CT lung cancer screening in China
Du, Yihui

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Chapter 10

General discussion
SUMMARY

This thesis focuses on three aspects for optimization of the target population in a potential computed tomography (CT) lung cancer screening program in China: (1) the evaluation of the risk factors for lung cancer, (2) the assessment of the findings from the first-round of CT screening for lung cancer in a Chinese population, and (3) the investigation of the cost-effectiveness and harms of CT lung cancer screening. Part I focuses on the first aspect of the thesis, in which the contribution of (passive) smoking and airflow limitation on the occurrence of lung cancer is studied, as described in Chapter 2 and Chapter 3, respectively. Part II describes the second aspect of the thesis, in which the study design of the NELCIN-B3 study in Tianjin and Shanghai, China are presented, as described in Chapter 4 and Chapter 5, respectively; and the results of the first-round screening of the NELCIN-B3 study in Tianjin, accompanied with the findings summarized from other screening studies in China in Chapter 6. Part III provides the third aspect of the thesis, in which the cost-effectiveness of lung cancer screening in Dutch and Chinese populations and the harms of lung cancer screening are evaluated, as described in Chapter 7, Chapter 8, and Chapter 9, respectively.

In Chapter 2 the association between passive smoking and lung cancer occurrence was examined in Chinese never smokers by using a systematic review and meta-analysis approach. Subsequently, a population attributable fraction was calculated for lung cancer occurrence associated with passive smoking. We found that approximately 16% of lung cancer cases among never smokers in China can be attributed to passive smoking. In addition, for never-smoking women, the number of lung cancer cases attributable to household exposure is about 3-fold of that attributable to workplace exposure.

In Chapter 3, the association between airflow limitation and the risk of lung cancer incidence was investigated in the Lifelines cohort of a general population from the Northern Netherlands. With a median follow-up time of 9.5 years, this study shows that airflow limitation increases the incidence of lung cancer in smokers, even when they stopped smoking, but not in never smokers. The association is found for squamous cell carcinoma and adenocarcinoma of the lung. In addition, compared with never smokers without airflow limitation, former and current smokers with airflow limitation have an approximately 2- and 4-fold increased incidence of lung cancer, respectively.

In Chapter 4, a population-based, one-arm prospective cohort design for lung cancer screening in the Hexi district of Tianjin is described. This study aimed to evaluate the performance of the NELCIN-B3 volume-based protocol in comparison with the NCCN diameter-based protocol for lung cancer detection and to optimize nodule management and the target population for lung cancer screening in China. Residents between 40-74
years were recruited. Two CT screening rounds were implemented at the 1st and 2nd year, and all participants were followed for 4 years. Of the screen-detected lung nodules, the diameter and volume were recorded.

In Chapter 5, the rationale and design of a population-based comparative study on the screening for lung cancer, COPD, and cardiovascular disease in the Shanghai population is described. This study aimed to assess the performance of the NELCIN-B3 volume-based protocol in comparison to the NCCN diameter-based protocol, to improve the effectiveness of CT screening for early detection of 3 diseases in the chest (lung cancer, COPD and cardiovascular disease), and to optimize the target population for lung cancer screening in China.

Two groups of residents between 40-74 years were recruited. In the intervention group, a chest and cardiac CT scan in the 1st and 2nd year were implemented according to the NELCIN-B3 protocol. In the control group, only a chest CT scan was implemented according to the routine CT protocol (based on NCCN guideline). In the 4th year from baseline, the diagnoses of the three diseases were collected.

In Chapter 6, the first-round results from lung cancer screening in the Tianjin community population are presented and compared with published lung cancer screening studies in China. A systematic search was conducted and registry-based clinical studies for lung cancer were identified. We found that in the first screening round, CT screening detects more early stage lung cancer in both high and low risk populations in China than clinical diagnosis in a non-screening setting. Nearly 70% of the screen-detected lung cancers in the low-risk population were identified in women. Lung cancer was 4 to 5 times more likely to be detected at an early stage by CT screening than by clinical diagnosis.

In Chapter 7 the cost-effectiveness of CT lung cancer screening in Dutch heavy smokers is assessed by a micro-simulation model. Scenarios with different screening intervals and starting and stopping ages were evaluated for men and women. At a cost-effectiveness threshold of 60 k€ per life-year gained, this study shows that CT lung cancer screening is cost-effective in the Dutch high-risk population. Moreover, the optimal screening scenario is annual screening of men from 55 to 80 years and biennial screening of women from 50 to 80 years.

In Chapter 8, the cost-effectiveness of lung cancer screening in a Chinese general population is evaluated with a micro-simulation model. This study shows that CT lung cancer screening in a general population (including never smokers) can be cost-effective for men, but not for women. The optimal strategy for men is biennial screening between 55 and 77 years.
In Chapter 9, the radiation harm of lung cancer screening in women is evaluated using a micro-simulation model. When the screening start age was decreased from 55 to 45 years, the increase in screen-detected and radiation-induced lung cancers was calculated. We found that in an annual lung cancer CT screening program for women, a decrease of the screening start age to 45 years leads to a 5.2% increase in the number of screen-detected lung cancers (from 112.4 to 118.2 per 1000 screened), and a 114% increase in the number of radiation-induced lung cancers (from 2.2 to 4.7 per 1000 screened). Therefore, when women start screening at a younger age the benefits of lung cancer screening are tempered by the increased probability of radiation induced tumors.

POTENTIAL BENEFITS OF LUNG CANCER SCREENING IN CHINA

China is facing a heavy lung cancer burden because lung cancer is the most common cancer type and the leading cause of cancer death. The benefits of CT lung cancer screening are observed primarily from trials in Western countries, such as the NLST study showing 20% lung cancer mortality reduction after 6.5-years follow-up and the NELSON study showing 24% lung cancer mortality reduction for men and 33% for women after 10-year follow-up. There is no such trial in the Chinese population yet, so it is unclear to what extent lung cancer screening would reduce lung cancer mortality in the Chinese context. This thesis illustrates the potential benefits of lung cancer screening in China from the perspective of cancer stage shift and modeled lung cancer mortality reduction due to screening. Chapter 6 shows that the lung cancer detection rate at the first screening round is 0.5% in a population-based cohort in Tianjin, and is 0.2%-1.6% in the screening studies in Chinese populations identified by a systematic search. Moreover, early-stage (stage I or less) detection of lung cancer is 4-5 times more likely in a CT screening setting as compared to clinical diagnosis. This is also supported by the findings from the first screening round in Tianjin where 70% of screen-detected lung cancers had stage I. Earlier detection allows earlier treatment and consequently better survival. Therefore, as demonstrated in Chapter 8, an annual screening program in a birth cohort from age 50 to 75 years could yield 12.8% lung cancer mortality reduction for men and 8.2% for women in a simulated general Chinese population, although this screening strategy would not be cost-effective in China.
THE SEX-SPECIFIC TARGET POPULATION FOR LUNG CANCER SCREENING

This thesis emphasizes that the target population for CT lung cancer screening in China should be defined for men and women separately. This is based on the following three aspects.

First, the national incidence of lung cancer in men is about 2-fold of that in women in China. According to the latest cancer statistics, the crude incidence of lung cancer is 73.90 and 39.78 per 100 000 for men and women, respectively. Consequently, the cost-effectiveness of lung cancer screening is different for men and women. As suggested in Chapter 8, if a national lung cancer screening program would be implemented in the Chinese general population aged 50 years or older, it would be cost-effective for men but not for women when applying the willingness to pay of 3-fold GDP per capita (217.3k Yuan per life-year gained) in China. The optimal screening strategy in men would be biennial screening between 55 and 75 years. Although two evaluated biennial screening strategies in men are cost-effective and efficient, the average cost-effectiveness ratio of those relative to no screening is close to the willingness to pay threshold (171k Yuan per life-year gained for biennial screening from 55 to 70 years, 174k per life-year gained for biennial screening from 55 to 75 years). For policymakers, screening all men aged 50 years or older is hardly resource-saving in a developing country. A further selection of a group of men in which lung cancer incidence is higher will make the screening program more cost-effective. The finding in women indicates that screening for lung cancer in all women aged 50 years or older is not wise for policymakers. Risk factors, such as the passive smoking discussed in Chapter 2, could contribute to the selection of a high-risk group of women in which lung cancer screening might be cost-effective. Chapter 7 of this thesis illustrates the cost-effectiveness of lung cancer screening in Dutch heavy smokers who are at high risk for developing lung cancer. This study indicates that lung cancer screening is cost-effective in both male and female heavy smokers and the optimal screening strategy is dependent on sex because of the different lung cancer incidence in men and women. Annual screening from 55 to 80 years is optimal for men and biennial screening from 50 to 80 years is optimal for women. Although the results from the Dutch population cannot be generalized to the Chinese population, we can envisage that if a high-risk group in China can be appropriately defined, a favorable incremental cost-effectiveness ratio of lung cancer screening will be achieved for both men and women at a national level.

Second, the (passive) smoking rate and its contribution to lung cancer occurrence are different in men and women in China. The smoking rate is extremely high in men but low in women. According to the 2015 Tobacco survey, the ever smoking rate is 63.7% in men while only 3.8% in women, in which majority are current smokers (81.8% for
men and 71.1% for women). About 96% of women in China are never smokers and nearly half of them have been exposed to passive smoking. The high rate of passive smoking in women is a consequence of the high smoking rate in men. Passive smoking, as illustrated in Chapter 2, is associated with 1.45 higher odds of developing lung cancer in female never smokers and with no increased odds in male never smokers based on the pooled estimation from the case-control studies in China. Consequently, 18% of lung cancer occurrence in female never smokers can be attributed to passive smoking. These findings are relevant to the necessity of defining sex-specific target populations because women are the major victims of passive smoking. Especially, as shown in the same chapter, among women exposed to household passive smoking, 20% of lung cancer cases are attributable to such passive smoking. It shows that the majority of women (66%) exposed to passive smoking have been exposed at home. These findings suggest that when defining the target women for lung cancer screening in China, the exposure history to passive smoking should be considered. Collecting the exposure history through questionnaires (self-reported) can be a cost-effective way, and as long as the reported measures on exposure can be appropriately implemented, the self-reported exposure history is accurate and reliable.

Third, radiation harm induced by repeated CT lung cancer screening is dependent on sex. According to the USPSTF broadened eligibility for lung cancer screening, heavy smokers aged 50 to 80 years are recommended to take annual screening. Therefore, a screening program will include up to 30 CT scans, plus short-term repeated CT scans and PET CT scans when applicable. The estimated lifetime risk of developing radiation-induced cancers over 10 years of annual screening is greater for women than for men, especially when exposure initiates at younger ages. Chapter 9 of this thesis emphasizes the radiation risk in developing lung cancer among women who received repeated CT screening and the effect of lowering the starting age of screening in women. The results suggest that when women start screening from a younger age, the potential benefit in the increase in screen-detected lung cancers is tempered by the increased risk of radiation-induced lung cancers. When annual CT screening is implemented from age 55 to 75 years, the lifetime incidence of radiation-induced lung cancer is 2.2 per 1000 screenees and the screen-detected spontaneous lung cancer is 112.4 per 1000 screenees. When annual CT screening is implemented from age 45 to 75 years, those numbers increase to 4.7 per 1000 screenees and 118.2 per 1000 screenees, respectively. When the age is decreased by 10 years to 45 years at which women commence screening, the benefits in spontaneous lung cancers detection still outweigh the harm in radiation-induced lung cancers, while the absolute number of radiation-induced lung cancers is doubled. This finding necessitates that the radiation dose from CT should be very well considered when balancing the benefits and harms of lowering the age at which women are offered their first screening. As indicated by the same chapter, when the dose of CT decreases by 50% from 2.7 mSv to 1.35 mSv, the lifetime incidence of
radiation-induced lung cancer decreases by 60% from 4.7 to 1.9 per 1000 screenees if screening from 45 to 75 years. Therefore, to minimize the radiation harm especially for women from screening, the radiation dose that conforms to the principle of as low as reasonably achievable (ALARA) is advised to apply in lung cancer screening.

**POTENTIAL ROLE OF AIRFLOW LIMITATION IN SELECTING HIGH-RISK INDIVIDUALS**

The prevalence of airflow limitation in China is increasing over the past two decades. According to a nationally representative survey in 2014–15, the prevalence of airflow limitation (defined based on spirometry according to the GOLD criteria) is 13.6% in general Chinese adults aged 40 years and older (19.0% in men and 8.1% in women)\(^{10}\), which is much higher than the 8.2% in 2002-04\(^{11}\). **Chapter 3** of the thesis illustrates the association between airflow limitation and the risk of lung cancer incidence in a large longitudinal Dutch cohort. The findings suggest that after correcting for pack-years of smoking, airflow limitation is associated with an approximately 1.6-fold risk of lung cancer incidence in current smokers and an approximately 1.5-fold risk in former smokers. In addition, compared to never smokers with normal lung function, current smokers with airflow limitation and former smokers with airflow limitation were associated with an approximately 4.2-fold and 1.9-fold increase in the incidence of lung cancer, respectively. A case-control study in a Chinese population also suggests that the presence of airflow limitation increases the risk of lung cancer\(^{12}\). Those evidence support that airflow limitation could improve the eligibility criteria for lung cancer screening in ever smokers. According to a study in a community-based lung cancer screening program in the UK, spirometry can be successfully incorporated and help to identify a large number of individuals with airflow limitation in smokers\(^{13}\), although the increased costs in budget and time due to this additional implementation should be evaluated.

**Chapter 3** also illustrates that lung cancer incidence increases with the increasing severity of airflow limitation. Although individuals with severe airflow limitation are at the highest risk of developing lung cancer, they are not necessarily the ones gaining the most benefits from screening, because comorbid disease and subsequent shorter life expectancy limit the benefits in mortality reduction yielded by lung cancer screening\(^{14,15}\). Studies show no mortality benefit from lung cancer screening in those with severe and very severe airflow limitation as defined by the Global Initiative on Chronic Obstructive Lung Disease (GOLD) criteria (GOLD 3 and 4)\(^{16}\), whereas lung cancer screening in those with undetected airflow limitation does reduce lung cancer mortality by 26%\(^{17}\). Therefore, spirometry, by detecting those asymptomatic individuals with airflow limitation, could help to identify a subgroup of eligible smokers who benefit most from lung cancer screening. According to the latest proposed lung cancer screening guideline in China,
patients with clinically assessed COPD, which are likely to be advanced COPD patients, are recommended to undergo lung cancer screening primarily based on their higher risk of developing lung cancer\(^\text{18}\). More evidence from the perspective of maximizing the screening benefits in the Chinese population is warranted for that recommendation.

### CONCLUSIONS AND FUTURE RESEARCHES

In conclusion, the necessity to define an optimal target population for CT lung cancer screening in China is explored in this thesis. Gender specific eligibility criteria for lung cancer screening should be developed due to the differences in risk factors and lung cancer incidence between men and women. Airflow limitation and a passive smoking history play a role in the identification of men and women at an increased risk for the development of lung cancer, respectively. Future studies on the optimization of the entry criteria for lung cancer screening in China should therefore focus on the identification of groups of people at a high risk for the development of lung cancer. Simultaneously, from the perspective of public health, a Chinese lung cancer screening program should be cost-effective, with optimized benefits and minimized harms.
REFERENCES


