Original Study

Assessment of Selection Criteria for Low-Dose Lung Screening CT Among Asian Ethnic Groups in Taiwan: From Mass Screening to Specific Risk-Based Screening for Non-Smoker Lung Cancer

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Abstract

We aim to investigate the impact of applying the NLST eligibility criteria to the population in Taiwan, and to identify additional risk factors to select subjects at risk of lung cancer. Our findings suggest that female gender and a family history of lung cancer are two important predictor. A prospective study design based on survival analysis in non-smoker lung cancer screening is warranted.

Background: The National Lung Screening Trial (NLST) showed low-dose screening chest computed tomography (CT) reduced the lung cancer mortality rate up to 20% in high-risk patients in the United States. We aimed to investigate the impact of applying the NLST eligibility criteria to the population in Taiwan, and to identify additional risk factors to select subjects at risk for lung cancer. **Patients and Methods:** We retrospectively reviewed the medical records of 1763 asymptomatic healthy subjects (age range, 40-80 years) who voluntarily underwent low-dose chest CT (1029 male, 734 female) from August 2013 to August 2014. Clinical information and nodule characteristics were recorded. The results of subsequent follow-up and outcome were also recorded. **Results:** A total of 8.4% (148/1763) of subjects would have been eligible for lung cancer screening based on the NLST criteria. However, only 1 of these eligible subjects would have a lung cancer detected at baseline. Among the 1615 subjects who did not meet the NLST criteria, the detection rates of lung cancer were 2.6% in women and 0.56% in men. Logistic regression showed that female gender and a family history of lung cancer were the 2 most important predictors of lung cancer in Taiwan (odds ratio, 6.367; $P = .003$; odds ratio, 3.017; $P = .016$, respectively). **Conclusions:** In conclusion, NLST eligibility criteria may not be effective in screening for lung cancer in Taiwan. A risk-based prediction model based on the family history of lung cancer and female gender can potentially improve the efficiency of lung cancer screening programs in Taiwan.

Clinical Lung Cancer, Vol. ■, No. ■, 1-7
Keywords: Adenocarcinoma, Lung cancer, Lung-RADS, Screening criteria, Smoking

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Submitted: Dec 10, 2015; Revised: Mar 11, 2016; Accepted: Mar 21, 2016

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Introduction

Lung cancer has been the leading cause of cancer-related mortality worldwide among both men and women in recent years.[1,2] The general prognosis of lung cancer is poor, as close to 70% of lung cancers are diagnosed at advanced stages.[3-5] The National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung–cancer-specific mortality with low-dose computed tomography (LDCT) compared with chest radiography when applied to a high-risk population (age, 55-74 years; current or former smokers who quit within 15 years with at least 30 pack-years of smoking history).[6] Worldwide, it is estimated that the prevalence rate of smoking is 5 times greater for men compared with women, but the ratio varies

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2016.03.004

dramatically across countries.[7] In Taiwan, the smoking rate among men has decreased from 60.4% in 1980 to 35.0% in 2010. By contrast, the prevalence of smoking among women has remained fairly constant and lingered at around 5% until 2010.[8] The difference in smoking prevalence between men and women has given rise to a dramatic change in the male to female lung cancer incidence ratio from 2.17:1 in 1995 to 1.6:1 in 2012.[5,9]

Smoking is the major risk factor for lung cancer, but lung cancer in women who are non-smokers is on the rise, especially in Asia.[10-13] Overall, 70.5% of all subjects with pulmonary adenocarcinoma were non-smokers in Taiwan. Women with pulmonary adenocarcinoma were more likely to be non-smokers than men (95.8% vs. 38.4%; $P < .001$), based on the Cancer Registry Annual Report 2012, Taiwan.[5]

Whether the NLST screening criteria is appropriate for the population outside of the United States remains an important question. The aim of this study was to clarify the impact of applying the NLST eligibility criteria to the population in Taiwan, and to identify additional risk factors to identify subjects not meeting NLST criteria within the population.

Methods

Screened Population

This retrospective cohort study was approved by the Medical Ethics Committee of Kaohsiung Veterans General Hospital, which approved the study protocol.

The requirement for written, informed consent was waived owing to the retrospective study design. From August 2013 through August 2014, a total of 1763 consecutive asymptomatic participants underwent self-paid LDCT of the chest for lung cancer screening (1029 male, 734 female) at our institution. The only inclusion criterion for subjects was age > 40 years. The exclusion criterion was a known history of lung cancer. Clinical information and healthcare records, including a family history of lung cancer and other cancers in first- and second-degree relatives, past history of chronic obstructive pulmonary disease (COPD), old pulmonary mycobacterial infection, and active pulmonary mycobacterial infection, were recorded by the nursing staff. Self-reported individual cigarette smoking history was recorded, including the number of cigarettes smoked per day and the duration of smoking for current smoking and former smoker, and, if applicable, the number of years since smoking cessation.

Low-Dose Chest CT Acquisition, Initial Imaging Interpretation, and Follow-up Recommendation

All scans were performed with a 16-slice multi-detector CT (Somatom Definition AS, Siemens Healthcare, Erlangen, Germany) or a 64-slice multi-detector CT (Aquilion 64; Toshiba Medical Systems) from the lung apex to the base without contrast enhancement. Scans were obtained with the subjects in supine position at end inspiration. The scanning parameters were 120 kVp, 50 mA, 1 mm collimation, and 1.5:1 pitch. The data were reconstructed with filtered back projection, a slice thickness of 2 mm, and an increment of 2 mm, using a smooth convolution kernel (Siemens B30f or Toshiba FC02). We also recorded the radiation exposure in dose-length product (conversion factor k = 0.014 mSv/mGy cm).

All studies were evaluated on lung and mediastinal windows on a picture-archiving and communication system and reported by 2 thoracic radiologists (FZW and YLH) with 7 and 11 years of experience, respectively. For participants with no pulmonary nodule at baseline, no further follow-up was recommended. For participants with pulmonary nodules, follow-up and management recommendations were made according to the Fleischner Society guidelines for incidental solid and subsolid lung nodules, as the American College of Radiology (ACR) management guidelines were not yet available during the initial enrollment period, and the inclusion criteria of the lung cancer screening program at our institution differ significantly from those in the United States (US).[14-16] The average follow-up time of subjects with suspicious nodules was 1.2 ± 0.46 years after initial LDCT.

Retrospective Assignment of the American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) Categories

The LDCT were retrospectively reviewed again by 2 experienced thoracic radiologists (FZW and YLH), with 7 and 11 years of experience in thoracic radiology, respectively. The attenuation, size, and number of nodules were recorded, and retrospectively classified into 4 categories according to the Lung-RADS classification system shown in the Supplemental Table 1 (available in the online version). The Lung-RADS classification in the baseline screening of the 1763 subjects enrolled in this study is shown in the Supplemental Table 2 (available in the online version).[13,17] In summary, for baseline screenings (in the absence of comparison examinations), the criteria are based on nodule size, as measured by average diameter, and nodule attenuation (solid, part-solid, or nonsolid). Categories 1 (negative) and 2 (benign appearance) correspond to negative screening results, and categories 3 (probably benign) and 4 (suspicious) correspond to positive screening results. Category 4 is further divided into 4A, 4B, and 4X, based on the level of suspicion. For baseline screenings, positive screening results for solid and part-solid nodules require a diameter of 6 mm, and for ground-glass nodules, an average diameter of 20 mm. The overall Lung-RADS screening category is determined by the nodule with the highest individual Lung-RADS score. Category 3 or 4 nodules with additional features (such as spiculation) or imaging findings that increase suspicion for cancer (such as enlarged lymph nodes) can qualify as category 4X.[13,17]

Statistical Analysis

All statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL). Continuous variables are presented as mean ± SD. Differences in continuous variables between 2 groups were compared by the independent Student *t* test. Categorical variables were summarized as frequencies and percentages and compared using the chi-square test to examine differences in demographic characteristics between men and women. The Fisher exact chi-square test was used to analyze the prevalence of lung cancer by gender. An additional analysis investigated differences in positive scan results among 2 subgroups classified by presence of "family history of lung cancer." The statistical significance for all tests was set at $P < .05$. Multivariate logistic regression was used to determine risk predictors for lung cancer, nodules with positive scan, and nodules with category 4 adjusted for clinical risk factors.