adjusted life years (QALY) gained and CAD$20,000 to 62,000 per life-year gained\textsuperscript{51}. The medical costs and thresholds for cost-effectiveness are country-specific, and the cost-effectiveness is too complex for direct transferring from one country/context to another, therefore, a health economic evaluation based on the country-specific costs and population characteristics is required\textsuperscript{51}.

**Radiation harm due to lung cancer screening**

Although lung cancer screening generates clear benefits in reducing lung cancer mortality in heavy smokers, the harms introduced by screening itself are not negligible\textsuperscript{36}. One potential harm is the radiation exposure in annual-repeated CT screening programs. With the advanced CT techniques, the USPSTF summarized that the cumulative radiation exposure (effective dose) for an individual from a 25-year annual screening program would be 20.8 to 32.5 mSv\textsuperscript{52}. This updated evidence including the harms of lung cancer screening with low dose CT suggests that the low dose CT screening causes rare radiation-induced cancers\textsuperscript{52}. The Chinese expert panel proposed the CT scanning parameters for lung cancer screening by considering the status quo of the CT scanners in China and the low dose requirement (\textbf{Table 1})\textsuperscript{40}. However, for younger individuals, especially women, the trade-off in benefits and harms from screening would be less favorable\textsuperscript{36,53}. This is because women showed to have a higher risk of developing radiation-induced cancer as compared to men\textsuperscript{54–56}. This emphasizes the importance of low and ultra-low-dose CT protocols for lung cancer screening. Given that women also have a longer life expectancy than men, the understanding of the lifetime radiation risk for women that may potentially participate in lung cancer screening is of importance for achieving a successful screening program.
Table 1: Scanning parameters for CT lung cancer screening in the latest recommendation by the Chinese expert panel (translated from the Chinese publication 40)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner</td>
<td>≥ 16-Slice Multi-detector Spiral Computed Tomography</td>
</tr>
<tr>
<td>Position</td>
<td>Supine, arms above the head</td>
</tr>
<tr>
<td>Automated patient instruction</td>
<td>Inspiratory breath-hold</td>
</tr>
<tr>
<td>Scan range</td>
<td>From the tip of the lung to the tip of the posterior costophrenic angle (including the whole lung and both chest walls, and the whole breast should be included for female participants)</td>
</tr>
<tr>
<td>Scan mode</td>
<td>Spiral, pitch ≤ 1</td>
</tr>
<tr>
<td>Rotation time (s)</td>
<td>≤ 0.8, the shortest time of the technique is recommended</td>
</tr>
<tr>
<td>Matrix</td>
<td>≥ 512x512</td>
</tr>
<tr>
<td>Scan mode</td>
<td>Spiral, pitch 0.758</td>
</tr>
<tr>
<td>Tube voltage (kVp)</td>
<td>120 if without iterative reconstruction technique; 100-120 if with iterative reconstruction technique</td>
</tr>
<tr>
<td>Tube current (mAs)</td>
<td>30-50 if without iterative reconstruction algorithms; &lt;30 if with iterative reconstruction algorithms</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>Section thickness = 1.00-1.25 mm</td>
</tr>
<tr>
<td></td>
<td>≤ 80% of section thickness if section thickness is 1.00-1.25 mm; no reconstruction interval if section thickness ≤ 0.625 mm</td>
</tr>
<tr>
<td>Dose report</td>
<td>Open scanner dose report</td>
</tr>
</tbody>
</table>

**Aim of the thesis**

This thesis aims to evaluate the necessity to optimize the target population for CT lung cancer screening. The first objective is to investigate the risk factors for lung cancers. The second objective is to assess the findings from the first screening round in a general Chinese population. The third objective is to evaluate the cost-effectiveness and harms of lung cancer screening in various screening scenarios.

**Outline of the thesis**

**Part I Risk factors for lung cancer**

**Chapter 2** evaluates lung cancer occurrence attributable to passive smoking among never smokers in China, which was based on a systematic review and meta-analysis. This chapter provides the proportion of lung cancer attributable to passive smoking among never-smokers and never-smoking men and women.

**Chapter 3** disentangles the association between smoking, airflow limitation, and lung cancer incidence. This study was based on the Lifelines cohort.
Part II NELCIN-B3 study: lung cancer screening in China

Chapter 4&5 separately describe the rationales and study designs of the NELCIN-B3 study in Tianjin and Shanghai. A population-based one-arm cohort study for lung cancer screening was designed in Tianjin. A population-based two-arm comparative study for lung cancer screening and also COPD and cardiovascular disease was designed in Shanghai.

Chapter 6 describes the findings from a community-based CT screening in Tianjin general population and compares the study results with findings from a systematic review of other screening and clinical studies for lung cancer in China. In this study, the baseline findings were reported; the detection rate of lung cancer was evaluated; the stage shift and change in histological type distribution was compared between screening and clinical settings.

Part III Cost-effectiveness and harm of lung cancer screening

Chapter 7 evaluates the cost-effectiveness of CT lung cancer screening in heavy smokers in a Dutch population. This study was based on a simulation model. Various screening strategies in men and women were assessed. The model input and output data were described extensively in Data in Brief.

Chapter 8 evaluates the cost-effectiveness of CT lung cancer screening in a Chinese general population. This study was also based on a simulation model. Several screening strategies with various screening start and stop ages and screening intervals were evaluated for men and women separately.

Chapter 9 assesses the effect of lowering the starting age of CT lung cancer screening in women. By using the simulation model, the benefits in the increased number of screen-detected lung cancer and the harms in the number of radiation-induced lung cancer were calculated for the screening scenarios with decreasing start age.
REFERENCES


Part I

Risk factors for lung cancer