Should Nonsmokers Be Excluded from Early Lung Cancer Screening with Low-Dose Spiral Computed Tomography? Community-Based Practice in Shanghai

Xiaoyang Luo*,†,2, Shanbo Zheng*,†,2, Quan Liu†,§, Shengping Wang†,‡, Yuan Li†,§, Lei Shen†,§, Guodong Li†,‡, Wentao Li†,‡, Yanping Zhao, Huilin Xu†, Jing Wang, Xiaohua Liu, Yunjian Pan†,‡, Hong Hu*,†, Yihua Sun*,†, Haiyan Yang, Su Xu**, and Haiquan Chen*,†

*Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China 200032; †Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China 200032; ‡Department of Radiology, Fudan University Shanghai Cancer Center, Shanghai, China 200032; §Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China 200032; ¶Center for Disease Control and Prevention, Minhang District, Shanghai, China 201100; #Health and Family Planning Commission of Minhang District, Shanghai, China 201100; **Shanghai Municipal Health and Family Planning Commission, Shanghai, China 200125

Abstract

**OBJECTIVE:** We investigated the efficacy of early lung cancer screening with low-dose spiral computed tomography (LDCT) in both smokers and nonsmokers based on the current situation of community health service, with integration of superior resources of medical institutions at all levels in Shanghai. **METHODS:** From August 2013 to August 2014, we screened 11,332 (male 7144; female 4188) high-risk individuals in selected communities of Minhang, Shanghai City, for early diagnosis of lung cancer with LDCT combined with multidisciplinary comprehensive treatment pattern including minimally invasive surgery, exploring the medical service network covering prevention, diagnosis, treatment, rehabilitation, and follow-up. **RESULTS:** Screening resulted in a diagnosis of cancer in 29 participants. Of these participants, 27 had primary lung cancer, 1 had lung metastatic cancer, and 1 had breast cancer. The detection rate of primary lung cancer was 238.26 cases per 100,000 person-years among all the participants. Specifically, the incidence of primary lung cancer was 336.97 cases per 100,000 person-years among the nonsmoking participants, as compared with 159.06 cases per 100,000 person-years among the smoking participants ($P = .054$). Among the 27 primary lung cancers, 22 (81.48%) had stage 0 to I lung cancer. **CONCLUSION:** Based on community health service, screening with LDCT could improve the early diagnosis rate of lung cancer in both smokers and nonsmokers with feasibility and validity, which could be applicable in qualified eligible medical centers and communities in China. It is not reasonable to exclude nonsmokers from screening with LDCT.

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Address all correspondence to: Haiquan Chen, MD, FCCP, Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China 200032. E-mail: chenhq@shca.org.cn

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2 These authors contributed equally to this work.

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Introduction
Lung cancer is the leading cause of cancer-related deaths worldwide, with more than 1.6 million new cases and 1.4 million deaths each year [1]. China is the largest consumer of tobacco in the world. The 2015 Chinese Adults Tobacco Survey Report revealed that, in 2015, about 27.7% of Chinese adults (defined as age ≥ 15 years; 52.1% of men and 2.7% of women), corresponding to more than 316 million people, were current smokers, and average daily consumption was 15.2 cigarettes [2]. In 2010, the Global Adult Tobacco Survey reported similar results. Furthermore, they showed that among those who had smoked at some time, only 16.9% had quit smoking and were not smoking currently, whereas 33.1% had quit smoking in the past but were currently smoking [3]. If the high smoking prevalence among Chinese adults persists, deaths in China caused by tobacco will rise from about 1 million in 2010 to 2 million in 2030 and 3 million in 2050 [4]. With the huge smoking population, the morbidity and mortality of lung cancer are expected to remain high in the coming decades in China. Early diagnosis and rational treatment are key methods to improve the prognosis of lung cancer.

There are still many problems to be explored in early-stage lung cancer screening in China’s current health service status. In this collaborative study, we carried out an early lung cancer screening project among high-risk population in pilot communities based on current community medical service in Shanghai and integration of medical institutions at different levels, aiming to explore a comprehensive work pattern for screening of this lethal disease.

Methods
From August 2013 to August 2014, we conducted an early lung cancer screening program in selected communities including Wujing, Gumei, Jiangchuan, Pujiang, Xinzhuang, Zhuanqiao, and Maqiao in Minhang District of Shanghai. Participants were inhabitants of these communities who were a high-risk population of lung cancer. This program was based on a previously founded database of high-risk population of lung cancer and combined medical resources from university hospitals, disease control institutions, and community health service centers. We explored a community-based lung cancer comprehensive prevention and control network using low-dose spiral computed tomography (LDCT) in a high-risk population of lung cancer.

We recruited participants according to the following eligibility criteria: age 50 to 80 years; asymptomatic; no history of malignant disease in the recent 5 years; adequate performance status (assessed on the basis of the patient’s eligibility to undergo thoracic surgery and no lethal disease); and 1) current or former smokers (quit smoking for less than 5 years) with a minimum of 20 pack-years smoking history, 2) passive smokers, or 3) never smokers with other risk factors of lung cancer including lung cancer family history, history of kitchen fume, or dust exposure. All participants gave written informed consent, and the ethics committee of Fudan University Shanghai Cancer Center approved the study.

In this multicenter collaborative study, we used LDCT and computer-aided detection for screening. The protocol of baseline screening was shown in Figure 1, and protocol of annually repeat screening was shown in Figure 2.

The imaging criteria were the same for baseline and annual LDCT screening. Unenhanced CT scans of the chest were made with Siemens Somatom 64-multidetector spiral CT scanners with a low-dose protocol: 120 kVp, 40 mA, and 1.5-mm collimation.
Minimally invasive surgery of positive patients was performed by Fudan University Shanghai Cancer Center. The specimens obtained from participants who underwent surgical resection were independently examined by two experienced pathologists.

Rehabilitation and follow-up after treatment were done by Fudan University Shanghai Cancer Center, the Sixth People’s Hospital Affiliated to Shanghai Jiaotong University, Xinhua Hospital Affiliated to Shanghai Jiaotong University, Minhang Cancer Center, Wujing hospital, Gumei, Jiangchuan, Wujing, Pujiang, Xinzhuang, Zhuanqiao, and Maqiao Community Health Service Center.

Data analysis was done by Fudan University Shanghai Cancer Center and Minhang District Health and Family Planning Commission.

**Results**

Thirteen thousand three hundred and twenty-two persons were enrolled from August 2013 to August 2014. Average age was 63.46 ± 6.79 years; 7144 (53.6%) were men. Table 1 shows the clinical characteristics of participants. At baseline examination, we detected 253 pulmonary nodules in 195 participants. The detailed information of these nodules is listed in Table 2. Primary lung cancer was pathologically diagnosed in 27 individuals, including 24 adenocarcinomas, 2 squamous cell carcinomas, and 1 malignant pleural effusion (Table 3). In addition, one metastatic lung cancer and one breast cancer were diagnosed. Fourteen participants underwent surgery for benign disease because of false-positive results, and the
distribution according to the type of diseases is shown in Table 4. The incidence of the primary lung cancer in baseline screening was 238.26/100,000. Twenty-two cases were diagnosed as stage 0 to I lung cancer, accounting for 81.48% of primary lung cancer. Specifically, the incidence of primary lung cancer was 336.97 cases per 100,000 person-years among the nonsmoking participants as compared with 159.06 cases per 100,000 person-years among the smoking participants ($P = .054$, Table 5).

Discussion
Lung carcinoma is the most fatal cancer worldwide, with a 5-year survival rate of only 16% [5]. Most early lung cancer patients have no clinical symptoms. Cough, chest pain, sputum with blood, and other clinical symptoms are often presented in advanced-stage patients. However, the cost for advanced lung cancer is high, and the prognosis is poor. Results from the International Early Lung Cancer Action Program demonstrated that the estimated 10-year survival rate of clinical stage I lung cancer was 88% (95% CI, 84-91), and among those with clinical stage I lung cancer who underwent surgical resection within 1 month after the diagnosis, the rate was 92% (95% CI, 88-95) [6]. To explore a practical and feasible method for early lung cancer screening, a series of clinical studies has been carried out. Early detection trials from Mayo Clinic with conventional sputum cytology and chest radiography proved unable to decrease lung cancer
Air pollution is suspected to be one of the etiologies of lung cancer [14]. Relationship between kitchen fume or inspirable fine particles and lung cancer carcinogenesis has not been clearly demonstrated. How to define the exposure dosage of kitchen fume and inspirable fine particles and include these risk factors into lung cancer screening is also a public health problem.

The radiation dose of LDCT is much less than that of ordinary CT [15]. A new generation of dual-source CT has a lower radiation dose. It is suggested that the interaction between radiation and smoking could increase the risk of lung cancer [16].

In making decisions about instituting cancer screening in communities, a number of factors need to be taken into consideration, including the sensitivity and specificity of the examination, cost-effectiveness, and even the customs and habits. Cancer screening in the community population should be acceptable for inhabitants, families, and society [9,13]. At present, it is generally believed that lung cancer patients detected by LDCT screening are mainly early-stage ones. Surgery for early-stage lung cancer is less than half the cost of late-stage treatment and results in better outcome [17]. Furthermore, a recent study suggested that lung cancer screening combined with smoking cessation guidance could reduce tobacco consumption [18].

In conclusion, it has become a consensus that LDCT screening can lead to early detection and intervention of lung cancer and improve the survival of lung cancer patients. More clinical data and community experience are needed for guiding the practice of LDCT screening in both smoker and nonsmoker populations of lung cancer in China. Shanghai community-based practice of early lung cancer screening with LDCT has improved the early diagnosis rate of lung cancer. We found LDCT screening for lung cancer among smoking and nonsmoking individuals to be feasible and could be applicable in qualified eligible medical centers and communities in China.

### Table 1. Clinical Characteristics of Participants

| Characteristics | Male (n, %) | Female (n, %) |
|-----------------|------------|---------------|
| Age             |            |               |
| 50-60 years     | 2506 (35.08%) | 1507 (35.98%) |
| 60-70 years     | 3568 (49.94%) | 1585 (37.85%) |
| 70-80 years     | 1070 (14.98%) | 1096 (26.17%) |
| Smoking history |            |               |
| Never smoker    | 522 (7.31%) | 1380 (32.95%) |
| Smoker          |            |               |
| Smoking dose ≤ 10 pack-years | 608 (8.51%) | 25 (0.60%) |
| Smoking dose 10-20 pack-years | 683 (9.56%) | 11 (0.26%) |
| Smoking dose 20-40 pack-years | 4558 (61.01%) | 7 (0.17%) |
| Smoking dose >40 pack-years | 592 (8.29%) | 3 (0.07%) |
| Passive smoker  | 381 (5.33%) | 2762 (65.95%) |
| Kitchen fume contact history | No 5355 (74.96%) | 586 (13.99%) |
| Yes             | 1789 (25.04%) | 3602 (86.01%) |

### Table 2. Morphology and Size of Nodules

| Morphology and Size | No. of Individuals | No. of Nodules |
|---------------------|--------------------|----------------|
| Size                |                    |                |
| Largest diameter < 5 mm | 133                | 179            |
| Largest diameter 5-10 mm | 27                 | 33             |
| Largest diameter 10-20 mm | 23                | 29             |
| Largest diameter 20-30 mm | 5                 | 5              |
| Largest diameter ≥ 30 mm | 7                  | 7              |
| Density             |                    |                |
| Pure GGO            | 88                  | 106            |
| Partly GGO          | 15                  | 17             |
| Solid nodule        | 20                  | 23             |
| Calcified nodule    | 72                  | 107            |

### Table 3. Primary Lung Cancer

| Pathology and TNM stage | No. | Note |
|-------------------------|-----|------|
| Adenocarcinoma          |     |      |
| AAH                     | 1   |      |
| AIS                     | 2   |      |
| MIA                     | 4   |      |
| T1aN0M0                 | 8   |      |
| T1bN0M0                 | 5   |      |
| T2aN0M0                 | 2   |      |
| T3aN0M0                 | 1   |      |
| Lung biopsy             |     |      |
| IV                      | 1   | Supraventricular lymph node biopsy |
| Squamous cell carcinoma|     |      |
| T2aN0M0                 | 1   |      |
| T3aN0M0                 | 1   |      |
| Lung biopsy             |     |      |
| Malignant pleural effusion| 1   | Pleural fluid cytology |

### Table 4. Benign Lesion

| Category                    | No. |
|-----------------------------|-----|
| Proliferation of fibrous tissue and inflammatory cell infiltration | 6   |
| Granulomatous lesion        | 3   |
| Hamartoma                   | 2   |
| Thymic cyst                 | 1   |
| Neurolemmoma                | 1   |
| B1 thymoma                  | 1   |

**Note:** Table 3 includes the pathologies and TNM stages of primary lung cancer patients. Table 4 lists the benign lesions found in the study. Table 2 provides a summary of the morphology and size of nodules. Table 1 and Table 4 present the clinical characteristics and pathological findings of participants, respectively.
Table 5. Detection Rate of Primary Lung Cancer in Smokers and Nonsmokers

|                    | Detection Rate | P    |
|--------------------|----------------|------|
| Smokers            | 159.06/100,000 | .054 |
| Nonsmokers         | 336.97/100,000 |      |

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