

The reviewer and editor comments and point-by-point authors responses

Reviewer A

Thank you for the opportunity to review this manuscript.

The authors found that 72.9% of lung cancer patients did not meet the NLST criterion of smokers with ≥ 30 pack-years of smoking. The OR of lung cancer detection in smokers with ≥ 30 pack-years of smoking was higher than that in never-smokers. However, the OR of lung cancer detection in smokers with < 30 pack-years of smoking was the same as that in the never-smokers. The authors therefore suggest that never-smokers and smokers with < 30 pack-years of smoking should be included in the target population for LDCT screening.

This manuscript contains important scientific information; however, I have a few more questions.

1. This study included 12,114 subjects. How was informed consent obtained from each of the participants?

Reply 1: A document explaining the contents of the screening and a questionnaire were mailed to the participants in advance. The document included the contents of the two-day screening, an explanation of the benefits and disadvantages of the screening, and a signing page to confirm consent. Just prior to the first day of screening, well-trained professionals explained the content, benefits, and disadvantages of cancer screening to each of the participants face-to-face. The participants had to agree to undergo cancer screening and sign the consent form as an indication of consent.

Changes in the text: We added the following sentences, on Page 7 to Page 8.

A document explaining the contents of the cancer screening and a questionnaire were mailed to the participants in advance. The document included the contents of the two-day cancer screening, an explanation of the benefits and disadvantages of the cancer screening, and a signing page to confirm consent. Just prior to the start of the first day of cancer screening, well-trained professionals explained the contents, benefits, and disadvantages of the cancer screening to each of the participants face-to-face. In order to participate in this cancer screening study, the participants had to sign the consent form as an indication of consent.

2. How were the pack-years of smoking measured? Was this based on medical records or objective collections? Please provide detailed information.

Reply 2: The pack-years of smoking were measured based on the results of questionnaires completed by the participants, and the responses in the questionnaires were confirmed face-to-face by well-trained professionals on the first day of cancer screening.

Changes in the text: We added sentences, as follows, on Page 8.

Information on the pack-years of smoking and status of exposure to second-hand smoke entered in the questionnaire were confirmed, face-to-face, by well-trained professionals just prior to the start of the first day of cancer screening.

3. Please use the 8th edition of the TNM staging system.

Reply 3: We reclassified the stages of lung cancer using the 8th edition of the TNM staging system. However, the authors of a paper related to the National Lung Screening Trial published in 2019

used the 7th edition of the TNM staging system. In addition, the researchers in the NELSON trial, the results of which were presented at the 19th World Conference on Lung Cancer in 2018 in Toronto§, used the 7th edition of the TNM staging system. Therefore, we have shown our results based on the 7th edition of the TNM staging system in Table 2, and the results based on the 8th edition of TNM staging system as supplemental data.

¶. The National Lung Screening Trial Research Team. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019;10:1732-142.

§. de Koning HJ. Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population-based screening trial. This study was published in the following paper. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020 Feb 6;382(6):503-513.

Changes in the text: We have added the following sentence to the footnote for Table 2 on Page 37: The results based on the 8th edition of TNM staging system are shown as supplemental data. We have also included the supplemental data on Page 39.

4. Please provide detailed information about lung cancer treatment.

Reply 4: Information for writing this paper is anonymized. Treatment is broadly classified as surgery, radiation therapy, and chemotherapy, but no further details are included in the anonymized data file. Therefore, we cannot provide detailed information about lung cancer treatment.

5. Multivariable analyses should be performed to clarify significant difference between the participants detected as having lung cancer in the never-smoker and smoker groups.

Reply 5: Frankly speaking, the corresponding author, i.e., Dr. Kakinuma, has already retired from the National Cancer Center. Although Dr. Kakinuma goes to the National Cancer Center every few months as a visiting researcher, new variables for additional multivariable analyses cannot be prepared in the short term.

Changes in the text: We have changed the title of the paragraph on Page 18. We have also changed the title of Table 4 and added information on age and gender adjustment for the multivariate analysis in the footnote on Page 38. We have added the following sentence to a paragraph in the *Study limitations* section on Page 27: Third, the multivariable odds ratio of lung cancer detection might be influenced by unmeasured confounding variables because we showed the results based only on adjustment for age and gender. Further evaluation is warranted.

Editor

1. In the text, references should be identified using numbers in round brackets in which they appear consecutively [e.g., "cancerrelated mortality (19)"; "denocarcinoma (29,30)"], they shouldn't be superscript.

Reply 1: We have shown the reference numbers in round brackets.

Changes in the text: The reference numbers are shown in round brackets.

2. Please provide Figure 1 with an editable form (i.e., .ppt, .doc, .eps format, etc.) for copy-editing, in which the words can be copied/edited directly. Attached please find some examples.

Reply 2: We have changed Figure 1 on the slide to an editable form.

3. Please provide the first column heading for Table 2.

Reply 3: We have used “Characteristics” as the heading for the first column in Table 2 on Page 35.

| 4. Please provide the number/ID of the Ethical approval as follows:

Reply 4: We have provided the Ethical approval number on Page 7.

Changes in the text: This study was performed with the approval of the institutional review board of the National Cancer Center (No. 2005-32).