Correspondence

Patient factors to consider before lung cancer screening

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We would like to appreciate Dr. Fan and Dr. Liu for bringing up an important issue about who should be screened for lung cancer in Asian population through their editorial entitled "*Lung cancer screening using low dose CT: screening population and positive results definition*" (1).

The benefit of lung cancer screening was proved by reducing lung cancer mortality in the low-dose computed tomography (LDCT) screening group compared to the chest X-ray (CXR) screening group as a result of National Lung Screening Trial (NLST) in the U.S. announced in October 2010 (2). However, lung cancer screening trials in Europe, which were smaller randomized controlled clinical trials compared to NLST, could not support the results of NLST because the mortality reduction was not significant with LDCT screening (3). The reduction of lung cancer mortality can be obtained by detecting lung cancers in their early stages and consequently managing with definitive surgery because 5-year survival rate is declining sharply as the clinical stage advances (4). But, unfortunately chest radiography and sputum cytology did not prove its usefulness in reducing mortality in lung cancers (5,6) and CT was expected to play a better role as a screening tool for the lung cancers since the CT provides cross sectional images of the thorax and makes it easier to identify lung parenchymal nodules and airway lesions. With excitement, NLST started as a randomized controlled clinical trial which was designed to screen persons aged 55 to 74 years who have cigarette smoking histories of 30 or more pack-years (2). This screening subject have been selected because the old age and cigarette smoking are well-known risk factors for lung cancers and the screening should be effective in the population at higher risk for lung cancer. Even though the NLST was ended up with positive results for lung cancer screening, it elicited many kinds of debate including who should be screened, how often and how long should be screened, and how to manage nodules found during LDCT screening for it to be effective for public health improvement.

In contrast with NLST results, clinical trials in Europe did not prove significant mortality reduction so far (3). All these clinical trials from the United States and European countries were designed to screen the high-risk subjects; high-risk group was defined in accordance with age and smoking history. In our retrospective cohort study including the subjects of various risk factors (7), the survival benefit of lung cancers was not obtained with LDCT screening compared to CXR screening in high-risk subjects. Whereas survival benefit of screening-detected lung cancers was significantly better with LDCT screening in non-high-risk subjects. In our study, the risk groups were defined according to NLST or European trial criteria and non-high-risk group was the younger and with the less smoking history compared to high-risk group in our study. The screen-detected lung cancers in non-high-risk and female never-smoker groups were predominantly adenocarcinomas (95–100%) in terms of cancer cell types and more frequently part-solid or nonsolid (68–77%) in nodule characteristics. Therefore, we concluded that the survival benefit in subjects having screening-detected lung cancers was mostly from resecting early-stage lung adenocarcinomas rather than managing rapidly progressing squamous cell carcinomas or small cell lung cancers which were closely related to heavy smoking. In the subset analysis of NLST by Pinsky *et al*. (8), the mortality relative risk of adenocarcinoma showed significantly below 1, thus demonstrating a substantial LDCT screening benefit, whereas the mortality relative risk of squamous cell carcinoma was not significantly different from 1 (0.75, less deaths in LDCT-detected adenocarcinoma

patients than CXR-detected adenocarcinoma patients). The mortality relative risk of squamous cell carcinoma was 1.23, suggesting no benefit from LDCT screening. In subset analysis for sex in this study, the mortality relative risk for women with LDCT screening found to be more protective compared to CXR screening than that for men (0.73 in women *vs.* 0.92 in men) with borderline significance (8).

With growing insight on genetic mutation and lung cancer subtypes, the subtypes of lung cancer can be classified according to its genetic alteration. Lung cancers with epidermal growth factor receptor (EGFR) mutations show a tendency to present with CT features of nonsolid or part-solid nodules (9). The main advantage of LDCT screening for lung cancers may be in the detection of nonsolid and part-solid nodules which can be missed with chest radiography. In Asian population, the incidence of EGFR mutation in lung cancer is high, especially in women. Therefore, LDCT screening may play a better role in detecting the lung cancers with EGFR mutation in Asian women. On the other hand, nonsolid nodules demonstrate overly slow growth thus annual screening for detecting the nonsolid nodules seems to be ineffective. Thus, further investigation need to be implemented and published regarding the usefulness of LDCT screening in Asian women particularly in terms of the mortality benefit. In conclusion, age and smoking status may not be the major factors for defining the screening group who could potentially benefit from LDCT screening, whereas subjects' sex and histologic subtype may be important factors related to a potential benefit from LDCT lung cancer screening.

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Footnote

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