

Peer Review File

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Reviewer A

Dr. Fu and colleagues have written a Narrative Review characterizing the benefits and harms in lung cancer screening and also proposing that low-risk individuals may derive benefit from LDCT for lung cancer screening. This topic is of high clinical relevance, especially as the USPSTF reviews eligibility criteria for screening, and more publications are highlighting issues such as racial differences in lung cancer risk. However, this Review does not provide rigorous evidence supporting the proposal that individuals who may be considered “low-risk” by existing guidelines would have a favorable balance of benefits/harms from undergoing LDCT.

Major points:

Comment 1: *The authors point out that non-traditional risk factors (i.e. other than smoking) may play a role in lung carcinogenesis. However, they do not review specific known and unknown risk factors (genetic alterations, environmental exposures, sociocultural variables, etc.). The premise of the manuscript about screening low-risk individuals (who may in fact be at high risk if other factors were taken into account) is lost if the risk factors themselves are not defined. If the large retrospective studies the authors have previously conducted (references 25 and 26) identified factors significantly associated with increased lung cancer diagnosis, they could be described*

in this manuscript.

Reply 1: Thanks for your valuable comment. There is no unified definition of high-risk population of lung cancer. As the reviewer pointed out, smoking, age, gender, environmental factors, and genetic factors may contribute to carcinogenesis of lung cancer. We have reviewed the association between these factors and lung cancer in the first part of discussion.

Changes in the text: Line 96-154, “In 2018, there were more than 2 million estimated new cases of lung cancer worldwide, accounting for 11.6% of all new cases with cancer(1). In the United States, 228 thousand patients were estimated to had lung cancer in 2020, accounting for 11.6% of all new cases with cancer (2). Especially in China, approximately 17.1% of new cancer cases had lung cancer(3). Therefore, to reduce the incidence of lung cancer, we need to identify risk factors.

Smoking. Cigarette smoking is considered to be a main risk factor. The association between the number of cigarettes and the risk of lung cancer was observed in previous studies(4,5). The second-hand smoking also contributed to the carcinogenesis of lung cancer(6). Smoking cessation could reduce lung cancer risk(6,7), and some guidelines also recommended smoking cessation while receiving lung cancer screening. Smoking addiction originated from the presence of nicotine in tobacco. However, it is not nicotine but the exposure to tar (the total matter of smoke after removing nicotine and water) that leads to the carcinogenesis of lung cancer(8). Tar consists of 3500 chemical substances and approximately 60 of them are known carcinogens(9).

Age. As time goes by, shortening of telomeres after many times of cell replication cycles and accumulative DNA damage may lead to the carcinogenesis of lung cancer. The young individuals have less possibility to develop lung cancer, compared with the old(10) . However, the detection rate depends on the methods of lung cancer screening

and the importance that ordinary persons give to lung cancer screening. Nowadays, with the wide application of LDCT and the development of the society, especially in some developing countries (such as China), the detection rate of lung cancer in young population increases(11,12).

Gender. Traditionally, men are more likely to develop lung cancer than women. However, the trends of lung cancer incidence in men and women changed dramatically. Jemal *et al.* reviewed the nationwide population-based incidence of lung cancer in America and found that the age-specific incidence decreased generally among both men and women with the age of 30 to 54 years old(13). Nevertheless, the declines among men have been steeper(13). During 2010 and 2014, lung cancer incidence was higher in women than men(13). In terms of mechanism, the expression of estrogen receptor (ER) alpha and ER beta were found to be increased in lung cancer tissues(14). ER ligands could activate MAPK pathway and promote cell growth(15).

Environmental factors. Environmental factors may also contribute to carcinogenesis of lung cancer. They consist of indoor air pollution, including coal(16-18), biomass(19), and cooking fumes(20), outdoor air pollution(21,22), and occupational agents, including asbestos(23), arsenic(24), and silica(25,26). If we reduce the exposure to these environmental factors, the incidence of lung cancer should be decreased.

Genetic factors. Individuals response to the same environmental exposure differently. For instance, although smoking is considered to be a main risk factor of lung cancer, the majority of smokers will not develop lung cancer in their lifetime(27) and some never-smokers might also develop lung cancer. Moreover, in west countries, the percentage of never smokers in lung cancer patients is about 10% to 20%(28), but it is as high as 50% to 63% in east-Asian population(29-31). Mechanically, genetic factors may play a significant role in these processes, and some genetic variations might contribute to the carcinogenesis of non-small cell lung cancer regardless of smoking history. In 2005, Bell *et al.*(32) reported a family with multiple cases of non-small cell lung cancer associated with the germline *EGFR*-T790M mutation. Subsequent studies identified relevant mutations in *HER2*, *TP53*, and *BRCA2*(33,34). Not only germline mutation but also single nucleotide polymorphism may contribute to the predisposition

to lung cancer. Genome-wide association studies have identified rs3769821, rs2293607, rs1200399, rs17038564, rs35201538, and rs4573350 as risk loci for lung cancer in Chinese population(35). ”

***Comment 2:** Section 4, “The necessity of LDCT screening for low-risk individuals,” does not provide rigorous evidence to show that, a). “low-risk” individuals have a favorable balance of benefits/ harms from LDCT screening, or b). that increasing the time interval between screens leads to a clinical benefit among these individuals. Section 4 in its current state includes primarily clinical anecdotes, so this part of the manuscript would be improved greatly by reviewing data related to nontraditional criteria for screening eligibility. (The authors do describe the MILD trial in Section 5, which included annual vs. biennial screening intervals, but this study included traditionally moderate to high-risk patients.) Similarly, the proposed algorithm (Figure 2) is not based upon lung cancer screening studies – perhaps the authors could instead propose a clinical trial to evaluate the impact of screening “low-risk” populations.*

Reply 2: Thanks for your suggestion. There are few existing clinical trials to investigate the use of LDCT in low-risk individuals. Wei *et al.*(36) investigated the performance of lung cancer screening with LDCT in 1411 high-risk and 558 non-high-risk individuals in China. The results demonstrated that the positive rate was 9.7% for all participants and 11.3% for the high-risk individuals, so LDCT also seemed necessary for low-risk individuals in China. Our algorithm toward lung cancer screening is based on our clinical experiments and previous work on lung cancer screening, and it needs the

confirmation from future clinical trials.

Changes in the text: Line 301-306, “There are few existing clinical trials to investigate the use of LDCT in low-risk individuals. Most of evidence came from NLST(37), which was not originally designed for this. Wei *et al.*(36) investigated the performance of lung cancer screening with LDCT in 1411 high-risk and 558 non-high-risk individuals in China. The results demonstrated that the positive rate was 9.7% for all participants and 11.3% for the high-risk individuals.”

Line 344-346, “Biennial screening could save about one third of LDCT scans with similar performance indicators as compared to annual screening(38)”

Minor points:

Comment 3: *The sentence that ends on line 52 needs a reference.*

Reply 3: Thanks for your advice. We have added the relevant references for this sentence.

Changes in the text: Line 67-69, “Among all screening technologies, low-dose computed tomography (LDCT) stands out for its high sensitivity and non-invasiveness(39,40).”

Comment 4: *The sentence that ends on line 63 may want to reference the 2019 JAMA*

Oncology paper by Aldrich and colleagues as well.

Reply 4: Thanks for your suggestion. The 2019 JAMA Oncology paper by Aldrich and colleagues is an important reference for this review. We have added it as a reference for this sentence.

Changes in the text: Line 79-81, “Nevertheless, based on the previous studies, an estimated 40-60% of patients with lung cancer did not meet the US Preventative Task Force (USPTF) criteria, originated from the NLST eligibility criteria(41,42).”

Comment 5: The authors provide a very interesting section on differences in lung cancer screening practice between China and the US (it may be more accurate to change the section title from “eastern countries” to “China,” as studies from other east Asian countries are not discussed).

Reply 5: Thanks for your advice. It is true that this section mainly focuses on the difference between China and western countries. We have changed the section title from “eastern countries” to “China”.

Changes in the text: Line 236, “4. The differences between China and western countries in lung cancer screening”

***Comment 6:** The manuscript would derive benefit from being reviewed again for minor grammatical errors.*

Reply 6: Thanks for your advice. We have re-read the manuscript carefully, and the grammatical errors have been corrected.

Changes in the text: N.A.

Reviewer B

The authors have focused in this paper on lung cancer screening in low-risk subjects.

This article cannot be accepted without major corrections.

Major concerns

***Comment 1:** Title should be changed: added non-smokers or light smokers in Asia rather than low risk individuals*

Reply 1: Thanks for your valuable advice. As the reviewer indicated, “low-risk individuals” might be not suitable in the title, because there is no consensus on the definition of low-risk individuals. However, not only smoking history but also age, one of important risk factors in our strategy, are two important factors in the previous guidelines of lung cancer screening. Therefore, we have changed our title from “low-risk individuals” to “non-high-risk individuals”.

Changes in the text: Line 1-2, “Lung Cancer Screening Strategy for Non-high Risk Individuals: A Narrative Review”

***Comment 2:** The discussion must be restructured with different paragraphs:*

- *International recommendations for lung cancer screening*
- *the epidemiological characteristics of lung cancer in Asia with specific risk factors: age, family history of cancer, passive smoking, environmental particulate, occupational exposures...*

Reply 2: Thanks for your good advice. We have added the international recommendations for lung cancer screening and risk factors of lung cancer in the revised manuscript.

Changes in the text: Line 238-250, “Most of lung cancer screening guidelines were released by western associations and societies. National Comprehensive Cancer Network recommended annual LDCT for either current smokers or former smokers quitting < 15 years with a smoking history of ≥ 30 pack-year, who was 55 to 77 years old, or individuals with a smoking history of ≥ 20 pack-year and additional risk factors (other than second-hand smoke), who was no less than 50 years old(43). American Association for Thoracic Surgery suggested annual LDCT for individuals with a smoking history of ≥ 30 pack-year, who was 55 to 79 years old, or individuals with a smoking history of ≥ 20 pack-year and a cumulative risk of developing lung cancer of 5%, who was no less than 50 years old(44). For either current smokers or former smokers quitting < 15 years with a smoking history of ≥ 30 pack-year, US Preventive Services Task Force recommended annual LDCT for individuals with the age between 55 and 80(45), while American Cancer Society suggested it for those with the age between 55 and 74(46).”

Line 96-154.

Comment 3: RCTs currently underway in Asia should be cited in the discussion

Reply 3: Thanks for your comments. RCTs currently underway in Asia is an important part of the discussion part. Unfortunately, the large and qualified RCTs about lung cancer screening were not found by the literature research.

Changes in the text: N.A.

Comment 4: Paragraphs 3, 4, 5 and the conclusion should be reviewed.

Reply 4: Thanks for your comments. We have added more references to support our conclusions. However, it is a relatively new concept, and there are only a few evidences to support it. We also modified the expression of some conclusions.

Changes in the text: N.A.

Minor Concerns

Comment 5: Introduction: It's not in the United States but in the retrospective study of Menesure and al. that 40% of patients with lung cancer did not meet the NLST eligibility criteria.

Reply 5: Thanks for your valuable suggestion. We have modified the sentence, and we also cited another reference (Aldrich MC, Mercaldo SF, Sandler KL, et al. Evaluation of USPSTF Lung Cancer Screening Guidelines Among African American Adult

Smokers. JAMA Oncol 2019).

Changes in the text: Line 79-81, “Nevertheless, based on the previous studies, an estimated 40-60% of patients with lung cancer did not meet the US Preventative Task Force (USPTF) criteria, originated from the NLST eligibility criteria(41,42).”

Comment 6: 2.2 :CT scan at 3 month in NELSON for nodule between 5 and 10 mm reduce the false positive rate

Reply 6: Thanks for your comments. The relevant contents have been added in the manuscript

Changes in the text: Line 215-217, “A proper CT scan strategy might help reduce the false-positive findings, and other methods to distinguish the malignant from the benign is also required in future studies.”

Comment 7: 2.3 :the nodule doubling time can predict the growth of lung nodule

Reply 7: Thanks for your advice. The description seems not appropriate. We have deleted this sentence.

Changes in the text: N.A.

Comment 8: 3: In the article of Zhang, there is a significant proportion of young, female and non smoking employees but significance is not reach and it's not a screening trial

Reply 8: Thanks for your comment. We have modified the relevant contents to clarify results of this study.

Changes in the text: Line 284-289, “The results demonstrated that the lung cancer detection rate was significantly greater in female than male (2.5% vs 1.3%, P=0.001). There was also a greater detection rate among nonsmokers than smokers, although there was no significant difference (2.2% vs 1.4%, P=0.092). The detection rate in young employees was greater than before. Moreover, 95.5% of LDCT-detected lung cancer radiologically presented as ground-glass opacity(11).”

Comment 9: Discussion: In the eligibility for screening, the role of the predictive risk models and not only the age and smoking history must be added

Reply 9: Thanks for your suggestion. We have added the contents about the risk prediction models of lung cancer.

Changes in the text: Line 250-257, “In addition, some risk prediction models have been developed(47-49). Based on data from the Beta-Carotene and Retinol Efficacy Study (CARET), Bach *et al.*(47) developed a lung cancer risk prediction model

incorporating smoking history, asbestos exposure, sex, and age to predict annual absolute lung cancer risk of ever-smoked individuals aged over 45 years. Nevertheless, the current models were not representative for generalization and the selection of factors might be different in different models. Therefore, no prediction model is utilized clinically, and a good and unified prediction model is needed currently.”

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