Peer Review File

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Major comments

Comment 1: Study selection The focus of this study is on the earlier ages, particularly <50yrs. However, only 10 studies were eventually included out of an initial 429 and only a few had an adequate sample size, given that the cancer rate in the initial screening was only about 1%. This is the problem with a strict systematic review. I suspect that some very good studies have been rejected because of only one or two criteria.

Response 1: Thank you very much for the comments on our work and all suggestions for improvement. As we know, there are many high-risk factors for lung cancer, such as tobacco smoking, radon, asbestos, etc. This study aimed to investigate the association between age and findings in initial CT scans. Therefore, we considered the factors above (smoking, radon, asbestos, etc.) were major confounding factors for this study. To minimize the bias, we set the strict selection criteria as you said. So, studies that focused on populations with some specific risk factors of lung cancer, such as exposure to asbestos or radiation were excluded. Hence, the cancer rate in the initial screening was about 1% because it is a study of the general population. Meanwhile, we have expanded the search builder and re-screened the literature as of October 8, 2020 (December 12, 2019, in previously). Finally, a total of 3,866 records were identified through database search, and 46 (36 studies previously) studies involving 163,442 participants were included. The conclusion based on 46 studies is similar to the results before. We hope our revised version better addresses your concerns.

Comment 2: Study selection It is not stated if all studies used the same LDCT settings and positivity criteria.

Response 2: Thank you for your reminder. We have added the LDCT settings and positivity criteria in Supplementary Table 1. Please see our revised manuscript. Thank you very much.

Comment 3: Methods In Data Synthesis, it states "Chi-squared test was used to compare the detection rates between different age groups". It needs to be stated clearly here that the analysis used Starting age as the independent variable. It also needs to be

stated how the chi-squared tests were performed. Were they only pairwise comparisons, and what was the denominator in the test (studies or participants)?

Response 3: Thank you very much for the comments. The chi-square test of independence is used to analyze the detection rate. We have revised the manuscript under your suggestion. Please kindly check the revised manuscript.

Change in the text: The Chi-square test of independence was used to compare the detection rates between different age groups under Bonferroni adjustment (Starting age of each group as the independent variable, total participants of each group as the denominator).

Comment 4: Methods For Starting age 45yrs, there were only two studies with adequate sample size. This means that pairwise comparisons between starting ages were of very different precision, and so it is difficult to interpret the p-values. Maybe a trend analysis would be preferable?

Response 4: Thanks for your valuable suggestion. As you said, it is hard for us to make pairwise comparisons across different starting ages as only two studies starting screening at 45 years of age. Therefore, we synthesized the data based on the same initial screening age (e.g. age of 40 as one group, age of 45 as another group, etc.) using single-arm syntheses weighted by sample size. The chi-square test of independence is used to analyze the detection rates. Because few RCTs and cohort studies have carried out CT screening before the age of 40, we analyzed the baseline results with CTs in our hospital and provided a trend for detection rate and age. In addition, it was found a new literature commencing screening at 35 years of age. We did not make comparisons using this cohort and only show it as a discrete point in Figure 2. We have tried our best to restate the method and analyses the data. Please kindly check the revised manuscript (Page 7, line 132-136, and Figure 2).

Comment 5: Results It is difficult to assess the results without seeing the cancer rate for each study. In particular it seems from Table S1 that there were very few cancers in the participants <50yrs old.

Response 5: Thank you for your comment. We have added the number of cancer (lung cancer and stage I cancer) in Table 1. There are 11 of 37 studies starting screening under 50 years old. However, due to the lack of individuals level data, we cannot know the exact number of cancers in the participants under 50. Thank you.

Comment 6: Results There should also be a summary table of numbers of participants, nodules, cancers, stage and screening round.

Response 6: Thank you for your suggestion. We have added the number of participants, nodules, lung cancer and stage I cancer in Table 1. We could not add the screening rounds in Table 1 since different nodules need to be followed up for different times (3 months, 6 months, 12 months, etc.), the screening rounds were not available in most studies. Please kindly check our revised Table 1.

Comment 7: Results The follow-up results are difficult to assess since no tables or figures (including Supplemental Figure 1) appear in the manuscript.

Response 7: Thank you for your suggestion. We have added the number of lung cancer and stage I lung cancer in follow-up in Table 1. Please kindly check the revised manuscript.

Comment 8: Results Since Starting age was the independent variable, it is not possible to compare cancer and stage by true age group in the Data Synthesis. The overall age difference between the four cohorts was not that great, only varying from about 56yrs to 61yrs. So it is not clear where the trends described were originating. This makes the results difficult to interpret.

Response 8: Thanks for your comment. We agree with your opinion that it is not possible to compare cancer and stage by true age group. As a result, we synthesized the data based on the same initial screening age (e.g. age of 40 as one group, age of 45 as another group) using single-arm syntheses weighted by sample size. The chi-square test of independence is used to analyze the detection rates. In addition, data from our single-center on patients who underwent chest CT scans (from April 2014 to May 2018) were analyzed as a supplementary cohort to explore trends in the overall population. Based on the above results, we consider that the population among younger age is the main reason for this trend. Thank you.

Comment 9: Discussion It was noted that the number of benign nodules increased with study starting age. It is suggested that CT scans on younger subjects are therefore "cleaner". This may be, but from a health economic point-of-view this is counteracted by there being a lower cancer rate, meaning more true negatives (i.e. wasted scans).

Response 9: Thank you very much for your valuable suggestion. In fact, we want to compare false-negative, true-negative and false-positive rates and analyze cost-effectiveness further. As you said, from a health economic point-of-view, this is counteracted by there being a lower cancer rate, meaning more true negatives. From a perspective of curing lung cancer, it may be less false positive in CT scans and a more higher rate of early stage of lung cancer. Everything has two sides. This study's design was based on the analysis of data reported in literature and we failed to access

individual-level data. This study did not address the diagnostic performance of screening. We will pay more attention to these key issues and hope can solve the problems in future research.

Comment 10: Discussion It is known that smoking history may be an even more important covariate than age. Indeed many lung cancer risk models do not even include age as a predictive factor. This should be discussed.

Response 10: Thank you for your valuable comment. We have modified our manuscript under your suggestion. Please see our revised manuscript (Page 12-13, line 233-242).

Comment 11: Discussion It is suggested that "Thus, in order to diagnose more patients at a curable stage of disease, the age threshold for lung cancer screening may require modification based on the benefits, harm, and cost-effectiveness." In fact the analysis did not consider cost-effectiveness. That would require detailed comparison of the predicted true-positive, false-negative, true-negative and false-positive rates.

Response 11: Thank you very much for your valuable suggestion. In fact, we want to compare the predicted true-positive, false-negative, true-negative and false-positive rates and analyze cost-effectiveness further. However, this study's design was based on the analysis of data reported in literature and we could not access individual-level data (e.g. the prognosis of surgery varies across ages). In addition, showing a beneficial effect of screening is a challenge, and this study did not address at the impact of adverse effects that flowed from a screen, such as the effect of over diagnosis and radiation. We will pay more attention to these key issues and hope can solve the problems in future research.

Comment 12: Discussion The manuscript does not include any comparison between the new Chinese cohort/study and the meta-analysis studies. This is important since it appears that the new cohort had an overall cancer rate of about 15% whilst in the meta-analysis studies it was only around 1%. This indicates a large difference in cancer risk between the two sets of participants.

Response 12: Thank you for your kindly reminder. We have added relevant content in the revised manuscript. Please see our revised manuscript (Page 11-12, line 217-221).

Comment 13: Conclusion It is suggested that "In summary, it is reasonable to start lung cancer screening at an earlier age than the current standard, in order to diagnose more patients at a curable stage of disease." Obviously if you widen the entry criteria more cancers will be found, but would that be cost-effective? This important question is not addressed in this paper.

Response 13: Thank you very much for your valuable suggestion. It is a big challenge to show cost-effectiveness in this populational-level analysis because individual-level data were not available. In addition, the cost of overdiagnosis (benign lesions being found after surgery) and radiation are difficult to assess. In fact, few studies focus on the commencing screening age in lung cancer, and we want to emphasize the importance of early screening by this study. We will pay more attention to these critical issues and try to solve these problems in future research. Thank you very much.

Minor comments

A few errors need correcting:

Comment 1: Table 2. The Totals and Lung cancers do not add up.

Response 1: Thank you for your kind reminder. We have correct the number. Please kindly check the revised Table 2.

Comment 2: Table S1: The Median age is incorrect for the Lanni study.

Response 2: Thank you for your kind reminder. We have revised the Median age in Table S1. Please kindly check.

Comment 3: Table S1: The last two columns are percentages not frequencies.

Response 3: Thank you for your kind reminder. We have replaced "frequencies" with "percentage". Please kindly check.

Comment 4: In the Introduction two statements are difficult to understand because of incorrect English grammar: "However, it is not clear that the association between age and findings in initial CT scans for the reason that no screening began before age of 40." "Understanding the findings in CT scans is conducive to formulating detailed screening programs further."

Response 4: Thanks for your kind comment. We apologize for the confusion generated by the previous version of the manuscript and sincerely hope that our logic is now easier to follow with this new version.
Changes in the text (Page 5, line 90-93): "However, the relationship between age and initial CT scan results is unclear, as few screening programmes have been performed before the age of 40." "Understanding the results of the CT scan (e.g. the association between age and lung cancer) will help to develop a detailed screening strategy."

Comment 5: Note that the statistical software SPSS is just "SPSS" not "Statistical Product and Service Solutions".

Response 5: Thank you for your suggestion. We have revised it in the manuscript. Please kindly check.