

Management of pulmonary nodules in non-high-risk population: initial evidence from a real-world prospective cohort study in China

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To the Editor: Lung cancer continues to be the most common cause of tumor-related death globally. Screening by low-dose computed tomography (CT) has been proven to greatly reduce the mortality of lung cancer patients. Although the recommended screened population varies among different guidelines, elderly smokers are always the most important subjects. However, a substantial group of lung cancer patients has been found to be young without tobacco consumption.^[1] Non-smoking lung cancer was even considered to be an independent disease and the seventh leading cause of cancer mortality. From the conventional point of view, these young non-smokers are not at high risk of lung cancer and are generally excluded for screening or management.^[2] Whether the non-high-risk individuals should be given attention to is not clear.

A prospective cohort study was initiated by West China Hospital of Sichuan University, China, to investigate the lung cancer incidence in high-risk or non-high-risk population. This is a real-world observation, and the participants were divided into a non-high-risk group or high-risk group, evaluated by the Chinese Expert Consensus on Diagnosis and Treatment of Pulmonary Nodules (2018 Edition). Non-calcified nodules with 4 mm or larger in diameter or suspicious lesions in the trachea or bronchus were regarded as positive findings and these subjects were included. Here, the initial results of the first two and half years were reported.

Ethical approval from the institutional review board at West China Hospital, Sichuan University, China (No. 2016-85) was obtained. The clinical data of subjects who underwent CT scanning for routine physical examinations or any other clinical requests with positive results at West China Hospital of Sichuan University since April 2018 were potentially

collected with informed consent. In case of multiple pulmonary nodules, the dominant one was selected.^[3] There were no specific exclusion criteria except that participants did not complete questionnaires for risk assessments or had a history of lung cancer before enrollment.

According to the Chinese Expert Consensus on Diagnosis and Treatment of Pulmonary Nodules (2018 Edition), the high-risk population of lung cancer in China was defined as those who were over 40 years old and had any of the following risk factors: current smoking for >20 pack-years, or having ever smoked for >20 pack-years and quitting smoking within 15 years; having a history of environmental or high-risk occupational exposure (such as asbestos, beryllium, uranium, radon, etc.); complicated with chronic obstructive pulmonary diseases (COPD), diffuse pulmonary fibrosis or previous history of pulmonary tuberculosis; having a history of malignant tumor; having a family history of lung cancer. Participants were categorized into two cohorts, non-high-risk or high-risk, on the basis of this evaluation. Clinical decisions about further follow-up strategies or diagnostic procedures were made by the experienced pulmonologists based on the Chinese consensus. The pathological diagnosis of lung cancer was made in line with the World Health Organization criterion, and the clinical stage was determined according to the International Association for the Study of Lung Cancer Lung Cancer Staging Project (Eighth Edition).

The primary outcome of this study was the detection rate of lung cancer in the non-high-risk and high-risk cohorts, which was calculated by the patients diagnosed with lung cancer to all the participants in each group. The secondary outcomes were the clinical stages and histopathological subtypes of detected lung cancers.

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Characteristics between the non-high-risk and high-risk cohorts were compared by Student's *t*-test for the continuous variables of age and nodule diameters, while χ^2 test was used for the rest of the categorical variables (Fisher exact tests when necessary). *P* value <0.05 was considered to be statistically significant. All the data analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

During the first study period between April 2018 and September 2020, a total of 2173 subjects with positive findings in chest CT scanning were invited. Four volunteers failed in completing the questionnaires for risk factor evaluation, and ultimately 2169 were eligible for this analysis. There were 1368 non-high-risk individuals (63.07%) and 801 high-risk participants (36.93%). Totally, 2196 positive lung nodules were detected in the non-high-risk group, whereas 1374 positive nodules were found among the high-risk cohort.

Until September 30, 2020, the follow-up interval was between 0 and 30 months for all participants, with a median time of 16 months. Four hundred forty-nine cases were confirmed by pathological examinations, including 303 in the non-high-risk group and 146 in the high-risk group. As shown in Supplementary Table 1, <http://links.lww.com/CM9/A821>, there were 390 lung cancers (86.86%) and 59 cases of benign diseases (13.14%) in all the patients receiving pathological examinations. For the 1368 non-high-risk participants, 264 lung cancers were identified with a lung cancer detection rate of 19.30% (264/1368), which was significantly higher than that in the high-risk group (15.73%, 126/801, $\chi^2 = 4.361$, *P* = 0.037). This was the most important result of the current study. The mean age of the lung cancer patients without risk factors was 51.89 ± 11.48 years (ranged 26–79 years), much younger than the risk ones (ranged 40–83 years with an average of 57.28 ± 9.34 years, *t* = -4.937, *P* < 0.001). In particular, there were 44 cases of lung cancer patients <40 years old, accounting for 16.67% (44/264) of the non-high-risk lung cancers and 11.28% (44/390) of all detected lung cancers. The proportion of lung cancer patients <50 years in the non-high-risk group was also much greater than the high-risk group (45.45% *vs.* 23.02%, $\chi^2 = 18.190$, *P* < 0.001). The results indicated that lung cancer cases without risk factors were more likely to be younger. In addition, females with lung cancer were also more frequent in the non-high-risk group (77.27% [204/264] *vs.* 50.00% [63/126], $\chi^2 = 29.382$, *P* < 0.001). As expected, in the non-high-risk group, the percentages of patients with active smoking, passive smoking, history of chronic comorbidities (tumors, pulmonary fibrosis, COPD, and pulmonary tuberculosis), family history of lung cancer, and occupational exposure were all significantly lower than those in the high-risk cohort (all *P* < 0.05).

The majority of cancerous nodules in the two groups were subsolid (78.03% [206/264] out of non-high-risk *vs.* 79.37% [100/126] out of high-risk, *P* = 0.764), especially pure ground glass nodule, accounting for >50% (50.38% [133/264] *vs.* 57.94% [73/126], $\chi^2 = 0.090$, *P* = 0.320). For the clinical stage, 92.82% of detected lung cancers were in

stage I (362/390). Specifically, in the non-high-risk group, 243 cases (92.05%) were classified as stage I, and 229 cases (86.74%) in stage IA. On the other hand, 119 lung cancer patients in the high-risk group were in stage I (94.44%) and 109 in IA (86.51%). The clinical stages of the two groups were similar (*P* = 0.072). Regarding the pathological types, lung adenocarcinoma was predominant in the two groups without a significant difference (94.32% [249/264] *vs.* 94.44% [119/126], *P* = 0.717).

Based on the results above, only 36.93% of the participants with positive CT findings could reach the standard of the high-risk population of lung cancer. Moreover, 2196 positive pulmonary nodules were found in the non-high-risk group, accounting for 61.51% (2196/3570) of all positive pulmonary nodules. Also, in all of the 390 cases of lung cancer patients diagnosed, 264 subjects (67.69%) did not conform to the characteristics of high-risk individuals of lung cancer. These results suggested that if we solely focused on the high-risk population of lung cancer according to the existing guideline, >60% of positive lung nodules and lung cancer patients would be ignored. In addition, 44 lung cancer patients were <40 years old, accounting for 11.28% (44/390) of all detected lung cancer, and they were all non-high-risk individuals. Another study^[4] among the population receiving health examination in China by our research group found that in the 15,996 participants completing the baseline screening, 142 cases of lung cancer were detected. However, only 24.40% of the lung cancer patients were high-risk individuals by the Chinese screening guideline evaluation. If only the high-risk subjects were enrolled, the missed diagnosis of lung cancer was as high as 75.60%.^[4] This so-called “non-high-risk population” does not seem to be as dispensable as previously considered.

Furthermore, compared with the high-risk group, the lung cancer detection rate of the non-high-risk population was even notably higher (19.30% *vs.* 15.73%, *P* = 0.037). The result strongly indicated that the screening and management for non-high-risk individuals, identified by the previous standard, should not be neglected. Moreover, up to 92.05% of the detected lung cancer patients in the non-high-risk cohort were in stage I, which was also similar to the clinical stage distribution of lung cancer patients with high-risk factors (92.05% [243/264] *vs.* 94.44% [119/126], $\chi^2 = 15.429$, *P* = 0.117). These findings deserved further attention for screening and management in non-high-risk subjects as well as those in high-risk group. In a recent commentary, non-high-risk individuals were recommended to receive lung cancer screening with an interval of 5 to 10 years.^[5]

Certainly, there were several limitations of this study. First, it was not a randomized controlled trial but a real-world cohort investigation in a single center. To overcome the tremendous amount of work on subjects without positive pulmonary nodules, only participants who were detected with nodules of clinical significance were enrolled. Second, the follow-up time of the cohort was not long enough and most of the patients with positive nodules are still being followed up with the final data unavailable at present. Third, the enrolled subjects were not representative of the

general population of China, as they received CT scanning and medical consultations at our hospital, which is one of the top hospitals nationwide. Therefore, they were probably at least of middle to high socioeconomic status.

In spite of these limitations, our data suggested that lung cancer screening or pulmonary nodule management focused on high-risk population only may lead to a great escaping diagnosis of lung cancer, and most of them are in the early stage. More attention should be given to the large group of non-high-risk individuals, and the value of lung cancer screening in the non-high-risk group needs further exploration.

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Conflicts of interest

None.

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