TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

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Reviewer A

The paper titled "Public opinion on implementing the National Lung Cancer Screening Program in Korea" is interesting. Public agreement and active participation of the eligible population are key factors to successful implementation of NLCSP. Our data would be a valuable resource in building appropriate strategies to maximize the benefits of nationwide lung cancer screening. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1: Under the task of strengthening early screening and diagnosis of lung cancer, how to introduce more accurate screening methods and establish a more complete screening path and model?

Reply 1:

Thank you for this insightful question. We completely agree that employing accurate screening methods and establishing a complete screening path are essential for strengthening the NLCSP. To achieve this, first, there is a requirement for CT scanners and standardization of the acquisition parameters so that quality of the screening method is assured (PMID 29962887) (1). The CT results must be evaluated in accordance with the lung imaging reporting and data system (Lung-RADS), suggested by the American Radiology Society (PMID 30776882) (2). Additionally, radiologists must complete relevant education in order to be qualified. Together, these standardized requirements can assure the quality of the LDCT-based lung cancer screening in the NLCSP.

Second, to establish a more complete screening path and to enhance the participation rate among high-risk individuals, all candidates for the NLCSP are required to undergo counselling for screening results and smoking cessation. This is another important aspect for the successful implementation of the lung cancer screening program. In the pilot study of the Korean Lung Cancer Screening Project (K-LUCAS), this proved to be effective in increasing the participants' willingness to quit smoking (this is described in the original manuscript, see page 18, lines 352 - 353) (PMID 30776882) (2).

We provided the survey participants with information about the implementation of the national lung cancer screening program, and have described the details of the same in the

methods section (pages 7-8, lines 131-141). Additionally, we have integrated these points in the discussion section of the revised manuscript (see pages 17 - 18, lines 336 - 343 in the revised manuscript).

Changes in the text:

Quality control is another important issue in this nationwide screening program. In order to standardize the screening process and consistently maintain the quality for accuracy among the screening units, there are several requirements that need to be met. First, CT must be a multichannel scanner with a minimum of 16 channels, and the results must be evaluated in accordance with the lung imaging reporting and data system (Lung-RADS) suggested by the American College of Radiology (23). Second, radiologists must complete relevant education and be qualified to conduct the screening. Together, these essential prerequisites can assure the quality of the LDCT-based screening. Besides these standardized setting for mass screening, a centralized monitoring system would be required for keeping screening quality by using indicators including participation rate among high-risk population, screening positive rate and smoking cessation rate after screening.

Comment 2: An important measure to improve the health and economic benefits of lung cancer screening is to select screening objects reasonably and accurately. Several large-scale screening studies that have been carried out or completed have selected high-risk groups. But in different studies, what is the definition of high-risk groups? How to unify?

Reply 2:

Thank you for your insightful comment. Several large-scale screening studies have been carried out in the United States (NLST, PMID 21714641) (3), the United Kingdom (UKLS, PMID 26645413) (4), and the Netherlands and Belgium (NELSON, PMID 31995683) (5). All these studies selected high-risk individuals for lung cancer screening, but their criteria varied.

The high-risk group in the NLST (United States) was defined by age (55–74 years old) and smoking history (at least 30 pack years). In the UKLS (United Kingdom), the Liverpool Lung Project (LLP) risk model accounted for respiratory diseases (COPD, emphysema, bronchitis, pneumonia, and tuberculosis), and smoking history was used to identify participants with ≥ 5% risk of developing lung cancer in the next 5 years. In the NELSON study (the Netherlands and Belgium), current or former (those who had quit ≤10 years ago) smokers, who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years, and were aged 50 to 74 years, were included.

These differences had earlier been described in the introduction section of the original manuscript (page 5, lines 83-100). However, the Korean lung cancer screening guidelines were developed based on the NLST (United States) data and the targets for the National Lung Cancer Screening Program (NLCSP) (page 6, lines 101-105). The criteria differ across studies primarily due to differences in population, epidemiology, smoking status, economic status, and healthcare systems between countries. Nonetheless, smoking status and age have been the common criteria used in all of these pivotal studies. Further, while it seems difficult to unify these criteria at present, cumulative evidence might provide insights that can help in arriving at a global consensus on the selection criteria for high-risk individuals. We have added these points in the discussion section of the revised manuscript (see pages 19 - 20, lines 378 - 389 in the revised manuscript).

Changes in the text:

Several pivotal studies have been conducted in different countries that have also commonly targeted high-risk individuals for lung cancer screening. However, the criteria used to define a high-risk individual vary from one study to another (6-8). This is primarily due to differences in population, epidemiology, smoking status, economic status, and healthcare systems between countries. Nonetheless, smoking status and age have been common factors used in all of these studies. Further, while it seems difficult at present to arrive at a global consensus on the selection criteria for high-risk individuals, cumulative evidence might provide insights for developing a risk prediction model that can help in reducing lung cancer mortality by more efficiently identifying high-risk individuals. This model may not only consider smoking history but also other risk factors such as family history, chronic lung disease, and carcinogen exposures in working sites.

Comment 3: If the mobile tumor screening vehicle is used to expand the early diagnosis of lung cancer, can the function of rapid detection of lung cancer risk be realized?

Reply 3:

In Korea, there are several well-established cancer screening units that have been responsible for peforming the national cancer screening program which targets stomach, colon, breast, cervix, and liver cancers. Also more than 2,000 hospitals nationwide has equipped 16 channel or more high-quality CT scans. Thus, the National Lung Cancer Screening Program (NLCSP) using low-dose chest CT could be carried out in hospitals that already have a high quality CT scan and a team of multidisciplinary experts for lung cancer diagnosis. Therefore, considering these circumstances, a mobile screening vehicle is currently not being used in

Korea for lung cancer screening.

Comment 4: Is there an innovative artificial intelligence system that can greatly reduce the burden of heavy follow-up tasks through functions such as automatic comparison, automatic identification, and trend analysis?

Reply 4:

Thank you for this valuable comment. We completely agree that repetitive CT exams can increase the burden for physicians. In the pilot trial for the Korean Lung Cancer Screening Program (K-LUCAS), a network-based diagnosis supporting system using computer-aided detection was adopted (PMID 30776882) (2). However, it has not been integrated into the nationwide screening program. There are studies that have validated an increase in positive predictive values and a reduction in false-positive rates for lung cancer screening when such computer-aided diagnostic algorithms are used (PMID 28872442) (6). Therefore, we foresee that artificial intelligence-aided CT diagnosis would greatly enhance the quality and speed of the nationwide screening program, if properly validated. We have added this in the revised manuscript (see pages 18 - 19, lines 359 - 367 in the revised manuscript).

Changes in the text:

Innovative artificial intelligence (AI) systems may greatly enhance the efficiency of radiologic evaluation. In the pilot trial for the Korean Lung Cancer Screening Program (K-LUCAS), a network-based diagnosis supporting system using computer-aided detection was adopted (9). However, this has not yet been integrated into the nationwide screening program in Korea. There are studies that have validated an increase in positive predictive values and a reduction in false-positive rates for lung cancer screening when such computer-aided diagnostic algorithms are used (28). Therefore, we foresee that AI-aided CT diagnosis would greatly enhance the quality and speed of the nationwide screening program, if properly validated.

Comment 5:) What are the key issues in lung cancer screening at this stage?

Reply 5:

This is a valid point that certainly needs to be addressed. The key issues are promoting the participation of the high-risk population in the lung cancer screening program, and minimizing the risk of unnecessary examinations by exercising screening quality control. The ultimate goal for this program is to improve the survival rate among individuals diagnosed with lung cancer by detecting the disease at its curable stages, and to decrease healthcare costs. We have highlighted these issues in the revised manuscript (see pages 16 -

17, lines 315 - 318 in the revised manuscript)

Changes in the text:

The key issues with implementing the nationwide lung cancer screening program are promoting the participation of the high-risk population in the screening program and minimizing the risk of unnecessary examinations by exercising screening quality control.

Comment 6: No matter how the imaging technology develops, it is still human beings who ultimately judge and decide on the detection results. How to guarantee the quality of personnel who perform lung cancer screening?

Reply 6:

We appreciate this valuable comment. As mentioned in response to the first comment, there are certain requirements for guaranteeing the quality of the screening personnel. First, only board-certified radiologists who have completed relevant education are qualified to conduct the screening. Second, CT results are evaluated in accordance with the lung imaging reporting and data system (Lung-RADS) suggested by the American Radiology Society, in order to standardize the reporting system (PMID 30776882) (2). These points have been included in the revised manuscript along with the changes made in response to comment #1 (see pages 17 - 18, lines 336 - 343 in the revised manuscript).

Changes in the text:

Quality control is another important issue in this nationwide screening program. In order to standardize the screening process and consistently maintain the quality for accuracy among the screening units, there are several requirements that need to be met. First, CT must be a multichannel scanner with a minimum of 16 channels, and the results must be evaluated in accordance with the lung imaging reporting and data system (Lung-RADS) suggested by the American College of Radiology (23). Second, radiologists must complete relevant education and be qualified to conduct the screening. Together, these essential prerequisites can assure the quality of the LDCT-based screening. Besides these standardized setting for mass screening, a centralized monitoring system would be required for keeping screening quality by using indicators including participation rate among high-risk population, screening positive rate, and smoking cessation rate after screening.

7) Due to the complex etiology of lung cancer and limited epidemiological data, how to determine the accurate incidence of lung cancer under the action of different risk factors?

Reply 7:

Thank you for this constructive comment. We completely agree that there are various etiologies of lung cancer, including oncogenic mutations that have less causal relationships with smoking. However, smoking is the most significant risk factor for lung cancer. And due to the paucity of epidemiological data related to risk factors other than smoking, it is impractical to implement a large-scale screening program for other etiologies of lung cancer at this point. However, we are working towards developing a risk prediction model that not only considers smoking history but also other risk factors such as family history, chronic lung disease and carcinogen exposures in working sites, in order to more efficiently identify high-risk individuals and reduce lung cancer mortality.

We have included this explanation in the revised manuscript (see pages 19 - 20, lines 383 - 389 in the revised manuscript).

Changes in the text:

Further, while it seems difficult at present to arrive at a global consensus on the selection criteria for high-risk individuals, cumulative evidence may provide insights for developing a risk prediction model that can help in reducing lung cancer mortality by more efficiently identifying high-risk individuals. This model may not only consider smoking history but also other risk factors such as family history, chronic lung disease, and carcinogen exposures in working sites.

Comment 8: In different countries, the assessment of the benefits, implementation costs, and potential risks of lung cancer screening must be based on the country's economic, cultural and social background. Compared with other countries, what are the specific rules and differences in screening policies and quality control in South Korea?

Reply 8:

We appreciate this insightful comment. The Korean National Cancer Screening Program, which targets common cancers in Korea, including gastric, colon, liver, breast, and uterine cervix cancers, has been widely implemented since 1999. Therefore, launching a nationwide lung cancer screening program could be easier and more favourably received by the general population. Another specific difference between Korea and other countries is the existence of the National Health Insurance Service, a nationwide social health insurance system with compulsory subscription, which supports the NLCSP. As the funding source comes from the general population, it is imperative to obtain widespread public agreement for implementing a program that is restricted to the high-risk population.

Additionally, in Korea, the abundance and widespread distribution of CT scanners, along

with the availability of several radiology specialists, enables even the more accessible small to medium-sized hospitals to implement the screening program.

These points have already been described in the introduction and discussion sections of the manuscript. Therefore, we do not believe that any additional revisions are necessary in order to describe or emphasize these points (see page 5, lines 78 - 83; page 15, lines 274 - 277; page 17, lines 320 - 323)

Reviewer B

Very good manuscript but needs the following clarifications/modifications:
Comment 1: Correct minor grammatical errors and make the text more concise.

Reply 1:

We really appreciate your encouraging feedback on our manuscript. As per your suggestion, we have proofread and revised the manuscript to remove any grammatical errors. The revised portions have been highlighted in the manuscript.

Comment 2: P4, L62: previous statement constradictory to the current one

Reply 2:

Thank you for this comment. However, we are unsure which statement is being referred to here. According to the original version of the manuscript, P4, L62 corresponds to the conclusion part within the abstract (copied below).

Conclusion

Public agreement and active participation of the eligible population are key factors in the successful implementation of NLCSP. Our data would be a valuable resource in building appropriate strategies to maximize the benefits of nationwide lung cancer screening.

The first sentence here states that the key factors in the successful implementation of NLCSP are public agreement and active participation of the target population. The second sentence states that our data can be used to establish policies that can potentially lead to greater public agreement and an increase in the participation of high-risk individuals in the program. In our opinion, these two sentences are not contradictory to each other. However, please let us know if there were any other sentences that seemed contradictory, and we would be happy to clarify or revise them as well.

Comment 3: Mention some sentences about how the survey is circulated, formulated and whether participation is voluntary

Reply 3:

Thank you for this comment. In the methods section, we have added a more detailed description of how the survey was conducted (see page 7, lines 124 - 128 in the revised manuscript).

Changes in the text:

However, to summarize, the respondents were chosen from across the country through a random sampling method, based on their age, geographic area, and gender. Survey responses were collected by a professional research agency that personally contacted the respondents. All respondents voluntarily participated in the survey (11).

Comment 4: P8, L162: It would be useful to guide the readers on how the authors made the argument for quality vs accesibility. I am assuming they meant people who were likely to go a large hospital favored quality.

Reply 4:

As rightly mentioned by you, people who preferred large hospitals tended to favour quality. Accordingly, we have clarified this in the revised manuscript (see page 8, lines 153 - 155 in the revised manuscript).

Changes in the text:

Participants who responded in favor of large hospitals (referral centers) instead of small hospitals were believed to have a preference for quality over accessibility, and vice versa.

References

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4. Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax 2016;71:161-70.

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