

Implementation planning for lung cancer screening in China

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Abstract

Lung cancer is the leading cause of cancer-related deaths in China, with over 690 000 lung cancer deaths estimated in 2018. The mortality has increased about five-fold from the mid-1970s to the 2000s. Lung cancer low-dose computerized tomography (LDCT) screening in smokers was shown to improve survival in the US National Lung Screening Trial, and more recently in the European NELSON trial. However, although the predominant risk factor, smoking contributes to a lower fraction of lung cancers in China than in the UK and USA. Therefore, it is necessary to establish Chinese-specific screening strategies. There have been 23 associated programmes completed or still ongoing in China since the 1980s, mainly after 2000; and one has recently been planned. Generally, their entry criteria are not smoking-stringent. Most of the Chinese programmes have reported preliminary results only, which demonstrated a different high-risk subpopulation of lung cancer in China. Evidence concerning LDCT screening implementation is based on results of randomized controlled trials outside China. LDCT screening programmes combining tobacco control would produce more benefits. Population recruitment (e.g. risk-based selection), screening protocol, nodule management and cost-effectiveness are discussed in detail. In China, the high-risk subpopulation eligible for lung cancer screening has not as yet been confirmed, as all the risk parameters have not as yet been determined. Although evidence on best practice for implementation of lung cancer screening has been accumulating in other countries, further research in China is urgently required, as China is now facing a lung cancer epidemic.

Key words: lung cancer; China; screening; recommendation; low-dose computerized tomography; risk factor; tobacco control; pulmonary nodule management.

Introduction

Lung cancer has an extremely high incidence and mortality rate, thus it is recognised as a major public health problem all over the world, increasingly so in developing economies that have not heeded the dangers associated with smoking uptake. China, the most populous country in the world, has approximately 20% of the world population but has over one-third of the newly diagnosed lung cancer cases and lung cancer deaths worldwide, which were projected at over 774 000 and 690 000 in 2018 by GLOBCAN¹ (**Table 1**). Lung cancer is the most frequently diagnosed cancer in Chinese men and the second in Chinese women². During 2000-2010, there was a slight but insignificant decrease in incidence rate in males of 0.2% per year, but an annually significant upward change of 0.9% in females². The male-to-female incidence ratio decreased from 1.56 to 1.35 in the period of 1989-2008³. Mortality had an increasing trend observed over the last decades, that is, 5.47/100 000 in the mid-1970s, 17.27/100 000 in the early 1990s, and 30.83/100 000 in the 2000s^{2,4}. Since then, lung cancer became the leading cause of cancer-related deaths for both genders² (**Figure 1A**).

Attributable Risk Factors

Internationally, smoking is considered to be the predominant risk factor for lung cancer. However, in China, the proportion of lung cancer cases attributable to smoking was 57.5% in males and 11.5% in females in 2013, respectively⁵, which is much lower than that reported in the United Kingdom (UK, 85% in males and 80% in females in 2010)⁶ and the United States (US, 84.4% in males and 78.9% in females in 2014)⁷. Lung cancer incidence among male and female non-smokers estimated from the 2010 national data was over three times the 1990 US never-smokers⁸. The attributable fraction of lung cancer cases and deaths to smoking are similar^{5,7}. Therefore, other risk factors, including outdoor as well as indoor air pollution (i.e. second-hand smoking exposure), prior lung diseases (i.e. tuberculosis infection, COPD), family history of cancer are considered to have a more important role in China, especially in never-smokers, than other regions or populations^{6,7,9}.

Second-hand smoking exposure was estimated to contribute to 3.0% of male and 22.0% of female lung cancers in never-smokers aged ≥ 30 years in China (2013)⁵. The attributable fraction of lung

cancer cases in Chinese never-smoking females is much higher than their counterparts in the UK (15.4% in all ages in 2010)⁶ and the US (2.3% in ages ≥ 30 years in 2014)⁷; similarly, lung cancer deaths^{5,7}.

Use of coal for household heating and cooking - another component of indoor air pollution - is also a significant risk factor in China⁹. The lung cancer mortality in Xuanwei County, Yunnan Province, ranking among the highest in China is the best example: 2-3 times and 4-7 times higher in local men and women residents, respectively, than other contemporary rural areas (in the early 1990s, mid-2000s and early 2010s)¹⁰. Using smoky coal and unimproved domestic stoves is the main reason¹⁰. Outdoor air pollution (i.e. particulate matter [PM]) becomes increasingly significant in China¹¹, with a lung cancer risk ratio of 1.03, 1.04 and 1.03 per 10 $\mu\text{g}/\text{m}^3$ in relation to PM_{2.5}, SO₂ and nitrogen oxides, respectively^{11,12}. Occupational history (i.e. construction)¹³, radiation (i.e. residential radon radiation)⁹ and unhealthy diet (i.e. low fruit/vegetable intake)⁵ also have a significant influence on lung cancer risk or death in China.

Recent data has demonstrated that genetic factors modulate cancer pathogenesis. Genome-wide association analysis has revealed susceptibility loci for lung cancer, e.g. the 15q25^{14,15} or 5p15^{16,17} locus yet with different profiles of genetic variants between Chinese and Caucasians. Evidence also shows significant gene-smoking interactions in lung cancer, e.g. rs1316298 and rs4589502 in the Chinese population, which may shed light on the lung cancer aetiology¹⁸. Investigations into familial lung cancers have indicated a number of predisposing germline mutations, e.g. EGFR T790M (mostly Caucasians), EGFR V843I and HER2 G660D (East Asians)¹⁹. Furthermore, somatic mutation profiles have differed between lung cancer subgroups in terms of smoking status, ethnicity and histological subtypes²⁰⁻²²; e.g. EGFR mutations are more likely present in non-smokers (vs smokers: 67.2% vs 27.0% in Chinese non-small cell lung cancers [NSCLCs])²⁰, East Asians (vs other ethnicities: 30% vs 8%)^{21,22} and lung adenocarcinomas (vs squamous cell cancer: 40.4% vs 2.5% in smoking lung cancers in China)²⁰. These results demonstrate that lung cancer is not a single disease^{20,23}. The nature of lung cancer in China is therefore not only attributable to environmental factors but further complicated with genetic influences.

Tobacco Use

Epidemiology

China is the largest tobacco producer and consumer in the world. It manufactured over 2.9 million tons of tobacco in the year 2016^{24, 25}. There was estimated to be over 300 million current smokers aged ≥ 15 in China including 288.1 million males and 12.6 million females in the 2010 Global Adult Tobacco Survey (GATS)²⁶.

In the China Health and Nutrition Surveys during 1991 - 2011, the prevalence of current smoking in individuals aged ≥ 15 has reported a successively decline from 60.6% to 51.6% in males and 4.0 to 2.9% in females²⁷ (**Figure 1A**). However, the ever-smoking prevalence in both genders did not alter greatly during that time²⁷. Specifically, females' smoking uptake rate decreased in generations who were born during the 1930s - 1970s²⁸, but increased in the younger generations born in the 1980s and thereafter²⁹. The prevalence of smoking in females aged 12-17 during 1981-2010 multiplied from 2.47% to 19.72% for ever-smokers and from 0.29% to 3.26% for current smokers²⁹. Collapse of “cultural prohibitions against smoking among young women” due to socio-economic and political changes²⁹ (i.e. probably reform and opening up in China since 1978) might be responsible for the uptake increase in Chinese young women, which was similarly witnessed in the US and UK during and after World War II³⁰ (**Figure S1**). Overall, the current smoking prevalence in both genders has slightly declined over the last 20 years²⁷; however, a slight increase in the younger female subgroup has been reported²⁹. Given China as the most populated country in the world, the number of smokers is strikingly high.

In contrast, the UK and the US observed a very different trend from China in smoking prevalence (**Figure 1B, 1C**). In the UK, the tobacco-uptake rate peaked at 82% in 1948 among males and 45% in the mid-1960s among females, respectively^{31, 32}. However, it saw a continuous decline in both men and women in the following decades³² (**Figure 1B**). In 2017, the UK now has an overall current smoking prevalence of 15.1%³³, which is among the lowest prevalence rates in Europe³⁴; although there are still significant gaps in smoking uptakes in specific regions within the UK (e.g. 22.0% in Manchester vs 6.4% in Chiltern located in South West England in 2017)³³, which is closely related to

deprivation status³⁵. The smoking trend in the US^{36, 37} is very similar to the UK (**Figure 1C**). One has to be cautious when comparing these data, as differing definitions for smoking rates and statistical methods have been used in reporting smoking cessation rates in different countries.

Smoking-related mortality

It is perceived that there would be a long delay between the peak of smoking prevalence and its full impact on mortality. Cigarette epidemiology was first described by Lopez *et al.* as a four-stage model in 1994³⁸(**Figure 1D**). The model precisely described the relationship between smoking and smoking-related deaths in males and females in economically developed countries, such as the UK and the US. It was largely reflected in the interaction between smoking and lung cancer mortality since smoking was attributed to over 80% of lung cancer deaths in these countries^{7, 39}. Both countries may be currently experiencing the fourth stage when smoking prevalence in both genders decreased in recent years yet with their mortality converging³⁸ (**Figure 1B, 1C**).

As for China, the situation seems more complicated. The earliest nationally representative prevalence survey on smoking in China was in 1984, only a little over 30 years ago (**Figure S1-S2**)⁴⁰, while there are over 60 years of records in the UK^{31, 32} and US^{36, 37}. China has made great efforts to move forward in cancer surveillance, especially after 2002 when National Central Cancer Registration (NCCR) was launched^{41, 42}. It has witnessed a surge in the number of both cancer registration points in total and those included in the reports of Cancer Incidence in Five Continents (CI5), the latter taken as an indicator of data quality⁴¹. The latest version of CI5 (CI5 Vol. XI) released in 2017, has included data from 35 points collected during 2008-2012, almost three times the previous version, indicating a significant improvement in data quality (Figure S2)^{41, 43}. However, concerns arise regarding the population coverage by cancer registry, data quality control and data representativeness, etc.^{41, 42}. Cancer registries providing data with good quality are more established in eastern, developed and urban areas^{2, 44}, which compromises data representativeness nationally^{41, 42}. Most of the rural cancer registries are established in high-risk regions of cancer^{41, 45} and have a lower level of population coverage⁴¹. Furthermore, the overall cancer mortality estimated from rural cancer registries was 13%

higher than the estimate of the third National Death Survey, indicating overestimation; the difference was even more significant in some specific cancer types⁴⁵.

Substantial healthcare disparities exist across China, as indirectly evidenced by geographical variations in all cancer mortality and its 5-year survival in 2015: the estimates for rural areas were considerably worse than the urban (149.0 vs 109.5 per 100 000 [age-standardised by world population] and 30.3% vs 42.8%, respectively); similarly Southwest China was worse than East China (170.2 vs 115.6 per 100 000, and 24.9% vs 40.3%, respectively)². In contrast to the urban, the rural population more likely underutilise healthcare resources (e.g. less likely to choose self-care, outpatient and inpatient care vs no care) due to inferior health insurance coverage and reimbursement procedures associating with the two-class social insurance system⁴⁶. Unbalanced health service supply⁴⁶ and a lack of qualified primary healthcare providers⁴⁷ impede rural individuals' equitable access to healthcare⁴⁶ and induce a high rate of misdiagnosis and/or inappropriate treatment thus poor management of chronic diseases⁴⁷. Factors, which potentially increase financial risks are also non-negligible⁴⁶, e.g. travelling distance⁴⁶ and low annual household income (rural vs urban: US\$2587 vs US\$4761 on average in 2011)⁴⁸. Western and central China have experienced similar healthcare inequalities, where the economy is less developed than eastern China⁴⁸. Encouragingly, the gaps between regions has been shrinking since continuous efforts made in healthcare reforms by the government^{46, 48, 49}.

Thus, cautions can never be overemphasized in data interpretation due to its potentially poor representation of what the rural and underdeveloped areas are currently experiencing. From current data, China is most likely experiencing the 'third stage' of the four-stage model at this time⁵⁰. In Stage III, males' smoking prevalence starts to decline; while females' could rise first, due to a resurgence of uptake in the younger generation²⁹ and peak at a later time. Both genders would have a continuous increase in mortality in Stage III³⁸. It's worth noting that the smoking patterns are changing in younger generations, regarding an earlier age of initiation (e.g. before 20 years old) and consuming more cigarettes daily²⁸. Moreover, the attributable fraction of smoking has probably not reached its full impact to date³⁰, considering the lower smoking attributable fraction to lung cancer in China⁵.

Hence, one is more likely to witness severe health consequences in China in the upcoming decades. However, these are only assumptions based on limited data, and the exact time smoking and mortality in both genders will peak or decrease is not yet defined (this information can only be revealed from national tobacco surveys/cancer registries in future years).

Social changes and historical events are also responsible for these different trends of smoking and mortality between China and the UK & US (**Figure S1**), and these differences continue even today. Interventions have been encouraged to reduce the growth in tobacco consumption and risk of death from tobacco-related diseases.

Interventions for Lung Cancer

More than one-half of lung cancer cases were diagnosed at a very late stage throughout these years, as evidenced by the retrospective data from West China Hospital⁵¹ and the US national cancer registries' statistics⁵². These late-stage lung cancer patients have a minimal chance of a successful therapeutic intervention, thus resulting in an inferior prognosis. The 5-year survival rate in this subgroup is only 5% in the US⁵² or well below 5% in the UK⁵³. It is now agreed that one requires an integrated programme of tobacco control with earlier detection through low-dose computerised tomography (LDCT) screening, which would facilitate an improvement in lung cancer survival.

Tobacco control

The protective effect of smoking cessation increases with the quitting duration in ex-smokers who stopped smoking either by choice (while still healthy) or due to illness^{28, 54, 55}. However, the mortality risk is still somewhat higher than never-smokers^{28, 54, 55}. Quitting before the age of 40 years would avoid over 90% of the excess deaths due to regular smoking^{54, 55}; and adults who had quit smoking early enough would gain ten extra years of life expectancy compared with those who continued to smoke⁵⁵.

In 2005, China ratified the World Health Organisation Framework Convention on Tobacco Control (WHO FCTC)⁵⁶. The framework aims to reduce tobacco use among countries worldwide. It has six elemental compositions called MPOWER, including **M**onitoring, **s**moke-free **P**olicies, **O**ffer help to

cessation, health Warnings, Enforcing advertising bans and Raising taxes⁵⁶. The enforcement of these measures in China is still weak, compared to the UK, who has adopted comprehensive MPOWER measures at a best-practice level⁵⁶. The major obstacle remains the state-owned tobacco industry^{40, 50}. The state tobacco monopoly in China is in charge of both tobacco manufacturing and selling, and tobacco control in the WHO FCTC⁴⁰. “The tipping point” was a documentary by the Party School in 2013, which discussed the historical and philosophical perspectives on tobacco and tobacco control in China, including conflicting interests of the Chinese tobacco monopoly⁴⁰. Since then, tobacco control initiatives have been conducted one after another including the tax readjustment in 2015⁴⁰ (**Figure S1**). Although the percentage of tax in the retail price (56%) is still lower than the WHO’s recommendation of at least 70%⁵⁷, some early positive impacts have been reported in 2018⁵⁸. Cigarette sales have dropped from 127 billion packs in 2014 to 117 billion in 2016; and a decline of 0.2%-0.6% estimated in adults’ smoking prevalence during this period, i.e. 2.2-6.5 million fewer smokers, could be related to the increased cigarette prices⁵⁸. China is moving forward in tobacco control albeit slowly. It is crucial for China to take further action in comprehensive legislation, taxation, education and tackling the current dual identity of the state tobacco monopoly⁴⁰.

Lung cancer screening outside China

A number of lung cancer screening trials were undertaken since the 1980s, but none of them showed mortality reductions by utilising chest X-rays (CXR) with/without sputum cytology^{59, 60}. However, LDCT was found to be more sensitive than CXR in detecting lung cancers in observational studies^{59, 61} and also potentially improve survival by detecting lung cancer at an early stage, i.e. in ELCAP⁶¹ (later in I-ELCAP as well⁶²). After that, lung cancer screening trials, mainly randomised controlled trials (RCTs), have been undertaken in the US (NLST)⁶³, Europe (eight RCTs)⁶⁴⁻⁷¹ and lately in Japan (JECS)⁷² to investigate benefits of screening by LDCT (**Table S1**).

Briefly, NLST was the first RCT to report mortality reduction by LDCT screening. In 2011, it demonstrated a 20% reduction in lung cancer mortality and 6.7% reduction in all-cause mortality in the LDCT arm when compared with the CXR arm after a median follow-up of 6.5 years post randomisation⁶³. Since then, multiple organisations in the US have approved annual screening for

high-risk individuals based on the NLST results⁷³⁻⁷⁷. Four European trials (DLCST, DANTE, ITALUNG and MILD) reported on mortality, despite not having sufficient study power to test this, and none of them demonstrated a protective role of LDCT concerning mortality reduction⁶⁵⁻⁶⁸. However, NELSON, the only fully powered trial in Europe, reported at the WCLC 2018 a 26% decrease of lung cancer mortality in males and an even higher reduction in its smaller-sized population of females, which ranged from 39% to 61% depending on the length of follow-up of 8 to 10 years⁶⁴.

Lung Cancer Screening in China

We have searched four Chinese databases (China National Knowledge Infrastructure database [CNKI], Wanfang Data, Chongqing VIP database and Chinese Clinical Trial Registry Centre Library) and four English databases (PubMed, Embase, Web of Science Core Collection Library and Cochrane Library) as of September 10, 2018 from the earliest dates available. Other sources (e.g. references in reviews/articles, policies/news from government websites and personal communication with principal investigators) were also used (**Supplementary**). Generally, most of the publications concerning LDCT and/or CXR were retrospective cohorts (e.g. in a population undergoing regular physical examinations), case-control studies (e.g. comparison in the performance of LDCT versus CXR in selected populations) or cross-sectional studies (e.g. with one-time LDCT/CXR screening). Therefore, we only considered prospective cohorts and RCTs here. There have been 23 associated programmes completed or ongoing in China since the 1980s, the majority after 2000; and one has recently been planned (**Figure 2, Table 2; Supplementary**).

Generally, studies in earlier times targeted occupational populations and applied CXR and/or sputum examination for lung cancer screening⁷⁸⁻⁸³. They mainly investigated the effectiveness of screening and lung cancer-associated risk factors (e.g. The *Yunnan Tin Corporation [YTC]* cohort⁸² and the *Kailuan* cohort⁸³). Municipal or city-level screening programmes⁸⁴⁻⁹² have been accumulating especially after the central government-led programmes (*RuraCSP*^{93, 94} in 2009 and *CanSPUC*^{95, 96} in 2012). Most of the programmes referred above are pilot or feasibility studies to investigate the effectiveness of LDCT screening.

Some institutes have built collaborative relationships with international organisations (i.e. *Zhuhai I-ELCAP*⁹⁷, *Beijing I-ELCAP*⁹⁸, *NELCIN-B3*⁹⁹), to help to clarify characteristics and to accumulate evidence of lung cancer screening in China. *NELCIN-B3*⁹⁹, a Netherlands-China collaborative, multi-centre study, will focus on the three major diseases of the thorax – lung cancer, cardiovascular disease and chronic obstructive pulmonary disease – by using one-stop CT imaging technology in the context of LDCT screening. *NELCIN-B3* would be expected to provide more evidence on the management of both nodules and other thoracic diseases⁹⁹.

Notably, the majority of the programmes are funded by central or local government, which is argued as unsustainable and unaffordable for a larger-scale programme in the long run⁹². The *Guangzhou Financing* demonstration project in planning will investigate the potential financing models which could be viable to cope with costs during the screening implementation⁹². Charity foundations and supports of companies could also play a role in the financing (i.e. *Guangzhou GMU-1stHosp* programme^{91, 92} and *Qinghai SH-Renji* programme^{100, 101}). The reader has to be aware of the limitations of the references to many of the Chinese CT screening programmes, which are only based on web pages or conference abstracts, thus one has to be cautious with the interpretation.

To date the majority of the studies have only reported their preliminary results, suggesting possible benefits of LDCT in detecting early lung cancers. However, concerning high-risk definition, nodule management and mortality outcomes, evidence in China is quite limited at this time. There is a different risk profile for lung cancer in China, as indicated by the baseline/preliminary results from *Beijing I-ELCAP*⁹⁸, *Tianjin CancerHosp*⁸⁴, *Shanghai CancerHosp* cohort⁸⁶ and *Shanghai ChestHosp* RCT⁸⁷: females and non-smokers could have a lung cancer detection rate comparable to or even higher than males and smokers in China. Therefore, risk stratification based on exotic guidelines or entry criteria could result in a significant misdiagnosis in the Chinese population.

Utilising microsimulation modelling, Sheehan *et al.*¹⁰² compared eligibility criteria of Centres for Medicare & Medicaid Services in 2015 (CMS 2015: ages 55-77 and smoking ≥ 30 pack-years, quitting ≤ 15 years if former smokers)⁷⁷ and the 2015 China National lung cancer screening (CNS 2015: ages 50-74 and smoking ≥ 20 pack-years, quitting ≤ 5 years if former smokers)¹⁰³ in Chinese population if

annual LDCT screening was applied from 2016 to 2050. Applying CNS 2015 criteria would have a lower mortality reduction in males (6.30% vs 6.58%), but a higher one in females (2.79% vs 1.97%), namely 2.9% more lung cancers prevented when compared to CMS 2015 criteria. However, more screens would be needed when using CNS 2015 criteria (1.43 billion vs 998 billion if CMS 2015 criteria applied)¹⁰². In a decision analysis way, Wang *et al.*¹⁰⁴ simulated a cohort of 100,000 Chinese urban smokers aged 45-80 who would receive a one-off screening. They found there would be a lung cancer mortality reduction of 17.2% and 24.2% by LDCT screening when compared to CXR screening and no screening, respectively. In the LDCT screening scenario, there would be 9387 false diagnosis and seven deaths attributed to false diagnosis; in CXR screening, the number would be 2497 and two, respectively. Lung cancer prevalence, LDCT sensitivity and proportion of early stage in lung cancers detected by LDCT would influence mortality reduction the most in the LDCT screening arm when compared to no screening¹⁰⁴. These results demonstrate the possible benefit of mortality reduction in China and also the urgent necessity of better definition in high-risk eligible individuals.

Many hospitals establish their independent programmes, but now need to collaborate to work to consensus protocols and data collection methods, to provide data which can be utilised throughout the whole of China. A good example of international collaboration is the European Position Statement on lung cancer screening¹⁰⁵, where a consensus approach throughout Europe has been agreed. Evidence specific to China is awaited as the majority of the programmes are still ongoing. It is essential to consider what other countries have done and combine with Chinese conditions; thus, we can better aim to curb lung cancer sufferings in this specific population in the long run.

Integrating tobacco control into screening programmes

It is considered that on-going lung cancer screening programmes would create a 'teachable moment' for the participating smokers, thereby motivating smoking cessation and maximising overall cancer prevention benefit, as had been introduced first and assessed in ELCAP in 2001¹⁰⁶. Subsequently, a positive effect of the screening programmes *per se* on quitting¹⁰⁷⁻¹⁰⁹, and CT abnormality-dependent smoking cessation^{108, 110, 111} have been illustrated in other trials. Researchers also found consistently negative scans were not necessarily related to a lower rate of smoking abstinence or a higher

percentage of relapse¹¹². Quitting smoking has also been reported to benefit participants' outcomes within the frame of lung cancer screening programmes, where the mortality reduction could be comparable to or even exceed that achieved by LDCT screening alone¹¹³, even in late quitters who stopped smoking during follow-up after baseline scan¹¹⁴. In 2018, a group of researchers launched a statement of the Smoking Cessation within the Context of Lung Cancer Screening (SCALE) collaboration in order to determine the optimal implementation strategy from this specific integration¹¹⁵.

Planning for Lung Cancer Screening Programme

High-quality medical research is necessary for prioritising health needs. Regarding real-world evidence, Sun *et al.*¹¹⁷ concluded a desperate lack of pragmatic clinical trials in China, in total, only amounted to 16, of which nine were on traditional Chinese medicine and most featured moderate sample sizes and short follow-ups. Undoubtedly, more efforts are demanded on population-specified and highly reliable medical research in China. We reviewed current evidence on lung cancer LDCT screening both in and out of China and discussed them below in the hope of facilitating its implantation in the Chinese population.

Population Recruitment

Most of the lung screening trials (**Table S2**) applied combined recruitment strategies to enrol participants. The detailed information on recruitment yields has been reported in a limited number of the screening trials (i.e. NELSON, ITALUNG, LUSI and UKLS). The overall yield of participation in all the approached population ranged from 1.4% to 4.5%. All the four trials approached the population by mailing. The recruitment rate was mainly dependent on the recruitment methods (closely related to the response rate) as well as the stringency of the selection process (i.e. risk-based selection).

Recruitment methods

Current smoking stigma and deprivation are the common factors compromising uptake in a lung cancer screening trial^{118, 119}. Younger individuals are less likely to respond to the first invitation approach¹¹⁸. Conversely, after assessing lung cancer risk and when approaching the eligible high-risk

cohort, older people are more likely refuse¹¹⁹. Differences in risk perception can also impact participation^{119, 120}. Practical barriers including travel and comorbidities, along with emotional barriers, were the most reported reasons for non-uptake¹¹⁹.

The minorities or underserved, who may be more vulnerable to morbidity and mortality^{121, 122}, were underrepresented in the screening trials¹²¹. It would impede generability of lung cancer screening programmes. These people are more likely to be less-educated, economically disadvantaged, uninsured¹²³ and also smokers¹²². The barriers to their participation include lack of awareness, lack of opportunity/access, individual beliefs¹²³, economic obstacles and weakness in study designs¹²⁴.

Targeted strategies have been suggested for this subgroup^{123, 125}, e.g. the more intensive face-to-face recruiting method^{123, 124}. A second or third contact¹²⁶, or using mobile CT scanners and one-stop lung health checks near local shopping centres¹²⁷ were also demonstrated beneficial for uptake in deprived areas. Some tactics are probably helpful, including cooperation with community-based clinics or organisations who have built trust in local people, employment of coordinators who are proactive and knowledgeable in programmes, complimentary transportation assistance and personalized post-screening navigation¹²⁵. Current evidence on the efficacy and effectiveness of recruitment strategies are limited, mostly because recruitment targeting the underserved was issued in the midway of a study^{123, 128} and data collection on recruitment methods were incomplete^{123, 128, 129}. It suggested a considerate preparation of trial design, population approach and cost estimation be needed.

Additionally, reporting the nature and effectiveness of recruitment strategies in screening trials is an essential requirement, as it is useful for later evaluation and comparisons in different settings.

Risk-based selection

How to define the high-risk population remains unanswered. Most of the screening trials defined their entry criteria on a solo combination of age and smoking exposure (**Table S2**). Specifically, NELSON selected its participants based on lung cancer mortality risk estimated from 2 large-scale cohorts, US Cancer Prevention Study I and II (CPS I/II)¹³⁰. UKLS and PanCan were the only RCT and cohort, respectively, to apply a risk model for such a selection. However, as for Chinese screening studies,

other risk factors (e.g. passive smoking, occupation, family history of cancer, kitchen fume, *et al.*), parallel to smoking exposure, were also considered in entry criteria (**Table 2**).

Age

The age eligibility in screening trials varies greatly, with the lower limit between 40 and 60, and the upper ranged from 69 to no limit (**Table S2**). Whereas the median age of the enrolled participants in all studies was normally around 60 years, ranging from 56 to 67 years old (**Table S3**). A lower age limit is not necessarily associated with an accordingly lower median age in enrollees of the trials. Conversely, younger individuals are less likely to participate due to a lower affective risk perception¹¹⁸, or to be eligible because of a generally lower predicted risk if any prediction models were applied that included age^{131, 132}. The lower cut-off point for age eligibility of at least 58 has been suggested by the UKLS researchers because the positive response rate in the high-risk population ≥ 58 was much higher than those below this age ($\geq 4.3\%$ vs 1.0%)¹¹⁸.

As for the upper age limit, discordance widely exist in recommendations^{73, 133}: 74 in ACCP, ASCO, ATSS⁷⁴, ACS⁷⁶ and NCCN¹³⁴ (all based on the NLST results), 74 in the CNS 2015/2018¹³⁵ and 79 in AATS⁷⁵ (based on the NLST results, age-specific incidence and life expectancy in the specific nations) and 80 in USPSTF⁷³ (based on data modelling). USPSTF modelled data from NLST, PLCO, the Surveillance, Epidemiology, and End Results program (SEER) and the U.S. Smoking History Generator. They selected the most advantageous screening scenario by maximizing lung cancer mortality reduction and reducing over-diagnosis as much as possible^{73, 136}.

However, it is widely presumed that older individuals would be not eligible for inclusion due to their existing comorbidities. In this subpopulation, harm from screening might outweigh the benefits, but this can be difficult to measure due to the competing causes of death. In another microsimulation modelling, Han *et al.*¹³³ incorporated over-diagnosis into the outcome measures (including lung cancer deaths prevented and life-year gained due to screening). They found that stopping screening at a younger age of 75 would have higher efficiency in maximizing the benefits (mainly life-years gained per over-diagnosed case) than at 80, and there was no gender difference.

In a trend analysis of national cancer registries-based lung cancers in China during 1989-2008, the average age in male and female patients significantly increased from 65.32 to 67.87, and from 65.14 to 68.05, respectively³. The change may be explained by our ageing population with time³. However, In West China Hospital, the average age at diagnosis in hospital-based lung cancer cases was 59.22 during 2008-2014⁵¹. The difference might be attributed to data sources, geographical factors *et al.* Therefore, it's better for us to comprehensively consider age- and geographical-specific lung cancer incidence, participation rate and also benefit-to-harm ratios before determining the age at entry.

Smoking status

Smoking is the other basic entry criteria after age. Heavy current and former smokers are the targets in most of the trials, except the Asian studies (**Table 2 and S2**). JECS in Japan only targets non- or light smokers. The Chinese ones (e.g. *Shanghai Cancer Hosp cohort*⁸⁶, *Shanghai Chest Hosp RCT*⁸⁷ and *China FeasiRCT*^{137, 138}) also recruited individuals exposed to other risk factors, not restricted to heavy current/former smokers only. Although PanCan and UKLS used a risk model for high-risk assessment and recruitment, the final studies included participants who were practically all ex- or current smokers (**Table S3**).

There are two types of smoking exposure criteria in the trials: cumulative pack-years, or smoking duration and intensity (average number of cigarettes per day), separately (**Table S2**). In the LLP model used by UKLS as a selection tool, smoking duration was demonstrated as the strongest predictor instead of other smoking-related factors, e.g. smoking status, intensity and time since quitting^{139, 140}. While ten Haaf *et al.*¹⁴¹ concluded little difference between the two criteria in the aspect of cost-effectiveness in their microsimulation modelling; the scenario with stringent smoking criteria, annual screening for persons aged 55-75 who smoked >40 pack-years and who currently or quit ≤ 10 years ago, were optimal¹⁴¹.

Most of the Western World trials and nearly all the screening guidelines concentrated on the smoking subpopulation. Additionally, both Ten Haaf *et al.*¹⁴² and Tammemagi *et al.*¹⁴³ demonstrated most never-smokers wouldn't benefit from lung cancer screening; notably, the two studies were based on a US dataset. Since there are different smoking profiles in lung cancer patients from the US and China

as discussed above, whether Chinese never-smokers could gain more significant benefits than harm, from early screening, is still unknown. Given other predisposing factors, it may indicate totally distinct entry criteria for lung cancer screening in China. This is somewhat evidenced by the baseline results from *Shanghai Chest Hosp RCT*⁸⁷ and *Shanghai Cancer Hosp cohort*⁸⁶, which had a less stringent smoking eligibility criteria^{86, 87}. The former had a similar prevalence rate of lung cancer between the NLST-ineligible males (1.1%) and females (1.4%) in the LDCT arm⁸⁷, which was comparable to NLST (1.0%)¹⁴⁴. In the latter, the incidence in never-smokers was two-fold that of smokers at baseline screening⁸⁶ (**Table 2, Table S3**). Some lessons could be learned by comparison with other Asian studies, where never-smoker lung cancer incidence is more comparable to China. However, this is difficult because of limited data.

Thus favourably, a pre-evaluation of lung cancer risk in the local population, and pre-estimation of cost-effectiveness for different scenarios of screening criteria in the setting of the corresponding economic structure would assist in the selection of the optimal eligibility criteria. Moreover, establishing a specifically optimised Chinese risk model would preferably simplify recruitment in China and could lead to a more effective screening program on the basis of an individual's risk.

Modelling for risk prediction in the population outside China

Many publications have implied the outperformance of risk models in improving screening effectiveness and efficiency over current eligibility criteria, used in the trials or recommended in guidelines^{143, 145-149}. UKLS and PanCan applied risk models (the LLP model and PanCan model, respectively) in selecting high-risk individuals for eligibility entry. The high-risk cut-off threshold was defined as the risk estimation of LLP_{v2} risk model $\geq 5\%$ in 5 years in UKLS^{122, 132}, and PanCan model (a prototype of PLCO_{m2012}) $> 2\%$ in 6 years in PanCan¹³¹. Generally, studies using models had a higher lung cancer detection rate^{122, 131} and cost-effectiveness¹²² than their counterparts (**Table S2-S3**).

There had been a large number of risk models established for predicting lung cancer risk^{150, 151}. The predictors in the models varied a great deal, from the simplest combination of age and smoking to more complicated models (integrated medical conditions, medical history, ethnicity and socio-

economic factors)^{150, 151}. Although with good discrimination (and calibration) in development datasets, the performance of most models in external validation was generally limited^{150, 151}.

A few studies^{146, 147, 152, 153} assessed and compared different risk models in respect to discrimination, calibration and clinical utility. However, wide variations exist in their performances. In a UK case-control dataset: Spitz and LLP were comparable in discrimination and positive/negative predictive values, both of which were better than Bach; LLP showed a better sensitivity but lower specificity than Spitz and Bach¹⁵². Ten Haaf, *et al.*¹⁴⁶ demonstrated that PLCO_{m2012}, Bach and the Two-Stage Clonal Expansion (TSCE) incidence model had the best overall performance with an AUC of 0.68-0.71 in NLST and 0.74-0.79 in PLCO for 6-year lung cancer incidence, superior to the other models (including LLP, Knoke and two versions of the TSCE model for lung cancer death). Katki, *et al.*¹⁵³ arrived at the conclusion that PLCO_{m2012}, Bach, the Lung Cancer Risk Assessment Tool (LCRAT) and the Lung Cancer Death Risk Assessment Tool (LCDRAT) outperformed the other five models, including Spitz, LLP, the LLP incidence (LLPi) Risk model, Hoggart and the Pittsburgh Predictor, in three US population-based datasets. However, in a German cohort, Li *et al.*¹⁴⁷ demonstrated only a modest superiority of PLCO_{m2012} over Bach and LLP in selecting high-risk population for screening.

On reflection, there may be a number of reasons for the varied performance. Firstly, some models, e.g. LLP and Spitz, were derived from case-control datasets, while others, e.g. PLCO_{m2012}, Bach and TSCE, were from cohorts^{150, 153}. Risk models developed from case-control datasets may lack generalizability in the population due to selection bias in cases and controls; they may also have the bias in risk estimations because recall bias exists in data collection¹⁵³. Secondly, all the models were derived from a specific ethnicity or region. This population-dependent feature would impair their performance in populations from other ethnicities and regions, e.g. PLCO_{m2012} under-rated lung cancer risk in Hispanics¹⁵³. Thirdly, some risk factors may be unavailable in another independent dataset, which may weaken the prediction. However, the impact may be limited. Ten Haaf and colleagues¹⁴⁶ found that full version and simplified version (only including age, gender and smoking) of risk models performed similarly, i.e. full PLCO_{m2012} and simplified PLCO_{m2012}, full LLP and simplified LLP. It indicated that the three variables in simplified models contributed to lung cancer risk the most.

Evidence of long-term benefits and harms, such as trade-offs between life-years gained, mortality reduction and over-diagnosis are limited. The optimal threshold for risk models, at which lung cancer screening programs or clinical practice should gain maximum benefits over harms, is still undetermined^{146, 150}. Thus, no preferential risk model and risk threshold have been recommended in risk prediction for screening eligibility across different populations. The European position statement¹⁰⁵ suggested that “either the PLCO_{m2012} or the LLP_{v2} would suffice if screening were to be implemented immediately” given their high level of prediction.

There are emerging models integrating clinical factors, e.g. molecular biomarkers from blood, pulmonary function and genetic biomarkers (e.g. single-nucleotide polymorphisms), which potentially are alternative ways to improve risk models’ overall performance. Some of them are extensions of the original existing models, which have only epidemiological factors, but the improvement was found to be generally moderate^{150, 151}. Specifically, the extended LLP model has been successively integrated with different SNPs twice, whose performance in discrimination increased from 0.72 to 0.75¹⁵⁴ and from 0.73 to 0.79¹⁵⁵, respectively, when compared with the original epidemiological model. However, a modest enhancement in the performance of the risk models would still be significant and meaningful, since the ‘improvement space’ is limited. It is also important to note that genetic risk is already captured to some extent in the LLP risk model through the inclusion of personal and family cancer history.

Risk models for participant selection in China

In mainland China, four studies explored this topic¹⁵⁶⁻¹⁵⁹ (**Table S4**). Among them, three models had good discrimination (AUC: 0.7037-0.885)¹⁵⁷⁻¹⁵⁹. Specifically, Lin *et al.*¹⁵⁷ constructed a model by using the first-degree pedigrees of patients and their spouses as cases and controls (633 proband pedigrees vs 565 spouse pedigrees). The higher the risk threshold was, the more accurate the prediction in clinical use: cut-off value <5, an accuracy of 68.3%; 5-10, 84.0%; ≥10, 91.9%. But no external validation was performed. Yang *et al.*¹⁵⁹ developed a model from a retrospective cohort; when the risk probability was calculated at ≥ 0.65, the model’s sensitivity and specificity was 14.9% and 94.5% in the development dataset, 13.0% and 98.3% in the external validation dataset,

respectively. The model built by Wang *et al.*¹⁵⁸ performed well in the aspects of discrimination and clinical use, but it had no external validation either. All the four models were derived from hospital-based data¹⁵⁶⁻¹⁵⁹, which potentially would introduce bias in data analysis. Further optimisation is desperately needed to produce new models. A prospective cohort to observe lung cancer incidence within a specific timeframe and validate the models is also worth consideration but may cause significant delay unless performed alongside CT screening, using the best current model.

In the future, a comprehensive, systematic reporting standard in the development and validation of screening would be helpful for comparisons between models from similar or different backgrounds, enabling extensive validation of various models in a unified cross-border dataset. Undoubtedly, further research is important and should be an integral part of any screening programme.

Screen protocols and related issues

Screening interval

There were only six screening trials which applied biennial LDCT screening in their intervention arms, including PanCan, NELSON (only once), MILD and the three Chinese trials (the *China FeasiRCT*^{137, 138}, the *Shanghai ChestHosp RCT*⁸⁷ and *Tianjin CancerHosp* programme⁸⁴). Others, except JECS with a 5-year screening interval, used annual screens for their enrollees (**Table 2, Table S1**).

In NELSON¹⁶⁰, there were an increasing number of interval cancers (5 vs 19 vs 28, respectively) and higher proportions of stage IIIB/IV in screen-detected lung cancers (6.8% vs 5.2% vs 17.3%, respectively) after a corresponding 1, 2 and 2.5-year interval¹⁶⁰. These results indicated that an interval of 2.5 years is most likely too long for a population screening programme.

No significant difference between annual and biennial screening in MILD has been found in respect to interval lung cancers, specificity, sensitivity and positive/negative predictive value¹⁶¹. Note that the population in MILD was much smaller than NELSON. In the UKLS modelling, annual screening would prevent more lung cancer deaths (956 vs 802), but induced more over-diagnosis (457 vs 383) and screening episodes (330,000 vs 180,000)¹⁶². By microsimulating NLST, the biennial screening

gained similar quality-adjusted life-years (QALYs) to the annual screening over 20 years (24,000 vs 23,000); but the former was more cost-effective regarding both incremental cost-effectiveness ratios and CT scans saved¹⁶³. Therefore, a 2-year interval might be a cost-effective alternative for screening.

The risk of screen-detected lung cancer depended strongly on the results of the first scan: 1.0% with a baseline-negative scan, 5.7% with an indeterminate result and 48.3% with a positive result over a 5.5-year follow-up¹⁶⁴. When compared to individuals with a nodule at the baseline scan, those without would possess a much lower risk in 2 years (0.2% vs 4.6%)¹³¹. Thus, a tailored screen interval is needed. For such a low-risk probability, the subpopulation with a negative baseline result might be safely screened every two years or even a longer interval; other subpopulations with distinct baseline nodule results might be managed according to their specific risk probabilities. The risk probabilities of the individuals with nodules could be implied by the cut-off value of nodule risk prediction models (discussed below). Evidence from the Chinese studies is limited because the results of interval screening rounds are still awaited.

Over-diagnosis

Over-diagnosis is always a critical issue disputed in the context of screening. It is defined as the detection of a cancer that would not have been clinically apparent if there were no screening¹⁶⁵. With over-diagnosis, unnecessary treatment, psychological problems and economic burdens would result¹⁶⁵. An upper bound of about 18% - 25% of all the cancers detected in the LDCT screening were estimated indolent, thus probably over-diagnosed^{165, 166}. The over-diagnosed lung cancers are more likely to be adenocarcinoma since it has a higher proportion in the LDCT arm than the control arm^{66, 165} and also a longer volume doubling time (VDT) than other lung cancer subtypes¹⁶⁶.

A contradictory indicator to over-diagnosis is stage shift. The primary aim of screening is to detect lung cancer at an earlier stage; thus we aim for a corresponding reduction in advanced lung cancers. It is therefore not expected that tumours detected might appear to be indolent. Over-diagnosis will be caused if there is no reduction in advanced lung cancers but only an accumulation of indolent cancers categorised into early stages⁶⁵. Only NLST⁶³ (Stage IV: 0.9% vs 1.3%) and DLCST⁶⁵ (T4N3M1: 0.4% vs 1.0%) showed a significantly lower proportion of advanced lung cancers in the intervention arm

than the control arm. There was no evident stage shift in DANTE⁶⁶ (stage IV: 2.1% vs 2.8%) and ITALUNG⁶⁷ (stage IV: 1.7% vs 2.2%). The reasons could be the larger study size, differing approach methods used for NLST and DLCST or some degree of over-diagnosis existed in these trials.

Additionally, the effects of over-diagnosis could be mixed with lead time. The latter is defined as “the difference between the time when diagnosis would have been made without screening and the time that the diagnosis was actually made as a result of early detection by screening”¹⁶⁵. A longer follow-up may be helpful to distinguish between over-diagnosis and lead time. There were a mean lead time of 3.6 years estimated for non-bronchioloalveolar carcinoma (BAC) NSCLCs and 32.1 years for BACs, to when they naturally become clinical significance without screening interventions.

Specifically, over 25% of the non-BAC NSCLC cases would have a lead time of >5 years, and a very low proportion of 6.3% would exceed more than one decade. However, for BACs, 73.2% would have a lead time of ≥ 10 years, and approximately 50% would be over-diagnosed throughout the whole life¹⁶⁵.

In ITALUNG, the cumulative number of lung cancers in the usual care group caught up with the LDCT group after a follow-up of 6 - 7 years from randomisation⁶⁷. However, in DANTE, after a median follow-up with 8.35 years since randomisation, there was still a lung cancer excess rate of 30.76% in the LDCT arm compared with the usual care arm⁶⁶. Apart from over-diagnosis, the difference in-between may also be explained by one more screening round in DANTE and the possibly different subtype distribution in the diagnosed lung cancers.

The results above indicated that certain screening rounds accompanying a specific and long enough follow-up timeframe might minimise over-diagnosis. Moreover, over-diagnosis would be affected by the possibly different distribution of lung cancer subtypes in screening participants.

Length of screening

As discussed above, screening length is closely associated with over-diagnosis; comparing with the usual care group, the LDCT group managed with three annual screens would have an over-diagnosis rate of 31% within a complete 7-year follow-up after baseline¹⁶⁵. Given the evidence from

ITALUNG⁶⁷ and DANTE⁶⁶ extended follow-ups (as above), it is better to estimate screening length, follow-up duration and corresponding over-diagnosis rate before a trial is started.

When compared with the unscreened Beta-Carotene and Retinol Efficacy Trial (CARET) cohort, the mortality reduction due to two annual screening rounds in the New York ELCAP cohort became apparent in the 4th year and reached the maximum in the 6th-8th year after enrolment. The overall mortality reduction would be 36% when standardised by the CARET entry criteria¹⁶⁷; the mortality would be reduced further if the screenings continued¹⁶⁷. In the COSMOS pilot cohort of 1035 individuals, a lung cancer mortality reduction of 31%-61% would be expected after seven years of annual screening when compared with the extrapolation from an age- and sex-matched unscreened CPS II smokers¹⁶⁸. Despite a lack of statistical significance in mortality reduction after a 9-year follow-up in ITALUNG, the researchers found a significant mortality reduction in the post-screening period⁶⁷. Therefore, extensions of screening and follow-ups could enhance mortality reduction.

In summary, for planning the screening length of a trial or national programme, some factors to consider are: 1) the mortality reduction expected in screening population; 2) cost-effectiveness ; 3) limiting over-diagnosis; 4) minimising other potential harms, e.g. radiological exposure, psychological impact.

Nodule management

The nodule management protocols of most screening trials largely follow or are modified from the ELCAP/I-ELCAP (**Table S5**). Henschke and colleagues published the protocols consecutively in 1999⁶¹, 2004¹⁶⁹, 2011¹⁷⁰ and 2016¹⁷¹ when new evidence accumulated. When comparing the modified versions with the 1999 protocol, the significant changes are as follows: 1) nodule cut-off value increased; 2) volumetric analysis and VDT introduced to define growth; 3) management differed among solid, part-solid and nonsolid nodules; 4) non-solid nodules managed less aggressively; 5) management differed in baseline nodules and new nodules detected at intervals (the latter managed more aggressively); 6) endo-bronchial solid nodules also specified.

The NELSON protocol was derived from the 2004 I-ELCAP protocol¹⁷². It was the first lung cancer screening trial to use volumetry as a nodule assessment method. It developed two classification systems for nodules detected at either baseline or interval scans: NODCAT (nodule categories) and GROWCAT (growth categories). Generally, the solid component, either in solid or part-solid nodules, is measured in volume (mm^3); while, the overall size of the part-solid, non-solid and pleural-based solid nodules are measured in diameter (mm). NODCAT is applied to all nodules detected on CT scans, assisting decision-making on follow-up; GROWCAT is applied when there are follow-up scans for assessing VDT or a new solid component growth in a nonsolid lesion¹⁷².

The UKLS trial nodule management largely followed that of the NELSON. The main difference between UKLS and NELSON categories is that UKLS picked 15-49 mm^3 nodules as a separate category to ensure the inclusion of cancers in nodules $<50\text{mm}^3$ to the largest degree in a single screen design¹⁷³.

A variety of guidelines about pulmonary nodule management have also emerged in different countries tailored to their own circumstances^{103, 135, 174-177}. Specifically, several risk models for nodule malignancy prediction have been recommended in these guidelines: the Mayo Clinic model by the American College of Chest Physicians (ACCP)¹⁷⁶ and the Fleischner Society¹⁷⁸, or the Herder model and Brock model by the British Thoracic Society (BTS)¹⁷⁵. As its guidelines are applicable to clinical practice, the Fleischner Society recommended adherence to the existing American College of Radiology Lung CT Screening Reporting and Data System (Lung-RADS) guidelines for lung cancer screening¹⁷⁸.

Associated guidelines have also been developed in Asia or China in the clinical¹⁷⁴ or screening setting^{103, 135}. Remarkably, evidence supporting these recommendations is predominantly from the Western countries. It is possible that they are inappropriate to the East whose features are distinct in demographic, geographic and genetic aspects, but unclear if this variation in the aetiology of lung cancer in the East is limited to the initiation of lung cancer, or extends to the biological features that influence nodule behaviour. In the absence of any large-scale LDCT trials in China and other Asian

countries, the slight modifications made in the Asian guidelines were basically from experts' opinions^{103, 135, 174}. Herein we discussed some crucial issues related to nodule management.

Measurement: diameter or volumetry?

There are several ways to evaluate nodule size in the screening trials: maximum axial diameter, the average of length and width, and three-dimensional (3D) volumetric computer-aid assessment¹⁷⁹. Specifically, amongst all the screening trials, NELSON, MILD and UKLS used volumetric-based measurement for nodule assessment; others mostly followed a diameter-based protocol (e.g. NLST), with some applying a computer-aided system at follow-up scans for nodule growth and VDT assessment (e.g. DLCST, LUSI) (**Table S5**).

Mean axial diameter (using the average of the long-axis diameter and that taken at right angles to it) for nodule risk assessment was first adopted in ELCAP⁶¹. The Fleischner Society statement in 2017¹⁷⁹ It commented that, due to substantial inter- and intra-observer variability, using the maximum dimension would lead to misclassification of nodules, especially in small nodules, thus resulting in a high false-positive rate¹⁷⁹. Large variance of intra-nodular diameters also existed in indeterminate nodules; it could reach up to a median value of 2.8mm, higher than the growth threshold of 1.5mm recommended by LUNG-RADS¹⁸⁰. Hence, nodule size represented by diameter is concluded as poor. Calculation of volumes based on the diameter was also used. However, compared with volume measured semi-automatically in a 3D software, a mean over-estimation of volume by 85.1% and 47.2% could occur in volume calculation by the maximum and mean axial diameter, respectively¹⁸⁰. Therefore, the European position statement¹⁰⁵ and BTS 2015¹⁷⁵ recommended volumetry as preferred assessment method.

Cut-off values

NLST defined ≥ 4 mm as its threshold of positive results; while most of the others applied the cut-off value of ≥ 5 mm (**Table S5**). With rising thresholds, the frequency of positive results and further work-ups decreases successively, thus saving medical resources. Precisely, when increasing the threshold from 6mm to 9mm in I-ELCAP¹⁸¹, the screening-positive rate dropped from 10.2% to 4.0% and the work-up would be reduced from 63% to 25%. The disadvantage was the corresponding increased rate

of lung cancer diagnostics delayed up to 9 months from 0% to 6.7%. Similar results have been concluded in the NLST LDCT-arm dataset^{182, 183}. The $\geq 6\text{mm}$ threshold has performed well in other aspects, including the avoidance of false positivity^{183, 184} and more positive predictive findings¹⁸⁵, but it impaired the sensitivity¹⁸⁵ when compared with the cut-off of $\geq 4\text{mm}$. There was no statistically significant effect on survival or mortality in different nodule sizes¹⁸³. Currently, the nodule-positive threshold of 6mm has been recommended by I-ELCAP (2016)¹⁷¹, the Fleischner Society (2017)¹⁷⁸ and LUNG-RADS¹⁸⁶. BRELT1 also increased its threshold from the original 4mm to 6mm during the implementation¹⁸⁷.

The lung cancer probabilities in different nodule sizes at baseline are also an essential factor when determining the appropriate threshold. In NELSON, the risk increased with the volumes (or diameters) of baseline non-calcified nodules: a low risk of 0.6% (or 0.4%) in nodules of $<100\text{mm}^3$ (or $<5\text{mm}$, respectively), comparable to those without nodules (0.4%); intermediate risk of 2.4% (1.3%) in $100\text{-}300\text{mm}^3$ (5-10mm); high risk of 16.9% (15.2%) in $\geq 300\text{mm}^3$ ($\geq 10\text{mm}$)¹⁸⁸. No additional CT scans or work-up are needed for low-risk nodules, while the high-risk should undergo diagnostic examination immediately. For intermediate-risk nodules, they should be risk-stratified by VDTs and managed differently. The authors concluded that lung cancer risk increased with reduced VDTs: 0.7% for VDTs $\geq 600\text{days}$, 4.0% for VDTs of 400-600 days, and 9.9% for those $\leq 400\text{days}$ ¹⁸⁸. Therefore, the management strategies should be tailored to risk stratification accordingly, to detect the most lung cancers whilst limiting the required resources.

The I-ELCAP researchers found non-solid nodules featuring a slow growth and a 100% curative rate by surgery¹⁸⁹. In MILD, only 16.7% of the non-solid nodules progressed after a mean follow-up of over 55 months¹⁹⁰. Annual follow-up for non-solid nodules of all sizes (except those with a new solid component at following CT scans) has been recommended in the I-ELCAP protocols^{170, 171}. The perifissural nodules have also been found as low malignancy^{191, 192}. In PanCan, perifissural nodules have been excluded from its nodule positive definition¹³¹.

Another issue is concerning de novo nodules, which are first detected at interval scans. It is demonstrated that lung cancers derived from de novo nodules have more aggressive features and a

poorer prognosis than those diagnosed from baseline-positive nodules¹⁹³. Lung cancer probabilities increased with the volumes (and diameters) of de novo nodules; in NELSON, the risk is 0.5% in nodules of $<27 \text{ mm}^3$ (3.7mm), 3.1% in $27\text{-}206 \text{ mm}^3$ (3.7-8.2mm), and 16.9% in $\geq 206 \text{ mm}^3$ (8.2mm)¹⁹⁴. A cut-off value of $\geq 27 \text{ mm}^3$ would achieve a sensitivity of 95.8% and specificity of 38.3% for lung cancer¹⁹⁴. Therefore, new nodules at incidence rounds and those from the prevalence round should be managed separately. The 2011¹⁷⁰ and 2016¹⁷¹ I-ELCAP protocols has suggested a diameter threshold of 3mm for these de novo nodules. Meanwhile, the European position statement recommended a cut-off value of $>30\text{mm}^3$.¹⁰⁵

Number of nodules

Generally, the radiological features of the largest nodule detected on CT have been assessed in trials. In I-ELCAP and Mayo LDCT study, the number of nodules required to be recorded was up to 6; In UKLS, the number reached 20; and in NELSON, all non-calcified nodules are measured (**Table S6**).

It is very frequent to find two or more nodules in lung cancer screening participants, about 48.5% in all NELSON baseline participants¹⁹⁵. 97.0% of the malignancies were diagnosed in the largest nodule at baseline¹⁹⁵. However, lung cancer probability in an individual is not necessarily associated with the nodule count at baseline: 3.6%, 4.1%, 4.8%, 6.3% and 3.3% in those with 1, 2, 3, 4 and >4 nodules, respectively. For this reason, assessing each nodule separately is suggested¹⁹⁵.

In short, nodule count does not necessarily indicate for a benign or malignant lesion, but the specific features of each nodule are important.

Modelling for risk prediction of nodule malignancy outside China

The aim of modelling is to reduce biopsy rate and increase malignant-to-benign ratio. BRELT1 is the only screening trial that used a risk model, namely The Mayo Clinic model, for malignancy prediction of pulmonary nodules (**Table S5**). The Mayo Clinic model was also the first one to be introduced for pre-test prediction by ACCP since 2007¹⁹⁶. It was initially developed and internally validated in a retrospective unscreened cohort of 629 patients with indeterminate solitary pulmonary nodules on CXR (malignant rate: 23%)¹⁹⁷. However, the model did not show superior performance in the baseline

biopsy rate and malignant-to-benign ratio in BRELT1 when compared to other trials¹⁸⁷ (**Table S3**), indicating future efforts in optimising.

The Brock model¹⁹⁸ was derived from the PanCan prospective cohort (malignant rate: 5.5%) and externally validated in the British Columbia Cancer Agency (BCCA). Both datasets were in the CT screening context and included ever and never smokers. It displayed great discrimination of over 0.89 in all settings and calibrated very well. Specifically, it could also perform well in individuals with nodules $\leq 10\text{mm}$. The Herder model¹⁹⁹ was modified from the Mayo Clinic model by integrating positron emission tomography (PET) results. It was developed from a hospital-based unscreened cohort of 106 patients with indeterminate solitary nodules from Netherlands (malignant rate: 57.5%), the same dataset that the Mayo Clinic model used for external validation. It improved the AUC by 13.6% when compared with the Mayo Clinic model. When validated in a hospital-based unscreened cohort from UK, there was a similar performance of the Brock model (AUC 0.902) and the Mayo model (AUC 0.895) in predicting nodule malignancy, but a higher accuracy of the Herder model (AUC 0.916) than the other two models above in patients undergoing PET-CT²⁰⁰. Therefore in the 2015 BTS guideline, the Brock model would be used for risk assessment in nodules $\geq 8\text{mm}$ or $\geq 300\text{mm}^3$, and the Herder model used following PET-CT if malignancy risk is $\geq 10\%$ in the Brock model¹⁷⁵.

Additionally, the Brock model has shown its excellent performance in heterogeneous populations, including LDCT screening trials, e.g. NLST (AUC 0.963)²⁰¹, DLCST (AUC 0.826–0.870)²⁰², a LDCT screen-detected sub-solid nodule cohort from Australia (AUC 0.89)²⁰³ and a multicentre unscreened cohort from Netherlands (AUC ≥ 0.90)²⁰⁴. Nonetheless, it may be suboptimal in other aspects, such as differentiating invasive lesions from sub-solid lesions (AUC: 0.671 in non-solid, 0.746 in part-solid nodules in a Korean unscreened cohort)²⁰⁵. The Herder model also had a good discriminatory power of 0.757 in an Italian retrospective cohort²⁰⁶, albeit inferior to the value previously reported in its development and external validation datasets¹⁹⁹. However, the Brock and the Herder model were derived from and confirmed only in post-hoc analysis (i.e. applied retrospectively in pulmonary

nodule data). Whether they could perform well within an ongoing LDCT screening trial, is still unknown.

Modelling for risk prediction of nodule malignancy in China

A great many risk models for predicting malignancy in nodules were developed in China (**Table S4**). All of them were constructed from hospital-based retrospective cohorts. Most do not specify calibration. The two models developed by Li *et al.*, 2012²⁰⁷ and Yang *et al.*, 2018¹⁵⁹, respectively, have spatially external validation. The model built by Li *et al.*²⁰⁷, also called the Peking University People's Hospital (PKUPH) model, discriminated quite well (AUC 0.810) when evaluated externally. At a risk threshold of 0.471, the sensitivity and specificity of the PKUPH model were 83.3% and 75.9%, respectively. For the model established by Yang *et al.*, the discriminatory power was very limited in the external validation dataset (AUC 0.584)¹⁵⁹. Additionally, three other risk models focused on sub-solid nodules^{208, 209} or ground glass opacities²¹⁰.

Notably, almost all the development datasets had a very high malignancy prevalence (except the Brock model)¹⁵¹, especially those in China (malignancy prevalence >50%) (**Table S4**). It may be mainly because only participants undergoing surgical procedures or biopsies were eligible for the analysis. The accuracy of a model is likely to depend on the lung cancer prevalence in a target population. Hence, these derived models may not be well calibrated in other datasets with a different prevalence¹⁵¹. However, because the decisions for invasive management in these datasets were often combined with the clinical experiences of doctors, models from these datasets may be more useful in the real world clinical practice. Still, it is unclear how these Chinese models would perform when applied in LDCT screen-detected nodules and ongoing screening trials.

Other Screening-related Issues

Significant other findings

It is believed that significant other findings on CT scans would maximise the benefits of screening programmes. 19.6% of the NLST population who were screened in LSS centres had potentially significant extra-pulmonary abnormalities after three screening rounds²¹¹. Some would bear

significant clinical implications and need further clinical assessment; this accounted for 1% of the NELSON baseline population²¹². Extra-thoracic cancers were diagnosed in 0.39% of the screened participants during the screening period in NLST, including kidney (0.26%), thyroid (0.08%) and liver (0.05%) cancers²¹¹. Once found, these clinically significant abnormalities could be managed immediately and systematically. In this case, the specific individual may benefit from the screening in a ‘by-product’ way, although dangers of over-diagnosis are relevant to incidental findings.

Moreover, some conditions, e.g. idiopathic pulmonary fibrosis are rare in the general population, but highly lethal. It is impossible to implement an independent screening trial for this kind of disease, so detection within a cancer trial is valuable. In 884 smokers from the NLST, the prevalence of interstitial lung abnormalities (ILA) was 9.7%, with fibrotic accounting for 2.1% and non-fibrotic for 5.9%. Among them, 37% of the fibrotic and 11% of non-fibrotic ILA progressed in a 2-year follow-up²¹⁴. This epidemiological and clinical information provided through the screening would allow us to optimise our current ILA management strategies.

The benefits of incidental findings are not limited to rare diseases, detection of common ones such as cardiovascular diseases and emphysema can also be provided to assist clinical management, e.g. significant role of coronary artery calcium score in predicting all-cause mortality and cardiovascular events²¹⁵, quantification of emphysema extent²¹⁶ and its potential implication on lower bone density²¹⁷.

However, regarding the cost-effectiveness of management for these extra findings in screening, the evidence is very limited. Given that some abnormalities in the context of screening might be clinically non-significant or indolent in nature, such as mediastinal masses²¹⁸, it’s better for us to manage these findings distinctively according to their characteristics.

Cost-effectiveness

Cost-effectiveness analysis could be used to evaluate if one trial design is superior to another concerning value for money and also investigate impact factors attributable to cost-effectiveness

improvement. Generally, related measures in the health-economic analysis include costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs).

Comparing to no screening, LDCT screenings in NLST provided an additional 0.02 QALYs per person and a corresponding ICER of \$81, 000 per QALY gained²¹⁹. Although with similar QALYs gained per person, UKLS had a mean ICER of \$12,106, much lower than NLST¹²². By comparing UKLS with NLST, researchers concluded some possible ways for cost-effectiveness improvement: 1) higher lung cancer prevalence in a target population; 2) lower unit costs for management; 3) more effective selection of the high-risk population recruited; 4) fewer screens arranged in protocols; and 5) more true-positive results throughout the protocol of nodule management¹²².

Cressman *et al.*²²⁰ analysed the factors driving program efficiency by comparing different scenarios applied to the NLST datasets. They found mortality reductions had the greatest impact on cost-effectiveness, followed by long-term improvements to the quality of life in lung cancer-free participants. Considering non-lung cancer outcomes in screening participants may be necessary in the cost-effectiveness analysis²²⁰. Using the same NLST dataset, Kumar *et al.*²²¹ stratified the participants into different deciles according to their pre-screening risk of lung cancer mortality. Although lung cancer deaths prevented per 10 000 person-year increased from the lowest to the highest risk deciles (extreme decile ratio: 7.9), the gradients across deciles were attenuated in the aspects of life-years, and QALYs gained (extreme decile ratio: 3.6 and 2.4, respectively). ICERs across risk strata were similar²²¹. The conflicting results may be explained by comparable roles between lung cancer and other diseases in the high-risk groups since they are more likely to be older and have more comorbidities^{220, 221}. Therefore, some scholars argued that all-cause mortality reduction should be the benchmark for cancer screening²²². However, to date, none of the CT screening trials really have sufficient power to provide all-cause mortality data.

In a post-hoc analysis of NLST screening participants, Young *et al.*²²³ demonstrated that smokers with higher lung cancer risk predicted by the PLCO_{m2012} model would have a COPD prevalence and likelihood of non-lung cancer deaths in a linearly increasing fashion. Limiting those of intermediate risk (predicted by PLCO_{m2012}) to screening eligibility would achieve a greater reduction in lung cancer

mortality compared with those of risks just over the cut-off value (28% vs 17%). Similar conclusions could be drawn from those with normal lung function or only mild-to-moderate COPD when comparing to those with severe or very severe COPD. Regarding lung cancer mortality reduction, it is better to exclude those with high risk and severe or very severe COPD who are presumed to negate the benefit from screening due to other competing causes of death and inoperability²²³.

Smoking cessation may be a good alternative for cost-effectiveness improvement at the population level, as indicated in a previously US health-economic analysis²²⁴, but does not address earlier detection of lung cancers in those currently at high risk.

In summary, cost-effectiveness varies widely in different settings. Short-term or long-term outcomes, and lung cancer per se or other health conditions, should be considered in the analysis. Overall mortality reduction may be more critical than lung cancer-specific mortality reduction in assessing the effectiveness of screening. Considerations should be taken when recruiting people who would potentially die from other causes, e.g. the effect of COPD in lung cancer screening²²³. Some interventions, such as smoking cessation, managing cardiovascular risk in advance and screening/clinical strategy optimisation, may be anticipated to improve cost-effectiveness in those screened.

Psychological impact

Four trials including NELSON, NLST, DLCST and UKLS had reported their results on psychological impacts. Generally, there was a temporarily increased lung cancer-specific distress in participants with a high affective risk perception²²⁵ or those with positive results^{122, 226}; but, it dropped with a long-term follow-up, e.g. 6 months²²⁵, 2 years²²⁶, or when individuals were reassured with a negative result²²⁷.

The psychological impact is presumed to be screening result-dependent. Those with false-positive scans, significant incidental findings or negative scans in NLST had no significant increase in anxiety²²⁸. Participants with true-positive scans who developed lung cancer within 1 year had a higher anxiety and lower health-related quality of life at 1 and 6 months after screening in NLST²²⁸, but this

is to be expected (and anxiety is likely to be less than if the subjects were diagnosed later with a higher stage disease).

There was no difference in psychological impact across the LDCT and CXR screening arms in NLST²²⁸. However in DLCST²²⁹, compared to the LDCT arm, the usual care arm experienced more negative psychological consequences²²⁹. These may be explained by the reassurance in those with normal screening results in the LDCT arm^{227, 229}.

In short, lung cancer screening would exert certain short-term, yet generally minimal long-term psychological harm on participants. The impacts are usually not severe²²⁵ or not to clinical levels²²⁶. However, special attention should be paid to those with positive scans and help should be provided if necessary after regular psychological assessment. Those who do not receive the reassurance of an early diagnosis or a negative LDCT scan (e.g. those randomised to usual care in a trial, or unable to have a screening scan) may also need help.

Radiation exposure

New CT scanners have a much lower level of radiation, e.g. in NLST, the effective dose was estimated at about 2mSv for LDCT but 8mSv for full-dose chest CT²³⁰. However, extra radiation exposure associated with screening is still a concern²³⁰. It is estimated that if a person aged 55 was followed up according to the Fleischner guidelines over 20-30 years (3 full-dose CT follow-ups over two years if nodules >4mm), he would experience a cumulative radiation dose of 280-420 mSv, a dose exceeding that of nuclear workers and atomic bomb survivors²³⁰. As a result, lung cancer risk would increase²³⁰. A male and female smoker would observe an increase of lung cancer risk induced by radiation about 0.23% and 0.85%, respectively, if he or she undergoes annual LDCT screening from 50 years-old until 75²³¹.

In ITALUNG, when assuming a lung cancer-specific mortality reduction of 20%-30% in current smokers, the potential fatal cancers associated with radiation exposure were 10 -100 times lower than the expected lives saved by screening in number, indicating a favourable benefit over the risk²³².

However, never or former smokers would benefit less in the same scenarios than current smokers²³².

In a secondary analysis of the COSMOS data, lung cancers and major cancers induced by ten years of LDCT screening were 1.5 and 2.4 in number, respectively. The additional risk of induced cancer was extremely low, namely one induced major cancer for every 108 screen-detected lung cancers²³³.

Therefore, we could expect a very low and acceptable risk of cancers induced by LDCT screening per se^{232, 233}, but cancers would occur if screening is conducted long enough²³⁰. Protocols for screening should be optimised to attenuate the possible increased cancer risk by modifying the screening frequency and age range in line with individualised lung cancer risks and emerging evidence on screening-induced cancers. A mortality reduction considerably over 5%²³¹ is required to outweigh the radiation-induced cancer risk, and this should be estimated before screening is conducted, especially for individuals aged <50 years²³⁴.

Recommendations on Chinese Lung Cancer Screening Programmes

Herein, we reproduced the figure from Field's review²³⁵ to conclude current evidence status in China (**Figure 3**). Most of the evidence in the 12 aspects are from outside China, thus requiring further research in the context of China taking population CT screening forward. We note several issues which require caution or further investigation and give our recommendations (**Table 3**).

Participation - recruitment of hard-to-reach

There are substantial health and healthcare disparities across different regions of China. The underserved are more likely to suffer from morbidities and mortalities, yet less likely to participate in the screening programmes. Some targeted recruitment methods have been suggested as efficient currently. In China, most of the programmes have targeted urban areas which are possibly featured with higher socio-economics. The *Guangzhou GMU-1stHosp* programme focused on underprivileged individuals, yet with low uptakes due to low awareness of preventive health care among the targeted population⁹¹.

In China, people have free access to any hospital, which leads to 'medical migration'²³⁶. Selection bias and more dropout could be anticipated when recruiting participants based on hospital catchment areas as these are not fixed and people 'migrate'. Community-based enrolment may be a favourable

alternative for lung cancer screening, by which people could be organised as a whole more effectively.

A significant number of the lung cancer screening programmes in China only have references, which are based on web pages or conference abstracts, thus the detailed protocols and results are unavailable. In order to harmonise the CT screening programmes in China, it would be beneficial to facilitate cooperation between the lung cancer screening groups, which would increase awareness and also provide consistency, governance control and transparency of all the programmes.

Risk-based selection

Risk-based selection is presumed to focus on individuals who are most likely to be at higher risk of developing lung cancer and minimise unnecessary scans in the low-risk population, thus more likely to be cost-effective. However, such high-risk populations are also more likely to be older and suffer from non-lung cancer deaths, thus questioning the net benefits²³⁷. The high-risk profile for lung cancer screening is still undetermined in China. The proportion of lung cancers attributed to smoking is much lower in China than the UK & US. Other risk factors may play more critical roles in lung cancer incidence in China. The preliminary results of various programmes in China indicated a different risk profile from US and European countries.

Risk models play a crucial role in lung cancer prediction in either general population screening or management of detected nodules, yet much work on optimisation is needed. Most of the risk models developed in China gave relatively poor discrimination, no calibration or no external validation.

Since there are different risk profiles for lung cancer in China, we need to consider to what extent these differences will influence the optimal Chinese lung cancer risk model. Whether risk models should be developed separately in males and females, or different thresholds should be set in different genders or those with different smoking status, are questions that remain to be answered (and might not be fully addressed until implementation based on the best model at the time and further data gathered as part of the screening effort).

Moreover, one needs to consider in the Chinese context, is that science is rapidly advancing on an exponential scale. Current lung cancer prevalence may reflect exposure levels of risk factors many years ago, similar to the delayed impact of smoking on mortality; or mis-represent the real status quo in China due to potential bias in data collection, i.e. from current incomplete cancer registries. A recent publication has illustrated a higher lung cancer incidence in young women compared to young men, noting that both genders were born after the mid-1960s in the US²³⁸. Different smoking behaviours between the genders could not fully explain this phenomenon²³⁸. Given the changing situations, the entry criteria into lung cancer screening programmes should be reconsidered.

Screening age range

Disputes exist in different microsimulation modelling studies; these studies often applied distinct outcome measures to assess the benefits and harms. In China, Lung cancer incidence is quite low in individuals aged ≤ 45 , but it increases with ages in those over 50^{103, 135}. Individuals in younger generation (i.e. <50 years) would suffer more harm from screening, e.g. excess cancer risk induced by radiation exposure²³⁴. While an older individual would not benefit from screening due to existing comorbidities and competing deaths of other causes. After combining the evidence above and life expectancy in China, the CNS 2015/2018 have recommended ages at 50 -74 for screening feasibility^{103, 135}. Optimal screening age range has not yet been specified in China.

Nodule measurement

Accumulating evidence has demonstrated that volumetrics and VDT are less variable and more sensitive in detecting nodule sizes and growth. *NELCIN-B3* will help to define it. It is also preferable to apply volumetry software to help optimizing nodule management strategies during implementation.

Identify 'Indeterminate' nodules

Different cut-off values would possess different lung cancer risks. By risk stratification, nodules would be managed accordingly. However, it is unclear if variations in the aetiology of lung cancer in the East would extend to the biological features that influence nodule behaviour. Risk models for

malignancy prediction of nodules were derived from post-hoc analysis. It is unsure if these models would perform well in an ongoing LDCT screening trial.

Mortality data

The two largest studies - NLST and NELSON - reported a benefit of mortality reduction by LDCT screening. In China, a microsimulation modelling study indicated a favorable role of LDCT screening over CXR and no screening in mortality reduction among urban smokers at 45-80 years-old¹⁰⁴. It is uncertain in China that to what extent LDCT screening would help to reduce mortality, either lung cancer-specific or all-cause, in the real world. Whether nonsmokers in China would benefit from screening is also undetermined.

Cost-effectiveness

Whenever it comes to real-life practice, cost-effectiveness should always be seriously considered. We should consider not just the health benefit provided by screening, but the associated financial benefits of reduced costs for cancer treatment and the improved economic output of those living longer and healthier lives.

The ageing population in China would be more vulnerable to both lung cancer and other causes of death. The latest papers indicated that it would be better to take into consideration the long-term outcomes and non-lung cancer outcomes of participants during the assessment^{220, 221}. There would always be compromises during the process, e.g. more screening rounds would lead to more lung cancer mortality reduction but result in more over-diagnosis and radiation exposures. Management should be individualised in screened participants according to their baseline scan results and nodule risk stratification, to reduce unnecessary scans in the low-risk and maximise the benefits. Currently, using a mathematical method to simulate different scenarios is a favourable alternative, and it may provide us with additional information which could not be obtained in real life because of limited research resources.

Screening intervals

Lung cancer risk is baseline result-dependent. Nodule size and nodule attenuation (solid, part-solid, non-solid) will also affect the risk of malignancy. Similarly, cost-effectiveness analysis leads the way. Data from the real practice is needed in China.

Smoking Cessation

Tobacco control can provide more benefit than we have seen so far. Apart from lung cancer, smoking is closely related to morbidities such as COPD, cardio-vascular diseases and ischemic stroke, *et al.* Smoking exposure is positively associated with mortality risks of these morbidities. Quitting would help to decrease the risks²⁸. Thus, tobacco control could save lives not only from lung cancers but also from other highly life-disabling conditions, thus improving the quality of life. When integrating tobacco control, lung cancer screening could achieve more cost-effectiveness. However, evidence of efficient and effective strategies of the combination is still limited.

In conclusion, lung cancer and smoking prevalence in China are very different from other countries. Increasing trends for lung cancer mortality are expected following a lag from smoking exposure. Other risk factors may play a significant role alongside smoking for lung cancer risk in China; broader entry criteria might be more expedient in China to accommodate non-smokers. Evidence from Chinese lung cancer screenings is limited, but the success of screening programmes and evidence from other countries could pave the way. Risk models should be optimised, and a prespecified analysis would be helpful for initial trials, adopting a re-iterative, adaptive approach as screening programmes develop.

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Authors' contributions

Conception development and article design: JKF, WML and YIC.. Manuscript writing and/or revision: YIC, JKF, MPAD, DL and WML. .

Other contributions

We give our special appreciation to Robert Carlton for proofreading the manuscript.

Conflict of Interest Statement

None declared.

Figure Legends

Figure 1 Trends in smoking prevalence, lung cancer incidence and mortality in China, UK and the US, by sex.

(A) China: Current smoking prevalence data (Chinese population-adjusted) extracted from the China Health and Nutrition surveys (1991-2011) ²⁷. Lung cancer incidence (world population-adjusted) from the World Health Organisation (1993-2007) ²³⁹ and annual reports of cancer statistics in China (2010-2014) ^{4, 44, 240-242}. Lung cancer mortality (world population-adjusted) from the First National Death Survey in China (1973-1975) ²⁴³, World Health Organisation (1987-2000) ²⁴⁴ and annual reports of cancer statistics in China (2006, 2010-2014) ^{4, 44, 240-242, 245}. (B) United Kingdom (UK, European population-adjusted): All data from the Cancer Research UK website (1948-2016) ⁵³. (C) United States (US): Smoking prevalence from the International Smoking Statistics (web edition) (1935-2014); nationally representative surveys included if possible; data with the highest value included if several prevalence rates are available (in many cases, more brands of tobacco products in a survey always contribute to a higher prevalence rate). Lung cancer incidence (world population-adjusted) from the WHO Cancer Incidence in Five Continents Time Trends (CI5plus) (1975-2007) ²³⁹. Lung cancer mortality (world population-adjusted) from the WHO Cancer Mortality Database (1950-2014) ²⁴⁴. (D) Lopez's model of cigarette epidemic (Lopez *et al*, 1994)³⁸.

Note: Because there were different definitions/metrics of smoking, different methods and sources used for analysis in the reported investigations, thus direct comparison may not be applicable. One has to be cautious when interpreting these figures.

Figure 2 The landscape of lung cancer screening programmes in China since the 1990s.

The programmes are displayed as 'the programme name plus the initiation year'. In order to prepare this figure for publication in English language, all of the Chinese trials and projects are referenced by the trial names. In many cases, it was not possible to translate the Chinese into English. For the

purpose of this review, the English name for each of the trials is linked to the Chinese city or region and the responsible hospital, unless there is already an international name available (i.e. *ELCAP* or *NELCIN-B3*). Please refer to Table 2 and Supplementary for details. The coloured areas are the regions covered by the corresponding national programmes⁹³⁻⁹⁶. *Abbreviations: CanSPUC*, Cancer Screening Program in Urban China; *China FeasiRCT*, China Lung Cancer Screening Feasibility RCT; *CICAMS*, Cancer Institute & Hospital Chinese Academy of Medical Sciences; *GMU-1stHosp*, Guangzhou Medical University First Affiliated Hospital; *Guangzhou Financing*, a demonstration project targeting Guangzhou to expand lung cancer screening and test innovative financing models; *NELCIN-B3*, Netherlands-China Big-3 screening; *RuraCSP*, Rural China Screening Programme; *Shanghai Baoshan*, lung cancer screening programme in old people in Baoshan District, Shanghai; *Shanghai CancerHosp*, Fudan University Shanghai Cancer Centre; *Shanghai ChangzhengHosp*, Shanghai Changzheng Hospital; *Shanghai ChestHosp*, Shanghai Jiaotong University affiliated Shanghai Chest Hospital; *SH-RenjiHosp*, Shanghai Jiaotong University Affiliated Renji Hospital; *Tianjin CancerHosp*, Tianjin Medical University Cancer Institute and Hospital; *Tianjin 4-cancer*, screening of the four common cancers (lung cancer, breast cancer, liver cancer and stomach cancer) in Tianjin; *WCH*, West China Hospital; *YTC*, Yunan Tin Corporation cohort.

* *NELCIN-B3*⁹⁹ has three study centers in China: two in Shanghai (Shanghai Changzheng Hospital and Shanghai General Hospital) and one in Tianjin (Tianjin Medical University Cancer Institute and Hospital).

§ Including three separate programmes sponsored by central government^{246, 247}: one in 2017 and another two (including a multicentre RCT) in 2018.

¶ The *Guangzhou Financing* project⁹² was proposed in 2017 and is still being discussed currently.

**Figure 3 Levels of evidence for the implementation of lung cancer CT screening in China
(permitted by and adapted from Field *et al.*).**

The colour codes are similar to Field *et al.*²³⁵. They refer to the current status in China in 2018, where green indicates we have sufficient evidence, orange is borderline evidence, and red requires further evidence (Chinese-specific). MDT, multi-disciplinary team; NCCN, National Comprehensive Cancer Network; CSCO, Chinese Society of Clinical Oncology; NLST, National Lung Screening Trial; NELSON, Nederlands Leuvens Longkanker Screenings Onderzoek (Dutch-Belgian randomised lung cancer multi-slice CT screening trial); UKLS, United Kingdom Lung Cancer Screening Trial; QALY, quality-adjusted life-year.

Tables

Table 1 Estimated incidence and mortality rate (World population age-standardized, per 100 000) of lung cancer in China, the UK and the US, all ages.

	Incidence			Mortality		
	Total	Male	Female	Total	Male	Female
China	35.1	47.8	22.8	30.9	43.4	19.0
UK	32.5	35.5	30.2	22.2	25.2	19.7
US	35.1	40.1	30.8	22.1	25.9	19.0

Data extracted from GLOBCAN 2018¹. UK, United Kingdom; US, United States.

Table 2 Lung cancer screening programmes in China.

Time	Trial/Study Name used in the manuscript (Ref.) *	Initiation Year	Targeted region/population	Study design	Interventions	Entry criteria	Population (recruiting time)
Before the 1990s	Mass photofluorography in early detection of peripheral lung cancer ⁷⁸	1979	N/A	Prospective cohort	Annual CXR for 5 years	Workers from 54 factories; no other restrictions	211 811 person-years (1979-1983)
	Mass screening in Hunan orpiment miners ⁷⁹	1986	Hunan orpiment miners	Prospective cohort	Baseline: sputum cytology + CXR; follow-up according to sputum atypia: If moderate or severe sputum atypia: sputum + CXR at 3 months, 6 months, 1 year and 3 years. -If no or mild atypia: sputum + CXR 3 years later.	Orpiment miners in Hunan; aged > 35.	601 (baseline)
	Screening lung cancer by Sputum Occult Blood Test (OBT) Study ^{80, 81}	1988	workers in Changchun automobile industries, Tangshan and Yunnan tin mines, Xuanwei and Beijing steel factories	Cross-sectional study	Sputum OBT and cytology with/without CXR	High-risk Workers from various manufacturing and mining factories, including some famers/cadres; aged ≥ 40 years	14 431 (1988-1990)
		2007	Laibing County, Xuanwei (Yunnan)	prospective cohort	Baseline CXR (CT for CXR positive); sputum OBT at 4 months later (sputum cytology and HRCT if OBT positive)	Residents aged 35-70 years	about 30, 000 at baseline (Jan, 2007 – Jul, 2007)
1990s	The Yunnan Tin Corporation (YTC) cohort ¶ ⁸²	1992	Around Gejiu City, Southern Yunnan.	Prospective cohort	Annual sputum sampled + annual CXR	Current/retired YTC workers, aged ≥ 40 years-old, with a history of underground mining/smelting ≥10 years	9143 (1992 - 1999)
2000s	Zhuhai I-ELCAP cohort ⁹⁷	2003	Zhuhai, Guangdong province	Prospective cohort	Annual LDCT	Asymptomatic participants aged ≥40 years.	3582 (2003-2009)
	Beijing I-ELCAP cohort ⁹⁸	2006	Beijing, China	Prospective cohort	Annual LDCT	Asymptomatic participants aged ≥40 years, no history of malignancy (except basal cell carcinoma and cervical carcinoma in situ) within 5 years	4690 (2007- 2012)
	Kailuan cohort ¶ ⁸³	2006	Kuailuan Group Company, Tangshan City, Heibei Province	Prospective cohort	biennial CXR ; annual follow-up in 11 hospitals affiliated to the Kailuan Company	Current or retired Employees aged ≥18 years in the Kailuan Group Company (mining industry)	133 273(2006-2011)
2010s	Rural China Cancer Screening Programme (RuraCSP) * ^{93, 94}	2009	Dagang Oilfield (Tianjin), Xuanwei (Yunnan), Gejiu (Yunnan), Beijing, Chengdu (Sichuan) and Shenyang (Liaoning)..	Prospective cohort	Annual LDCT and sputum cytological examination (for 3 years).	Inclusion criteria are region-dependent: 50-74 years (in Tianjin), 45-69 years (in Yunnan), staff aged 50-74 years and smoking history of ≥20 pack-years (in the Dagang Oilfield). The Xuaiwei centre included indoor air pollution as a risk factor.	19 068 (2010-2017, baseline participants)

Time	Trial/Study Name used in the manuscript (Ref.) *	Initiation Year	Targeted region/population	Study design	Interventions	Entry criteria	Population (recruiting time)
	Cancer Screening Program in Urban China (<i>CanSPUC</i>) ¶ ^{95, 96}	2012	20 provincial/municipal-level regions in China by 2018	Prospective cohort	Annual LDCT for 5 years	Urban residents (residing >3 years) aged 40-69 (some areas defined ages at 40-74) with high risk of lung cancer; high-risk criteria are region-dependent.	210 000 (planned in the first stage during 2012-2016)
	The China Cancer Screening Trial Feasibility Study (<i>China FeasiRCT</i>) * ^{137, 138}	2014	3 cities (Changsha[Hunan]; Lanzhou[Gansu]; Haining[Zhejiang])	RCT	Arm 1: Annual LDCT for 3 years (T0, T1, T2) and baseline colonoscopy (T0); Arm 2: 2 LDCT (T0, T2) plus annual faecal immunochemical test (T0, T1, T2); Arm 3: Annual InSure-faecal immunochemical tests combined with Septin 9 test (T0, T1, T2).	Local permanent residents; Aged 50-74 years; smoking >30 pack-years, quit ≤15 years if former smokers (or second-hand smoke exposure in females: living with a regular daily smoker for > 20 years); no previous history of lung cancer or colorectal cancer.	2700 (as of March 31, 2015)
	<i>Beijing CICAMS</i> programmes §, §§ ^{246, 247}	2017, 2018	Beijing	N/A	N/A	N/A	N/A
	<i>Tianjin CancerHosp</i> cohort ⁸⁴	2012	Tianjin	Prospective cohort	LDCT at Baseline and 1 or 2 years later	Asymptomatic, of ≥40 years-old, tolerant of possible invasive procedures and not screened by CT within 1 year.	650 (2014-2016)
	<i>Tianjin 4-Cancer</i> programme * ⁸⁵	2017	Selected districts in Tianjin: Hexi and Jinzhou in 2017; will cover up to 7 districts planned in 2018	Prospective cohort	LDCT screening; and then follow-up for LDCT result- positive participants	Healthy Residents will undergo risk assessment first and the high-risk ones undergo LDCT screening	52 092 risk assessed; 992 LDCT screened(2017)
	<i>Shanghai CancerHosp</i> cohort ⁸⁶	2013	7 selected communities In Minhang District, Shanghai.	Prospective cohort	Annual LDCT; community-based, LDCT + CAD for screening.	Asymptomatic individuals aged 50-80, and eligible to ≥ 1 risk factors: 1) smoking ≥20 pack-years, and if former smokers, quit smoking < 5 years; 2) passive smokers; 3) never smokers with other risk factors, including lung cancer family history, kitchen fume or dust exposure.	11332 (2013 -2014)
	<i>Shanghai ChestHosp</i> RCT ⁸⁷	2013	6 selected communities in Xuhui District, Shanghai.	RCT	Biennial LDCT vs Usual care arm (for three rounds)	Asymptomatic residents aged 45–70 years, with ≥ 1 risk factors: 1) a smoking history ≥ 20 pack-years, and if former smoker, quit ≤15 years; 2) family history of cancer; 3) personal cancer history; 4) occupational exposures; 5) long-term exposure of passive smoking (>2h/day at home/indoor workplaces for ≥10 years); 6) long-term exposure to cooking oil fumes (>50 dish-years).	6717 (2013 -2014):
	<i>Shanghai-ChangzhengHosp</i> cohort ^{88, 89}	2013	Physical examination centres in 7 tertiary hospitals and their surrounding communities	Prospective cohort	Baseline LDCT + CAD; interval scans were not specified.	Asymptomatic; any age;	14506 (2013-2016)

Time	Trial/Study Name used in the manuscript (Ref.) *	Initiation Year	Targeted region/population	Study design	Interventions	Entry criteria	Population (recruiting time)
	Netherlands-China Big-3 screening (NELCIN-B3) ¶, §§ ⁹⁹	2016	Shanghai Changzheng Hospital, Shanghai General Hospital and Tianjin Medical University Cancer Institute & Hospital.	N/A	LDCT screening	N/A	N/A
	Shanghai Baoshan Programme * ^{90, 248}	2018	Baoshan District, Shanghai	Prospective cohort	one-time CT; referral to a hospital for further assessment if with positive results; and follow-up	Ages ≥75 years-old, or ≥65 years-old yet with cough/expectoration ≥2 weeks and abnormal CXRs.	1 4005 (as of September 2018)
	Chengdu WCH cohort §§	2013	Chengdu, Sichuan Province	Retro-prospective cohort	Annual CXR or LDCT	Workers of specific industries/ enterprises/ organisations undergoing annual physical examinations (CXR or LDCT) (records back to the year 2006)	Baseline: 46 317 (by CXR); 15 996 (by LDCT)
	Guangzhou GMU-1stHosp Programme ^{91, 92}	2015	Guangzhou, Guangdong Province	Prospective cohort	Annual LDCT	Low-income residents aged ≥50 years; or residents in Yuexiu district, aged 50-74, with high risk; or volunteered residents aged ≥40 years in the whole province (the former two will get a free screening; but the latter a 1/5 discount on screening costs).	808 (as of Dec 2017)
	Guangzhou Financing project (in planning) * ⁹²	N/A	Guangzhou, Guangdong Province	Prospective cohort	N/A	40-80 years; residents undergoing health checks through their employers' health insurance or out-of-pocket payments, or occupational workers at higher risk of air pollution in working environment.	10 000 (planned)
	Qinghai SH-RenjiHosp programme ^{100, 101}	2016	Deprivation areas in Qinghai (would be expanded to Henan, Xinjiang and Shandong Province)	N/A	N/A	Aged 50-74; or aged ≥35 but with ≥ 1 risk factors including long-term smokers, long-term exposure to severe air pollution, radiation, coal smoke and kitchen fume, with a family history of lung cancer, a personal history of cancer or pulmonary diseases.	N/A

Most of the CT trial/programme (since 2010) names have been provided in the above table to identify the targeted region and the hospital in which they are undertaken otherwise stated for the purpose of this review. *

Named after the studies' characteristics by the author: *RuraCSP* - Rural China Screening Programme; *China FeasiRCT* - China Lung Cancer Screening Feasibility RCT; *Tianjin 4-cancer* programme - screening of the the four common cancers (lung cancer, breast cancer, liver cancer and stomach cancer) in Tianjin; *Shanghai Baoshan* programme - lung cancer screening programme in old people in Baoshan District, Shanghai; *Guangzhou Financing* project – a demonstration project targeting Guangzhou to expand lung cancer screening and test innovative financing models. ¶ Yunan Tin Corporation cohort, Kailuan cohort, CanSPUC and NELCIN-B3 are formal names of the programmes, respectively. § Including three separate programmes funded by central government: one in 2017 and another two (including a multicentre RCT) in 2018. §§, personal communication with the corresponding principal investigators Professor Wu Ning, Professor Ye Zhaoxiang, Professor Li Weimin, respectively. Please see the Supplementary for details.

Abbreviations: LDCT, low-dose computerised tomography; CAD, computer-aided diagnosis system; N/A, not applicable or not available; *CICAMS*, Cancer Institute & Hospital Chinese Academy of Medical Sciences; *GMU-1stHosp*, Guangzhou Medical University First Affiliated Hospital; RCT, randomised controlled study; *Shanghai CancerHosp*, Fudan University Shanghai Cancer Centre; Shanghai ChangzhengHosp, Shanghai

Changzheng Hospital; *Shanghai ChestHosp*, Shanghai Jiaotong University affiliated Shanghai Chest Hospital; *SH-RenjiHosp*, Shanghai Jiaotong University Affiliated Renji Hospital; *Tianjin CancerHosp*, Tianjin Medical University Cancer Institute and Hospital; *WCH*, West China Hospital;

Table 3 | Recommendations for implementation of lung cancer screening in China.

- Screening programme coverage to be expanded to underserved areas. Recruitment criteria suggested by other countries should be considered. The involvement of international investigators in lung cancer screening trials in China should be considered.
- Community-based recruitment may be a more favourable approach in China: utilising face-to-face clinical appointments and trustworthy collaborations with local clinics/organisations.
- To make cohort profiles or study protocols public is suggested. Collaboration between lung cancer screening trial groups should be considered. Developing consensus protocols and also the agreement to utilise common databases and minimum datasets would enable pooling of data from different trials in China.
- In China, consider adapting the entry criteria, i.e. a lower threshold of smoking exposure; consider including other risk factors: second-hand smoke, family history of cancer, occupation and indoor/outdoor air pollution (the latter requires a harmonised approach).
- Risk-based selection of eligible participants for study entry into lung cancer CT screening programmes (e.g. risk prediction modelling) would be advisable.
- The current Chinese risk models (for either individual risk or nodule malignancy prediction) should be validated externally, especially in an ongoing lung cancer LDCT screening programme, which could help to confirm the efficacy and effectiveness in the real world. Further optimisation may be integrated over time, i.e. integration with liquid biomarkers and genetic factors.
- Development of new risk prediction models, specifically for the Chinese population, should be priority, utilising optimal data sources.
- Cost-effectiveness analysis of all current CT screening programmes should be undertaken, taking into consideration the selection criteria/risk threshold utilised, which would achieve the maximum net benefits over harms.
- Evaluation of related parameters involved in the screening programmes requires further research in China, e.g. screening interval, screening length, nodule management.
- Lung cancer screening programmes should be integrated with tobacco control strategies. An a priori design and a detailed record on participants' behaviours/perspectives and study costs including personnel cost, is required for cost-effectiveness evaluation.

Supplemental Materials

Supplemental Figure

Figure S1 Historical events associated with tobacco and tobacco control in China, the UK and the US

Figure S2 Timeline of selected nationally/sub-nationally representative surveys or important historical events associating with tobacco use (above the arrow) and cancer (below the arrow), and development of cancer registrations in China.

Supplemental Tables

Table S1 Study designs in Lung cancer low-dose computerised tomography (LDCT) screening programmes outside China.

Table S2 Recruitment procedures and entry criteria in lung cancer low-dose computerised tomography (LDCT) screening programmes

Table S3 Baseline participant characteristics, and baseline and overall low-dose computerised tomography (LDCT) screening results in lung cancer screening studies

Table S4 Lung cancer risk models from China.

Table S5 Nodule management criteria for low-dose computerised tomography in lung cancer screening trials.

Supplemental information:

Searching Strategies for Lung Cancer Screening Studies in China

Lung cancer screening programmes in China.

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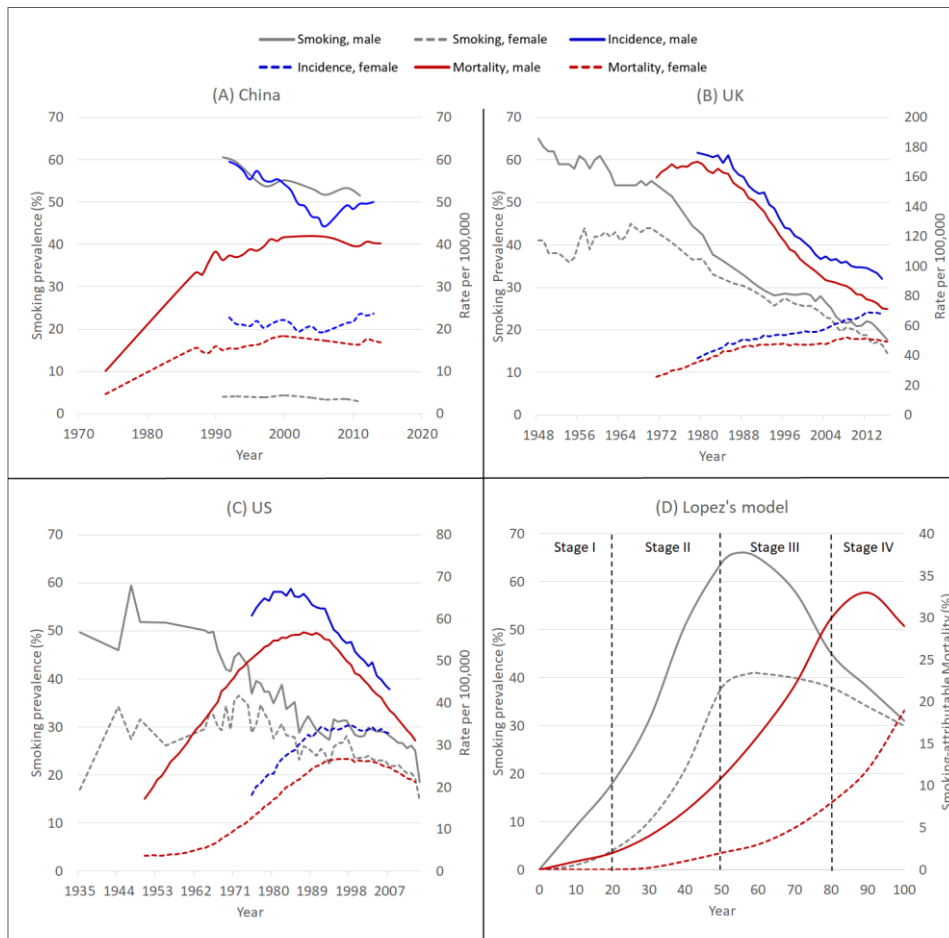


Figure 1 Trends in smoking prevalence, lung cancer incidence and mortality in China, UK and the US, by sex. 125x124mm (300 x 300 DPI)

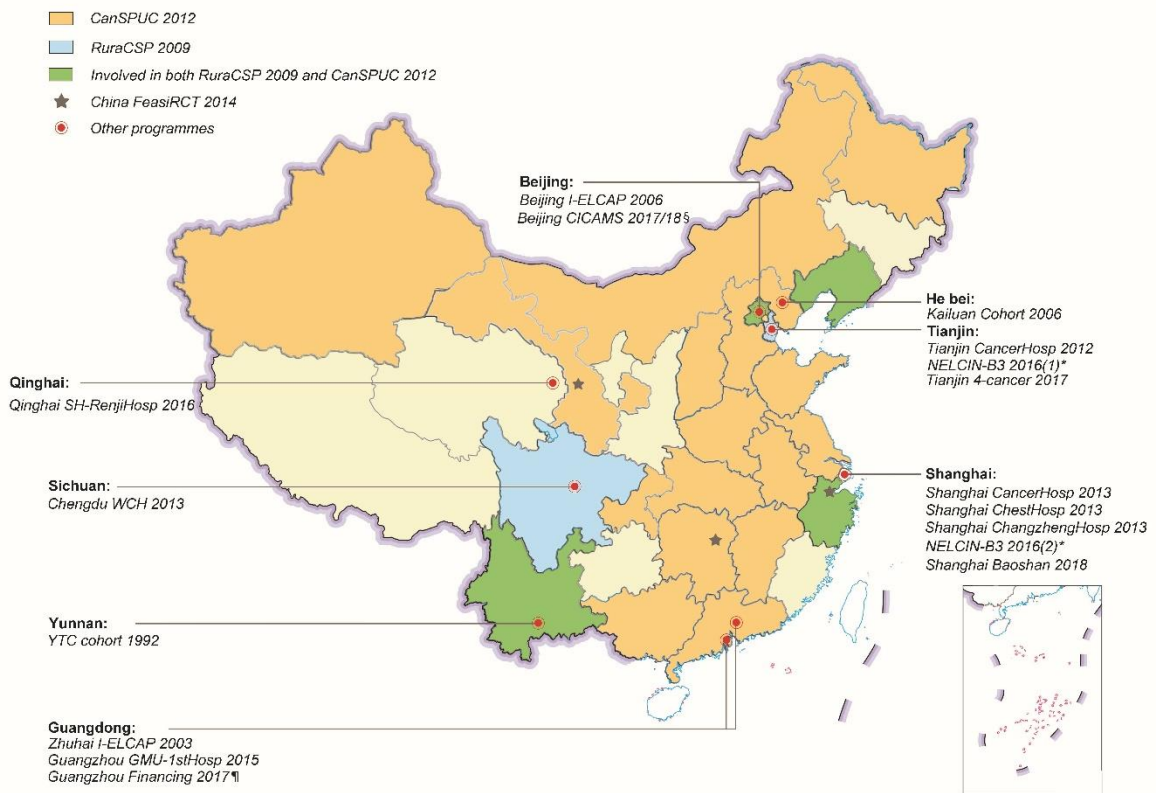


Figure 2 The landscape of lung cancer screening programmes in China since the 1990s.

525x375mm (300 x 300 DPI)



Figure 3 Levels of evidence for the implementation of lung cancer CT screening in China.

90x67mm(300 x 300 DPI)

Supplemental Materials

Implementation planning for lung cancer screening in China

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Supplemental information

Searching Strategies for Lung Cancer Screening Studies in China

Lung cancer screening programmes in China

Figure S1 Historical events associated with tobacco and tobacco control in China, the UK and the US.

Abbreviations: UK, United Kingdom; US, United States; WW I, the First World War; WW II, the Second World War; CPC, The Communist Party of China; WTO, World Trade Organization; FCTC, Framework Convention on Tobacco Control; GYTS, Global Youth Tobacco Survey; GATS, Global Adult Tobacco Survey. Information excerpted from references ¹⁻⁶.

Figure S2 Timeline of selected nationally/sub-nationally representative surveys or important historical events associating with tobacco use (above the arrow) and cancer (below the arrow), and development of cancer registrations in China.

Abbreviations: CRP, cancer registration point; NCCR, National Central Cancer Registration; IACR, International Agency for Research on Cancer CI5, Cancer Incidence in Five Continents; N/A, not available.

The first table displays the total number of CRPs at a specific time in China; the percentage in the bracket is the population covered by CRPs in relation to the contemporary total population from the census. The second table displays the number of CRPs which NCCR submitted to CI5 and CI5 included in its separate reports, the latter taken as an indicator of data quality. Only CRPs in mainland China have been considered here. References are for smoking ⁶⁻¹³ and cancer/cancer registrations ¹⁴⁻¹⁹, respectively.

Table S1 Study designs in Lung cancer low-dose computerised tomography (LDCT) screening programmes outside China.

Study design	Allocation group	Study Name [Ref.]	Country	Initiation year	Cancer-related mortality endpoint	Study Powered	Smoking cessation program	No. in study/control arm	Intervention regimen	Control regimen	Planned screening rounds in LDCT arm	Screening interval (years)	Follow-up years (Median/mean person-years) ¹
Non-RCTs	LDCT Prospective cohort	I-ELCAP ²⁰	US	1993	No	No	No	31567/-	Annual LDCT	NA	10 ²	1	10 (planned for those LCs diagnosed)
		Mayo LDCT ²¹	US	1999	No	Yes	No	1520/-	Annual LDCT + sputum samples	NA	5	1	4 (after baseline)
		COSMOS ²²	Italy	2004	No	No	Yes	5201/-	Annual LDCT; baseline spirometry	NA	5	1	10 years (planned)
		PanCan ²³	Canada	2008	No	Yes	No	2537/-	LDCT at 1 st , 2 nd and 4 th year	NA	3	1,2	5.5 (after baseline)
		BRELT1 ²⁴	Brazil	2013	No	No	Yes	790/-	Annual LDCT	NA	NS	1	NA
RCTs	LDCT vs. CXR	LSS ²⁵	US	2000	No	No	No	1660/1658	Annual LDCT	Annual CXR	2	1	NA (followed-up only LCs)
		NLST ²⁶	US	2002	Yes	Yes	Yes	26722/26732	Annual LDCT	Annual CXR	3	1	6.5 (after baseline)
		Depiscan ²⁷	France	2002	No	No	No	385/380	Annual LDCT	Annual CXR	3	1	NA
		JECS ²⁸	Japan	2012	No	Yes	No	NA ³	LDCT at 1 st and 6 th year; with CXR encouraged annually	CXR at 1 st year; with CXR encouraged annually	2	5	10 (planned)
	LDCT vs. Usual Care	DANTE ²⁹	Italy	2001	Yes	No	No	1403/1408	Annual LDCT; baseline CXR+ sputum	Annual usual care; baseline CXR+ sputum	5	1	8.35 (after baseline)
		NELSON ³⁰	Netherlands & Belgium	2003	Yes	Yes	Yes	7915/7907	LDCT at 1 st , 2 nd , 4 th , 6,5 th year	Usual care	4	1,2, 2.5	10 (planned)
		ITALUNG ³¹	Italy	2004	Yes	No	Yes	1613/1593	Annual LDCT; smoking cessation program	Usual care; smoking cessation program	4	1	8.5 (after baseline)
		DLCST ³²	Denmark	2004	Yes	No	No	2052/2052	Annual LDCT	Usual care	5	1	9.80 (after baseline)
		MILD ³³	Italy	2005	Yes	No	Yes	1186/1190 /1723 ⁴	Biennial/annual LDCT	Usual care	3; 5	2,1	4.4 (after baseline)
		LUSI ³⁴	Germany	2007	Yes	Yes	Yes	2029/2023	Annual LDCT + baseline smoking cessation counselling	Annual usual care + baseline smoking cessation counselling	5	1	3-6.5 (minimum and maximum years)
		UKLS ³⁵	UK	2011	No	No	Yes	2028/2027	LDCT with the Wald single-screen design	Usual care	1	NA	NA

Abbreviations: RCT, randomised controlled trial; non-RCT, non-randomised controlled trial; LDCT, low-dose computerised tomography; CXR, chest X-ray; NA, not applicable; LC, lung cancer; yrs, years. ¹ Mean person-years displayed if no median ones reported. ² In the 2006 manuscript²⁰, only 2 screening rounds- the baseline and the 2nd screen round were reported. ³ the initial design in 2012 was to recruit 35 000 participants, and then revised to 26000 on March 2016. ⁴ Data displayed as population in the biennial/annual/control arm.

Table S2 Recruitment procedures and entry criteria in lung cancer low-dose computerised tomography (LDCT) screening programmes

Study Name [Ref.]	Recruitment procedures					Entry criteria			
	Recruiting time	Recruiting methods	Population source	Multi-centre	Recruitment Completed	Age	Sex	Smoking status	Smoking exposure
I-ELCAP ²⁰	1993-2005	GPs and local newspaper, radio and television	Hospital/volunteer-based	Yes	Yes	≥40	Both	Current /former /passive	Varied by sites
Mayo LDCT trial ²¹	Jan,1999-Dec,1999	Local and regional television and newspaper coverage.	Volunteer-based	Yes	Yes	≥50	Both	Current /former	>20 PYs, quit <10yrs
COSMOS ²²	Oct, 2004-Oct, 2005	Newspaper and television campaign ¹	Volunteer-based	No	Yes	≥50	Both	Current /former	≥20 PYs, quit <10yrs
PanCan ²³	Sep, 2008-Dec, 2010	Newspaper, TV radio, public posters, laboratories, study websites, friends and GPs	Volunteer-based	Yes	Yes	50-75	Both	Current /former	PanCan model: >2% lung cancer risk in 6 years
BRELT1 ²⁴	Jan, 2013-Jul, 2014	Public calls through communication vehicles.	Volunteer-based	No	Yes	55-74	Both	Current /former	≥30 PYs, quit ≤15yrs
Shanghai CancerHosp ³⁶	Aug, 2013-Aug, 2014	Network established in selected communities.	Community-based	Yes	Yes	50-80	Both	≥1 of below: current or former smokers (≥20 PYs), and if former smoker, quit < 5yrs; or passive smokers; or never smokers with other risk factors of lung cancer including lung cancer family history, history of kitchen fume, or dust exposure.	
LSS ³⁷	Sep, 2000-Nov, 2000	primarily mass mailings; other including media and GPs.	Population-based	Yes	Yes	55-74	Both	Current /former	≥30 PYs, quit <10yrs
NLST ³⁸	Aug, 2002-Apr, 2004	primarily mass mailings; other including media and GPs.	Population-based	Yes	Yes	55-74	Both	Current /former	≥30 PYs, quit ≤15yrs
Depiscan ²⁷	Oct, 2002-Dec, 2004	GPs and occupational physicians	Hospital-based	Yes	Yes	50-75	Both	Current /former	≥15 cigs/day for ≥20yrs, quit <15yrs
JECS ^{28,39}	May,2012-	Invitation letters	NS	Yes	No	50-70 ²	Both	non/light	<30 PYs

Study Name [Ref.]	Recruitment procedures					Entry criteria			
	Recruiting time	Recruiting methods	Population source	Multi-centre	Recruitment Completed	Age	Sex	Smoking status	Smoking exposure
DANTE ⁴⁰	Mar, 2001-Feb, 2006	GPs, mass mailings, advertising leaflets and local media.	Population-based	Yes	Yes	60-74	Males	Current /former	≥20 PYs, quit <10yrs
NELSON ³⁰	Sep, 2003-2006	Invitation letters	Population-based	Yes	Yes	50-75	Both	Current /former	≥15 cigs/day for ≥25yrs or ≥10 cigs/day for ≥30yrs, quit ≤10yrs
ITALUNG ⁴¹	2004-2006	Invitation letters to subjects registered with selected GPs	Hospital-based	Yes	Yes	55-69	Both	Current /former	≥30 PYs since last 10yrs, quit <10yrs
DLCST ⁴²	Oct, 2004-Mar, 2006	Free newspapers, weeklies or GPs	Volunteer-based	No	Yes	50-70	Both	Current /former	≥20 PYs, quit <10yrs after age of 50
MILD ³³	Sep, 2005-Jan, 2011	Ads, TV broadcast and articles in the lay press.	Volunteer-based	Yes	Yes	≥49	Both	Current /former	≥20 PYs, quit ≤10yrs
LUSI ⁴³	Sep, 2007-Dec, 2010	Mass mailings	Population-based	No	Yes	50-69	Both	Current /former	≥15 cigs/day for ≥25yrs or ≥10 cigs/day for ≥10yrs, quit ≤10yrs
UKLS ³⁵	Aug, 2011-Aug, 2012	Mass mailings	Population-based	Yes	Yes	50-75	Both	LLPv2 model: ≥5% lung cancer risk in 5 years	
Shanghai ChestHosp ⁴⁴	Nov, 2013-Nov, 2014	GPs and advertising leaflets in selected communities	Community-based	No	Yes	45-70	Both	≥1 of below: current /former (≥20 PYs and/or quit ≤15yrs); or passive (>2h/day for ≥10yrs); or occupational; or cooking (frying >50dish-yrs); or family history of cancer	
China FeasiRCT ⁴⁵	2014-2015	NS	NS	Yes	Yes	50-74	Both	Current/former (>30 PYs); or passive (living with a regular daily smoking for >20yrs)	

Abbreviations: Non-RCTs, non-randomised controlled trials; RCTs, randomised controlled trials; PYs, pack-years; yrs, years; cigs, cigarettes; NS, not specified. ¹ extracted from *Pastorino et al, 2003*⁴⁶. ² aged 50-64 years in entry criteria before March 2016.

Table S3 Baseline participant characteristics, and baseline and overall low-dose computerised tomography (LDCT) screening results in lung cancer screening studies

Study Name [Ref.]	I-ELCAP ²⁰	Mayo LDCT trial ^{21, 47}	COSMOS ^{22, 48}	PanCan ²³	BRELT1 ²⁴	Shanghai Cancer Hosp ³⁶	LSS ^{25, 37}	NLST ^{26, 49, 50}	Depiscan ²⁷	J ECS ^{28, 39}	DANTE ^{29, 40}	NELSON ⁵¹⁻⁵³	ITALUNG ^{31, 41, 54}	DLCST ^{32, 42}	MILD ³³	LUSI ^{34, 43}	UKLS ⁵⁵	Shanghai Chest Hosp ⁴⁴	China FeasiRCT ^{56, 57}
Baseline characteristics																			
age (years) ¹	61	59	58	62	62	63	NR ²	61	56	NA	64	59	61	58	57	NR ³	67	60	60
Male,%	NR	52%	66%	55%	50%	54%	59%	59%	71%	NA	100%	84%	65%	55%	66%	67%	75%	47%	53%
Female,%	NR	48%	34%	45%	50%	46%	41%	41%	29%	NA	0%	16%	35%	45%	34%	33%	35%	53%	47%
Smokers,%	82.8%	100%	100%	100%	100%	55.5%	100%	100%	100%	NA	100%	100%	100%	100%	100%	100%	100%	28% ³	54%
Current smokers,%	NR	61%	80%	63%	55%	NR	58%	58%	60%	NA	57%	55%	65%	76%	77%	62%	39%	21%	46%
Former smokers,%	NR	39%	20%	37%	45%	NR	42%	42%	40%	NA	43%	45%	35%	24%	23%	38%	61%	7%	8%
smoking exposure (PYs) ¹	30	45	44	54	54	NR	54	54	NR ⁴	NA	45	38	39	36	39	NR	NR ⁵	11 ⁶	NR ⁷
Baseline results at the LDCT screening arm																			
LC prevalence, %	1.3%	2.0%	1.1%	5.4%	1.3%	0.2%	1.9%	1.0%	2.4%	NA	2.2%	1.0%	1.5%	0.8%	0.9% /0.9% ⁸	1.1%	1.7%	1.6%	NA
Stage I, %	85.9%	71.0%	65.4%	74.3% ⁹	80.0%	81.4% ⁹	53.0%	57.4%	37.5%	NA	57.1%	64.9%	52.3%	52.9%	NS	73.9%	60.6%	94.2%	NA
Stage III/IV, % ¹⁰	NS	9.7%	29.1%	17.6%	20.0%	7.4%	30.0%	34.4%	72.5%	NA	32.0%	25.7%	28.6%	41.1%	NS	17.4%	15.2%	1.9%	NA
Adenocarcinoma, %	77.6% ¹¹	74.2%	72.7%	80.9%	70.0%	88.9%	63.0%	57.8%	62.5%	NA	36.0%	50.0%	47.6%	70.6%	NS	68.2%	54.5%	92.3%	NA
Overall results at the LDCT screening arm																			
LC incidence, %	1.5%	4.3%	1.8%	6.5%	NA	NA	2.4%	4.0%	NA	NA	8.2%	3.9%	4.8%	4.9%	2.1% /2.9% ⁸	3.1%	2.1%	NA	NA
LC cumulative incidence (/10 000 person-years)	NA	NA	NA	138.1	NA	23.8	NA	64.5	NA	NA	NA	NA	49.9	51.4	45.7 /62.0 ⁸	67.4	NA	NA	NA
Stage I, %	85.1%	59.1%	66.3%	62.9% ¹²	NA	NA	48.0%	49.1%	NA	NA	45.2%	69.0% ¹³	35.8% ¹³	50.0%	70.0%/ 62.1% ⁸	69.4%	66.7%	NA	NA
Stage III/IV, % ¹⁰	NS	13.6%	28.3%	22.4% ¹²	NA	NA	40.0%	42.2%	NA	NA	41.3%	22.7% ¹³	49.3% ¹³	46.0%	25.0%/ 31.0% ⁸	21.0%	14.3%	NA	NA
Adenocarcinoma, %	71.4% ¹¹	54.5%	NS	74.3% ¹²	NA	NA	60.0%	46.2%	NA	NA	42.3%	51.0% ¹³	43.3% ¹³	58.0%	85.0% /51.7% ⁸	72.6%	59.5%	NA	NA
Biopsy rate, % ¹⁴	1.7%	NS	1.9%	5.4% ¹⁵	3.2% ¹⁶	0.6% ¹⁶	3.3% 16,17	6.5% ¹⁷	NA	NA	7.1% ¹⁵	1.2% ^{16,17}	2.7% ^{13,15}	1.2% ^{16,17}	1.8% 15,18	4.0%	2.0% ¹⁵	1.7% ^{15,16}	NA
Malignancy-to- benign ratio	11.4	3.9 ^{15,19}	5.7	7.6 ¹⁵	0.7 ¹⁶	1.9 ¹⁶	1.5 16,17	1.4 ¹⁷	NA	NA	4.3 ¹⁵	NA	8.5 ^{13,15}	3.0 ^{16,17}	10.2 ¹⁵	2.5	8.8 ¹⁵	11 ^{15,16}	NA

Abbreviations: PYs, pack-years; NR, not reported; NA, not applicable; LC, lung cancer. Data are number or percentage (%); ¹ mean values displayed if no median value reported. ² 68% in 55-64 years-old. ³ 46% in the age of 50-54 years. ⁴ 44% were females who had passive-smoking exposure of ≥ 20 pack-years. ⁵ 93.8% with a smoking duration of 20+ years. ⁶ estimated from the LDCT arm. ⁷ 44% in the 30-39 pack-years; 47% were females who had passive-smoking exposure of ≥ 20 pack-years. ⁸ Data displayed as biennial arm/annual arm. ⁹ Including stage 0 lung cancers. ¹⁰ Including small cell lung cancers at extensive stage. ¹¹ Only subtypes in stage I lung cancers were reported. ¹² Percentages in lung cancers with stage 0 lung cancers (5.9%) excluded. ¹³ Not include clinically detected lung cancers among non-compliant participants in the LDCT arm. ¹⁴ the proportion of

subjects undergoing invasive procedures in individuals undergoing baseline LDCT screening.¹⁵ Calculated for those with surgeries.¹⁶ Calculated from baseline results.¹⁷ Any invasive procedure.¹⁸ Overall in Biennial and annual screening arms.¹⁹ Calculated from baseline, 2nd and 3rd rounds

Table S4 Lung cancer risk models from China.

Author, year	Dataset	Study design	Population	Sample size	Malign. rate (%)	Formula displayed	Discrimination (AUC or c-statistics)	Calibration (P-value)	Prediction rules (risk threshold)	Acc.	Sen.	Spe.	Predictors in the model						
Risk model for high-risk population selection																			
Li <i>et al</i> , 2012 ⁵⁸	Development	Case-control	Hospital-based	5068	NA	Yes	0.637	0.154	NS	61.7%	54.2%	67.8%	Smoking status (never, light, heavy); 4 candidate SNPs - rs2736100 (TERT), rs402710 (CLPTMIL), rs4488809 (TP63) and rs4083914 (RGS17).						
	Internal validation			5068										0.641	\	\	\	\	
	Internal validation			3801										0.633	\	NS	61.7%	54.7%	67.5%
	Internal validation			1267										\	NS	61.5%	52.6%	68.4%	
Lin <i>et al</i> , 2012 ⁵⁹	Development	Case-control (cases pedigrees vs spouses pedigrees)	Hospital-based	1198	NS	Yes	0.75	\	<5; 5-10; ≥10	68.3%; 84.0%; 91.9%	\	\	Gender, smoking history (never, light, heavy), lung disease history occupational exposure, number of Lung cancer-affected individuals as first-degree relatives (0, 1, ≥ 2).						
	Internal validation													0.71	0.62	\	\	\	
Wang <i>et al</i> , 2015 ⁶⁰	Development	Case-control	Hospital-based	1693	NA	No	0.885	\	0.35	\	0.87	0.79	Age; sex; education level; family history of cancer; smoking cigarettes; COPD history; BMI; pesticide and cooking emission exposure; dietary intake of specific foods (seafood, vegetables, fruits, soybean products and nuts, dairy products, meat)						
Yang <i>et al</i> , 2018 ⁶¹	Development	retrospective cohort	Hospital-based	389	39.9%	Yes	0.7037	\	high-risk: ≥ 0.65	\	14.9%	94.5%	Age, sex, smoking status and history of cancer ; 4 serum biomarkers progastrin-releasing peptide (ProGRP), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), and cytokeratin 19 fragment (CYFRA21-1)						
	External validation (spatially)	retrospective cohort	Hospital-based	326	42.9%		0.7190	\	\	13.0%	98.3%								
Risk model for nodule malignancy prediction																			
Dong <i>et al</i> , 2014 ⁶²	Development	retrospective cohort	Hospital-based	3358	77.2%	Yes	0.935	\	0.659	\	90.7%	81.2%	Age; smoking status; family history of cancer; nodule diameter, spiculation, clear border, calcification, lobulation; satellite lesions; serum CEA level; serum CYFRA-21 level						
	Internal validation													77.7%	0.917	0.571	\	\	\
Hu <i>et al</i> , 2016 ⁶³	Development	Retrospective cohort	Hospital-based	112 (with GGNs)	73.2%	Yes	\	\	NS	84.8%	93.9%	60.0%	Solid component, vascular convergence sign, and diameter.						
Jin <i>et al</i> , 2017 ⁶⁴	Development Internal validation	Retrospective cohort	Hospital-based	273	58.2%	Yes	0.894 NS	\ Excellent (in graph)	0.65 \	80.2% \	78.6% \	82.5% \	Nodule diameter, spiculation, solid proportion; CT attenuation; vascular convergence; pleural tag						

Author, year	Dataset	Study design	Population	Sample size	Malign. rate (%)	Formula displayed	Discrimination (AUC or c-statistics)	Calibration (P-value)	Prediction rules (risk threshold)	Acc.	Sen.	Spe.	Predictors in the model
Li <i>et al</i> , 2012 ⁶⁵	Development	retrospective cohort	Hospital-based	371	61.7%	Yes	0.888	\	0.463	\	\	\	Age, diameter, spiculation, family cancer history, calcification, and clear border
	External validation (temporally)			145	67.6%		0.874						
	External validation (spatially) ⁶⁶	retrospective cohort	Hospital-based	107	72.9%	0.810	\	0.471	\	83.3%	75.9%		
Yang <i>et al</i> , 2017 ⁶⁷	Development	retrospective cohort	Hospital-based	1078	66.9%	Yes	0.807	\	NS	\	85.7%	60.4%	gender, age, pack-years of smoking, a previous history of malignancy, previous extrathoracic disease, nodule size, lobulated and spiculated edges, lobulation alone and spiculation alone, irregular edges, calcification
	External validation (temporally)			344	68.6%		0.784						
Yang <i>et al</i> , 2018 ⁶¹	Development	retrospective cohort	Hospital-based	163	NS	Yes	0.915	\	0.94	\	60.4%	94.2%	
External validation (spatially)	179			NS	0.584		\						65.6%
Zhang <i>et al</i> , 2015 ⁶⁸	Development	Retrospective cohort	Hospital-based	294	59.9%	Yes	\	\	\	\	\	\	Age; smoking status; nodule diameter, spiculation, clear border; serum CYFRA-21 level
	External validation (temporally)			120	60.0%		0.91						
Zheng <i>et al</i> , 2015 ⁶⁹	Development	Retrospective cohort	Hospital-based	405	63%	Yes	(1) 0.856	\	\	\	\	\	
	Internal validation			198	(1) 0.808		\						\
							(2) 0.838						
							(2) 0.845						

Abbreviations: Malign., malignancy; Acc., accuracy; Sen., sensitivity; Spe., specificity. GGO, ground-glass opacity; SPN, solitary pulmonary nodule. NS, not specified; NA, not applicable. \, indicates no data reported.

Table S5 Nodule management criteria for low-dose computerised tomography in lung cancer screening trials.

Study Name [Ref.]	Diameter Measurement	Volumetric Measurement	Baseline Positive def. ¹	Growth def.	Suspicious of LC at baseline ²	Incidence positive def.	Suspicious of LC at incidence ²
I-ELCAP ²⁰	Average of length and width	Measured on conventional CT or 3D software.	Largest non-calcified SNs/PSNs ≥ 5 mm; largest NSNs ≥ 8 mm; any endo-bronchial SNs; No. ≤ 6 .	Diameter percentage change: $\geq 50\%$ in nodules < 5 mm, $\geq 30\%$ in nodules 5-9mm, $\geq 20\%$ in nodules ≥ 10 mm ⁷⁰ ; or VDT: 30-360 days ⁷¹	≥ 15 mm; or nodule growth, or PET-positive.	Any new nodules	Nodule growth or without regression, or PET positive.
Mayo LDCT trial ²¹	Average of length and width	\	Any-size of non-calcified nodules, later changed to ≥ 4 mm; No. ≤ 6 .	NS	> 20 mm; or nodule growth	Any new nodules	As baseline
COSMOS ²²	Maximum axial diameter.	Calculated on the largest lesion diameter using an electronic calliper.	Non-calcified nodules ≥ 6 mm, or nodules with benign imaging features > 8 mm.	VDT 30-400 days	Nodule growth, or PET-CT positive SUV > 2.0 ; enhanced CT delta enhancement > 20 HU	Any new nodules	As baseline
PanCan ²³	Maximum axial diameter.	\	≥ 1 mm non-calcified or non-perifissural nodules or areas of non-solid density	\	NS	As baseline	As baseline
BRELT1 ^{24, 3}	Maximum axial diameter.	Calculated by semi-automated software	≥ 5 mm nodules; later changed to 6mm	NS in Volume threshold.	Nodule risk prediction $> 60\%$; PET/CY SUV > 2.5 and/or nodules' morphologic appearance	NA	As baseline
Shanghai CancerHosp ³⁶	Maximum axial diameter.	Measured by a computer-aided detection software	Largest non-calcified SNs/PSNs ≥ 5 mm; largest NSNs ≥ 8 mm; any endo-bronchial SNs	Volume percentage change $\geq 25\%$	≥ 15 mm; or nodule growth; or PET-positive.	Any new nodules	Nodule growth or without regression, or PET positive.
LSS ^{25, 37}	Maximum axial diameter.	\	≥ 4 mm non-calcified nodules or masses; ≤ 3 mm spiculated non-calcified nodules; focal parenchymal opacification; Endo-bronchial lesions.	\	≥ 4 mm non-calcified nodules	As baseline	As baseline
NLST ²⁶	Maximum axial diameter.	\	Non-calcified nodules Nodule(s) ≥ 4 mm	NS	Non-calcified nodules > 10 mm; or Enlarging nodules ≥ 7 mm; And PET/CT abnormal activity or CT enhance ≥ 15 HU	As baseline	As baseline
Depiscan ²⁷	Average of length and width	Measured on conventional CT or 3D software.	Non-calcified nodules > 5 mm	VDT: 30-360 days	≥ 10 mm, or nodule growth, or PET-positive.	As baseline	As baseline
JECS ⁷²	Average of length and width	\	≥ 5 mm SN/PSNs	NS	(SNs) ≥ 10 mm, (PSNs/NSNs) ≥ 10 mm or nodules growth	Any new nodules	New SNs ≥ 10 mm or nodule growth
DANTE ⁴⁰	Maximum axial diameter.	\	≥ 5 mm, with malignant radiological features, or NSNs	NS	Non-smooth SNs/PSNs ≥ 5 mm, or NSNs > 10 mm, no regression	As baseline	As baseline

					after antibiotics and PET-positive		
NELSON ⁷³	Average of length and width (NSNs); Diameter perpendicular to the costal pleura (PSNs and pleural-based SNs).	(SNs or solid component in PSNs) 3D volumetric computer assessment with manual adjustment. VDT estimation by volume in SNs or diameter in PNs, NSNs, pleural-based nodules.	<i>NOTCAT III</i> SNs 50-500mm ³ ; pleural based SNs 5-10mm d _{min} ; PSNs, non-solid component ≥8mm d _{mean} ; PSNs, solid component 50-500mm ³ ; NSNs ≥8mm <i>NOTCAT IV</i> SNs >500mm ³ ; pleural based SNs >10mm d _{min} ; PSNs, solid component >500mm ³ All nodules measured.	Percentage volume change (PVC) ≥25% after ≥ 3 months interval; VDT<400 days or new solid component in NSNs.	SNs or PSN solid component >500mm ³ ; pleural-based SNs >10mm; nodule growth.	As baseline	As baseline
ITALUNG ³¹	Average of length and width	\	SNs ≥5mm, NSNs ≥10mm, or PSNs	≥ 1mm increase in mean diameter of SNs or increase of the solid component in PSNs	SNs ≥10mm or PET-positive, or nodule growth.	Any new nodules	Nodule growth or PET-positive in SNs/solid in PSNs ≥8mm
DLCST ⁴²	Maximum axial diameter	Measured by a computer-aided detection software	Non-calcified nodules ≥5mm	Increase in volume of ≥25%, VDT <400 days	Nodules ≥15mm, or nodule growth	As baseline	As baseline
MILD ³³	\	Measured by a computer-aided detection software	No. ≤4; non-calcified nodules ≥60 mm ³ (≥5mm)	Volume increase ≥25% after 3 month interval	Non-calcified nodules ≥250 mm ³ (≥8mm), nodule growth	As baseline	As baseline
LUSI ⁴³	NS	Measured by a computer-aided detection software	Non-calcified nodules ≥5mm	VDT ≤400 days	Non-calcified nodules >10 mm, nodule growth, or other malignant features	As baseline	As baseline
UKLS ³⁵	Similar to NELSON	Similar to NELSON	<i>CATEGORY 2</i> SNs 15-49mm ³ or 3-4.9mm; PSNs solid component <15mm ³ or <3 mm; NSNs 3-4.9mm <i>CATEGORY 3</i> SNs 50-500mm ³ or 5-9.9mm; PSNs nonsolid component > 5mm, solid component 15-500mm ³ or 3-9.9mm; NSNs ≥5mm. <i>CATEGORY 4</i> SNs >500mm ³ or ≥10mm; PSNs solid component > 500mm ³ No. ≤20.	VDT <400days	SNs >500mm ³ or >10mm; PSNs solid >500mm ³ ; Nodule growth.	As baseline	As baseline
Shanghai ChestHosp ⁴⁴	Maximum axial diameter	\	Non-calcified nodules Nodule(s) ≥4mm	<i>Nodules <15mm</i> : mean diameter increase (Average of length and width) ≥ 2mm in SNs/NSNs/solid in PSNs; <i>Nodules ≥15 mm</i> : mean diameter increase ≥15%	SNs/PSNs >8mm, and PET-positive; nodule growth.	As baseline	As baseline

China FeasiRCT ⁴⁵ 56	NS	NS	NS	NS	NS	NS	NS	NS
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Abbreviations: SN, solid nodules; PSN, partially solid nodules; NSN, non-solid nodule; NS, not specified; NA, not applicable or not yet available. ¹ Individuals with LDCT positive results need to be recalled to further radiological or pathological examinations apart from the pre-planned rounds. For example, in an annually screening project, individuals will have a LDCT in 6 months if with nodules ≥ 5 mm, but have a LDCT one year later if with 3-5mm nodules; we define 5mm as the positive threshold, not 3mm. We redefined the definition here due to some discordances among these studies. ² Of which individuals undergoing invasive procedures directly. ³ BRELT1 applied the Mayo Clinic risk model in nodules >8 mm for pre-test malignancy risk prediction.

Searching Strategies for Lung Cancer Screening Studies in China

Database	Query (as of 10 September 2018)	Items Found
Chinese Database		
Chinese Clinical Trial Registry	((Target disease: lung cancer) AND (Intervention: CT)) OR ((Target disease: lung cancer) AND (Registered title: screening)) Use lung cancer, CT and screening associated Chinese characters.	85
Chongqing VIP database	Search in Title or Keywords with using 'lung cancer' and 'screening' associated Chinese words	1412
Wanfang Data	Search in Title or Keywords with 'lung cancer' and 'screening' associated Chinese words	657
China National Knowledge Infrastructure database [CNKI]	Search in Abstract with 'lung cancer' and 'screening' associated Chinese words	463
English Database		
Cochrane Library	(lung cancer):ti,ab,kw AND (screening):ti,ab,kw AND (CT):ti,ab,kw AND (China):ti,ab,kw	8
PubMed	((((((((((("Tomography, X-Ray Computed"[Mesh]) OR "Mass Chest X-Ray"[Mesh])) OR computed tomography[Text Word]) OR chest X-ray[Text Word])) OR early detection[Text Word]) OR screening[Text Word]) OR (((cancer screening[Text Word]) OR early detection of cancer[Text Word])) OR "Early Detection of Cancer"[Mesh])) AND (((China[Text Word]) OR Chinese[Text Word])) AND "China"[Mesh])) AND (((lung cancer[Text Word]) OR pulmonary cancer[Text Word]) OR "Lung Neoplasms"[Mesh])	148
EmBase	#1 'lung cancer':ti,ab,kw #2 'china':ti,ab,kw OR 'chinese':ti,ab,kw #3 'screening':ti,ab,kw OR 'early cancer diagnosis':ti,ab,kw OR 'computer assisted tomography':ti,ab,kw OR 'thorax radiography':ti,ab,kw #4 #1 AND #2 AND #3	249
Web of Science (Core Collection Library)	#1 TS=(lung cancer) OR TS=(pulmonary cancer) #2 TS=(screening) OR TS=(early detection of cancer) OR TS=(computerised tomography) OR TS=(radiography) #3 TS=China OR TS=Chinese #4 #3 AND #2 AND #1	549

Lung cancer screening programmes in China (Table 2 & Figure 2)

In the 1980s, the targeted population mainly focused on occupational workers⁷⁴⁻⁷⁷, in order to identify the possible benefit of early screening by CXR and/or sputum examination. Later in 1992, Cancer

Institute and Hospital Chinese Academy of Medical Sciences (CICAMS)^{78, 79} had issued a prospective occupational cohort with the collaboration of the US National Cancer Institute (NCI) and Yunnan Tin Corporation (YTC), targeting radon- and arsenic-exposed tin miners who currently worked in or retired from YTC in Gejiu City at Southern Yunnan (referred as the *YTC* cohort). The participants underwent annual sputum cytological examination and CXR scan. This *YTC* cohort had demonstrated moderate or severe atypia in sputum as risk indicators of lung cancer^{80, 81}. It was an important study in the Chinese lung cancer screening history since, as it has demonstrated various risk factors attributable to lung cancer in the occupational population. It is still under investigation with the aim of identifying potential early biomarkers of lung cancer⁷⁹.

In the 2000s, two institutes - the 5th Affiliated Hospital of Sun Yat-sen University, Zhuhai in 2003⁸² and CICAMS, Beijing in 2006⁸³ - have participated in I-ELCAP (referring as *Zhuhai I-ELCAP* and *Beijing I-ELCAP*, respectively). After following the I-ELCAP protocol during 2003-2009, *Zhuhai I-ELCAP* has demonstrated a higher proportion of stage I lung cancer (91% vs 67%) and 5-year all-cause survival (94.2% vs 72.8%) than during 1994-2002⁸². Lung cancers were mainly diagnosed in the subgroup aged 51-70 years-old⁸². In *Beijing I-ELCAP*⁸³, when applying risk classification according to the National Comprehensive Cancer Network lung cancer screening guidelines (NCCN version 1.1, 2012), the lung cancer prevalence in 4690 participants at baseline were not significantly different among the high-risk, moderate-risk and low-risk subgroup (0.9% vs 1.1% vs 0.4%). Female never-smokers with second-hand smoking (SHS) exposures had a higher detection rate of lung cancer compared to male SHS-exposed never-smokers and the NCCN-high-risk subgroup (1.4% vs 0.4% vs 0.9%). 76% of LDCT-detected lung cancers were at stage I⁸³.

Another prospective occupational cohort, the *Kailuan* cohort, was undertaken by the Kailuan Hospital affiliated to the Kailuan Company in Tangshan, Heibei in 2006⁸⁴. The ongoing cohort targeted employees of the company, aged ≥ 18 . These participants received biennial CXR. Its primary aim was to investigate risk factors and interventions for cardiovascular, cerebrovascular and other non-communicable diseases. It provided important evidence on risk factors concerning lung cancer risk, including body mass index⁸⁴.

In around 2010s, a number of LDCT lung cancer screening programmes were instigated (**Figure 2, Table 2**). Two national programmes granted by the Chinese Central Government were: the Rural Cancer Screening Programme (*RuraCSP*) in 2009⁸⁵ and the Cancer Screening Programme in Urban China (*CanSPUC*) in 2012⁸⁶. In *RuraCSP*, the high-risk definitions were different among screening sites. The enrollees would have annual LDCT for 3 years. *RuraCSP* expanded from the very first two sites (Tianjin and Xuanwei [Yunnan]) to ten from six provinces in 2015 (including Tianjin, Xuanwei [Yunnan], Gejiu [Yunan], Beijing, Sichuan, Zhejiang and Liaoning). The lung cancer detection rate at baseline and interval was 1.0% and 0.4%, respectively. In LDCT-detected lung cancers, 39.8% (at baseline) and 56.0% (at interval) were at an early stage⁸⁷. The 2015 China National lung cancer screening (CNS) guidelines⁸⁸ and the revised 2018 version⁸⁹ were developed upon the *RuraCSP* protocol⁸⁷. *CanSPUC* is a community-based project with annual LDCT screening for five rounds in urban residents aged 40-69 (some areas defined ages at 40-74) with high risk of lung cancer⁸⁶. Definition of high risk is region-dependent. Until 2016, it has covered 18 provinces/municipalities⁹⁰. In 2018, Hubei Province⁹¹ and Jiangxi Province⁹² have also initiated the programme. 31 provinces/municipalities would be included if possible. The nodule management protocol followed that in *RuraCSP*⁸⁵. Both *RuraCSP* and *CanSPUC* are feasibility studies and plan to investigate health economics of lung cancer screening in the context of China⁸⁵⁻⁸⁷. Following the two national programmes, regional programmes in several municipalities/cities have been consecutively conducted, most of which were funded by local government.

Beijing Municipality

In Beijing, another feasibility study for both lung and colorectal cancer screening was issued in multiple sites by CICAMS again in collaboration with US NCI in 2014 (referred as the *China FeasiRCT*)⁴⁵. It randomly allocated participants into three arms and ran for a duration of 3 years⁴⁵. At baseline, the rate of participant appliance to LDCT was 89.0%; and the rate of LDCT results suspicious for lung cancer was around 6.0%^{45,93}. The results were quite limited. It has been already completed by 2017.

In 2017, CICAMS has initiated another central government-funded programme, which is concerning lung cancer screening, intervention and investigation of management strategies ⁹⁴. Again in 2018, there are two other programmes being funded by the central government: one is a multicentre screening RCT and prospective cohort of lung cancer and colorectal cancer, and the other has included the lung cancer screening project as a part of it (by personal communication with Professor Wu Ning; funding information of both have already been made public online)⁹⁵ The three are referred as *Beijing CICAMS* programmes.

Tianjin Municipality

In Tianjin, a lung cancer screening programme has been initiated in 2012 in Tianjin Medical University Cancer Institute and Hospital ⁹⁶ (referred as *Tianjin CancerHosp* programme). It is eligible for people who are asymptomatic, of ≥ 40 years-old, tolerant of possible invasive procedures and not screened by CT within 1 year. Participants would undergo scans at baseline and at 1 or 2 years after baseline. Positive nodule definition were based on NLST and NELSON, that is, non-calcified nodules at baseline of average diameter ≥ 4 mm or volume ≥ 50 mm³, or new nodules at interval scans of average diameter ≥ 3 mm or volume ≥ 30 mm³. The nodule growth was defined as VDT < 400days or percentage of volume change $\geq 25\%$ based on NELSON. From Feb 2014 to Jun 2016, 650 individuals were enrolled for baseline screening and 548 finished interval scans. Six lung cancers (0.92%) have been diagnosed. When stratified risk profiles according to NCCN (v1 2016), the lung cancer detection rate in the high-risk subgroup (0.75%, 2/265) was lower than the moderate- and low-risk subgroup (1.04%, 4/385) though non-significant. Female non-smokers (1.59%, 2/126) had a non-significant higher detection rate of lung cancer than male smokers (1.04%, 4/383) ⁹⁶. In this preliminary report, computer-aided detection (CAD) volume measurement was more sensitive in detecting nodule growth than average diameter measurement ⁹⁶. The project has been completed by 2017 and undergoing follow-up at present. Its final results haven't been published to date.

In 2017, Tianjing Municipal Commission of Health and Family Planning supported a screening programme of four common cancers in Tianjin – lung cancer, breast cancer, liver cancer and stomach cancer ⁹⁷ (Referred as *Tianjin 4-Cancer* programme). The programme was also conducted by Tianjin

Medical University Cancer Institute and Hospital. Hexi District and Jinzhou District were the pilot sites. In last year, 52092 community residents underwent risk assessment, of which 992 were at high risk. 54 individuals were suspicious of lung cancer by LDCT. 14 was surgically diagnosed and the other 35 have been followed-up closely. The programme plans to cover up to 7 districts in 2018 ⁹⁷.

Shanghai Municipality

In Shanghai, multiple community-based screening programmes have been issued. Fudan University Shanghai Cancer Centre has conducted a prospective study in selected communities from Minhang District in 2013 to evaluate the efficacy of LDCT screening in both smokers and non-smokers (the *Shanghai CancerHosp* cohort) ³⁶. The eligibility criteria are asymptomatic individuals aged 50-80 years with tolerance of possible surgery, no malignancy history in the last 5 years and ≥ 1 risk factors as following: current/former smokers (≥ 20 pack-years, quitting < 5 years if former smokers), never-smokers with other risk factors (e.g. lung cancer family history, kitchen fume exposure, or dust exposure). The entry criteria is very similar to the CNS (2015/2018), except a higher stopping age (vs an upper age of 74 in the CNS [2015/2018]). Participants would have annual LDCT scans. The lung cancer prevalence at baseline was 0.2%; and the incidence rate (/100,000 person-years) was 159.06 in smokers and 336.97 in non-smokers, indicating a marginally significance ³⁶.

Shanghai Chest Hospital, Shanghai Jiaotong University, has conducted a community-based RCT in Xuhui District (referring as the *Shanghai ChestHosp* RCT) in late 2013 ⁴⁴. Asymptomatic participants aged 45-70 would be eligible if with any of the risk factors including an exposure history of smoking consumption (≥ 20 pack-years, quitting ≤ 15 years if former smokers), passive smoking, cooking oil fumes, occupational history or family history of cancer ⁴⁴. Compared to NLST criteria, it also had a lower age eligibility (55-74 in NLST), yet a broader entry criteria than NLST (only age and smoking exposure included in NLST) ^{44, 49}. It defined nodule diameter ≥ 4 mm as a positive result as NLST. The nodule management for positive nodules followed the National Comprehensive Cancer Network (NCCN 2014.V1) guidelines ⁴⁴. In the LDCT arm, the baseline results were quite similar to that of NLST in the aspects of positive nodule rate (22.9% vs 27.3%) and lung cancer detection rate (1.5% vs 1.0%), but the former had a higher early-stage lung cancer rate than the latter (Stage I: 94.1% vs

54.1%)^{44,49}. In addition, only 7.1% of its participants were NLST eligible; in its NLST-ineligible subgroup of the LDCT arm, the lung cancer detection rate was 1.3% in males and 1.4% in females. The information in the baseline result suggested that individuals with passive-smoking exposures and other risk factors should not be ignored in Chinese lung cancer screening⁴⁴.

Shanghai Changzheng Hospital has issued a collaborative programme with other six hospitals located in Shanghai in the same year^{98,99} (referred as *Shanghai Changzheng Hosp* programme).

Asymptomatic participants of any age from physical examination centres in seven tertiary hospitals and their surrounding communities would be enrolled into the study. Positive nodule was defined as any nodule of any size including calcified nodules. In the preliminary report, 14 506 individuals aged between 26-90 years underwent LDCT scans. The positive rate of detected nodules (of any size) was 29.89%; the overall lung cancer prevalence was 1.23%. 81.09% of the detected lung cancers were at stage I; 52.94% were diagnosed in nonsolid nodules⁹⁸.

In 2016, an international collaborative, multicentre programme between China and Netherlands has been initiated. The programme will help to assess three diseases of the thorax (lung cancer, cardiovascular disease and chronic obstructive pulmonary disease) by using one-stop CT imaging technology in the context of LDCT screening. It has been funded by central government. There are three study sites in China including: Shanghai Changzheng Hospital, Shanghai General Hospital and Tianjin Medical University Cancer Institute & Hospital. It has been named Netherlands-China Big-3 Screening, short for *NELCIN-B3*. Big-3 here stands for the 'big' three diseases and it will run until the end of the year 2020^{99,100}.

In addition, Baoshan District Commission of Health and Family Planning has supported a community-based screening programme to target 70 000 elderly people (≥ 75 years-old, or ≥ 65 years-old yet with cough/expectoration ≥ 2 weeks and abnormal CXRs) within this district in March, 2018 (referred as the *Shanghai Baoshan* programme). It will last until the end of 2018¹⁰¹. As of September 2018, 63 769 individuals have been assessed and 14 005 have undergone CT scans¹⁰².

Chengdu, Sichuan Province

In Chengdu City, Sichuan Province, West China Hospital has conducted a retro-prospective cohort from 2006, to recruit a population from corporations or industry team groups (referred as the *Chengdu WCH* cohort). The participants would undergo annually physical examinations with CXR or LDCT. The accumulative detection rate of lung cancer was 0.06% in the CXR group and 0.89% in the LDCT group after five annual scans, thus demonstrating LDCT is more sensitive in detecting lung cancer. Researchers stratified participants into risk groups according to recommendations of the American Association for Thoracic Surgery (AATS) guidelines in 2012¹⁰³ or the Chinese Society of Radiology (CSR) in 2015¹⁰⁴. The detection rate of lung cancer in AATS- and SCR-eligible subgroups would be higher than the overall detection rate, either in the LDCT or CXR group. The results haven't been published yet.

Guangzhou, Guangdong Province

The Guangzhou Medical University First Affiliated Hospital have conducted screening programmes consecutively with the support of the Guangzhou municipal government (referred as *Guangzhou GMU-1stHosp* programme)^{105, 106}. In Dec 2015, it initiated a lung cancer screening project by using LDCT scan and serum biomarkers. The programme targeted low-income citizens aged ≥ 50 years in Guangzhou. However, the positive response rate was low¹⁰⁶. In June 2017, a separate demonstration project was conducted to target 120 000 residents aged 50-74 with a high risk of lung cancer in Yuexiu District. High risk of developing lung cancer was defined as long-term smokers (20 pack-years, quitting ≤ 5 years if former smokers) or individuals with a family history of lung cancer. Until Dec 2017, the programme has enrolled and scanned 808 eligible participants, of which 18 were suspicious of lung cancer and 5 were pathologically diagnosed¹⁰⁵. The Guangzhou Medical University First Affiliated Hospital established a collaborative group with other institutes and hospitals to facilitate the diagnosis and treatment of lung cancer. It also build a partnership with China Mobile, the biggest telco in China, to establish a digital platform in the aim of prioritizing registration, recruitment, follow-up and data collection^{105, 106}. The expenditures of the programme has been mostly "covered by the city government, with the rest shouldered by the hospital and the Guangzhou Charity Association"¹⁰⁶. Both low-income individuals aged ≥ 50 and high-risk participants aged 50-74 in the

selected district will get free screenings. Low-income participants can also claim a pension for the follow-up tests if with positive screening results ¹⁰⁵. Since Nov 2017, the programme has also provided a one-fifth discount on the screening costs for other residents aged ≥ 40 years in the whole province if they are volunteered to take part in ¹⁰⁵.

There would be a significant number of expenses from the screening per se, follow-up tests, public education, health-care specialist/staff training, limited availability of screening and data collection optimism; all of the factors above are barriers which would compromise “expanding the screenings to a wider population” in a populous and aging country ¹⁰⁶. A working group from Milken Institute, a non-profit organisation aiming at improving global prosperity and advancing affordable healthcare, case-studied the *Guangzhou GMU-1stHosp* programme and recommended some innovative and potentially viable financing models targeting the barriers above. They proposed a comprehensive demonstration project to target the 40-80 year-olds in Guangzhou, by integration with financing considerations in population selection, price subsidies, hospital selection, awareness campaign and data tracking (referred as the *Guangzhou Financing* project). The design of the study will be further discussed in their subsequent working sessions ¹⁰⁶.

Qinghai Province

A number of other programmes sponsored by charity groups have also been conducted, e.g. Shanghai Cijing Charity Fund has supported a lung cancer screening project within deprivation areas in Qinghai since 2016 (referred as the *Qinghai SH-RenjiHosp* programme) ^{107, 108}. The programme targets high-risk individuals who are eligible with the criteria: aged 50-74; or aged ≥ 35 but with ≥ 1 risk factors including long-term smokers, long-term exposure to severe air pollution, radiation, coal smoke, kitchen fume, with a family history of lung cancer, a personal history of cancer or pulmonary diseases. The programme was initiated in Shanghai Jiaotong University Affiliated Renji Hospital. It has also been planned to target underserved populations in other provinces including Henan, Xinjiang and Shandong Province ^{107, 108}.

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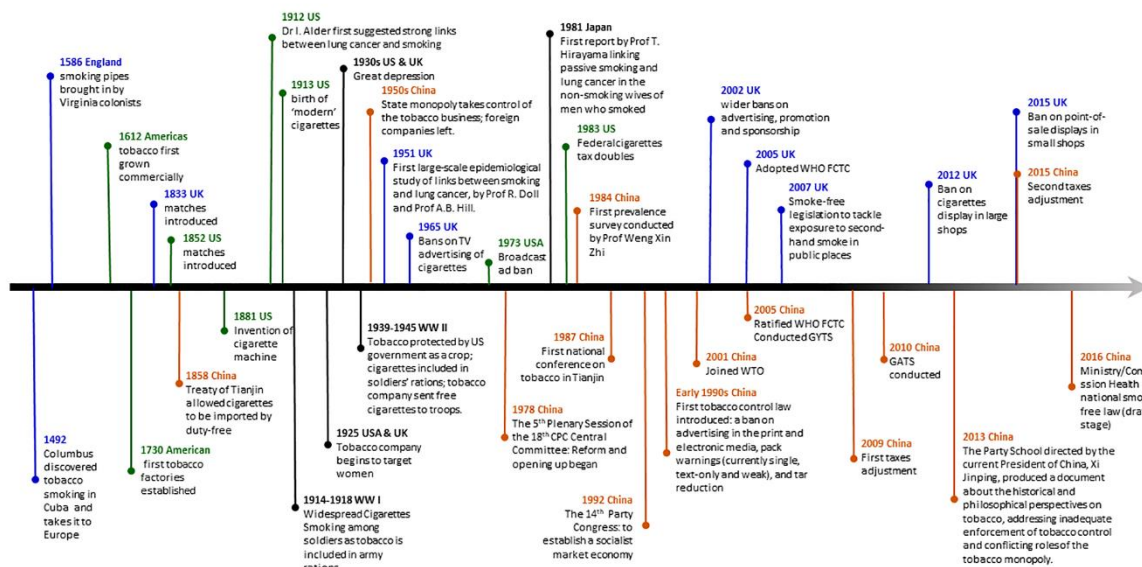


Figure S1 Historical events associated with tobacco and tobacco control in China, the UK and the US.

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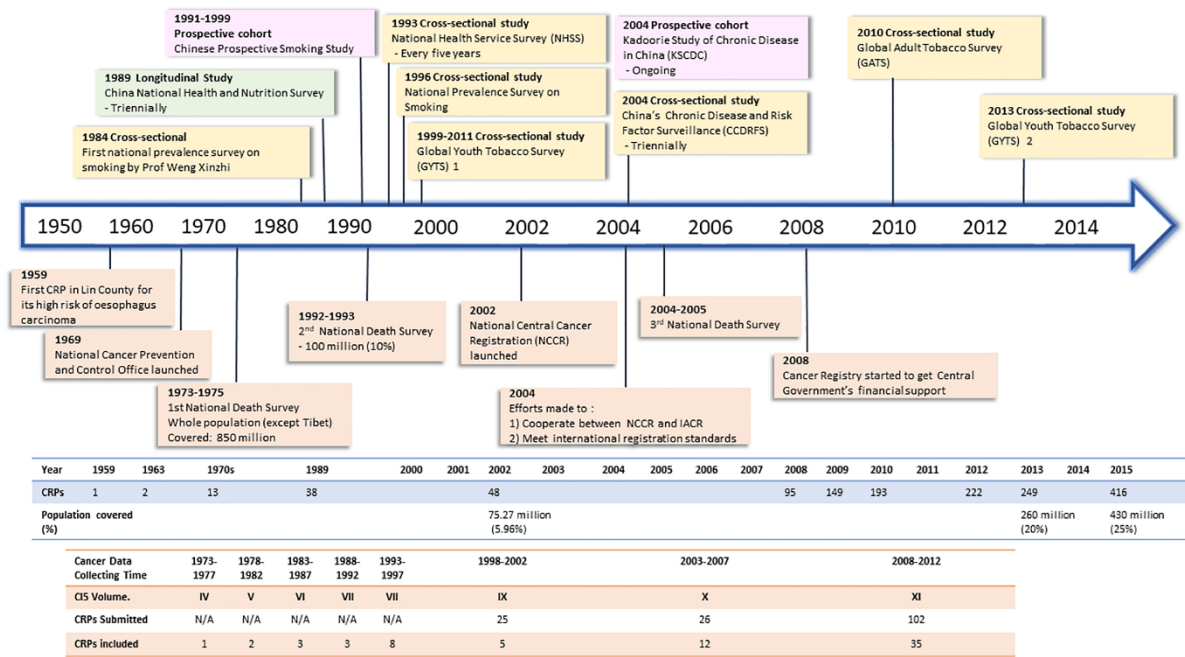


Figure S2 Timeline of selected nationally/sub-nationally representative surveys or important historical events associating with tobacco use (above the arrow) and cancer (below the arrow), and development of cancer registrations in China.

209x118mm (300 x 300 DPI)