

Editorial

# Prevention and treatment of chronic respiratory diseases in China

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The Healthy China Initiative (2019–2030) states that chronic non-communicable diseases are now the main cause of death and represent the largest disease burden in China. Deaths due to cardiovascular and cerebrovascular diseases, cancers, chronic respiratory diseases, diabetes, and other chronic non-communicable diseases account for 88% of the total deaths and more than 70% of the total disease burden.<sup>1</sup> In China, the three principal causes of chronic respiratory diseases are severe air pollution, smoking and second-hand smoke, and major acute respiratory diseases. In an article published in *The Lancet* in June 2019, Zhou et al.<sup>2</sup> reported that the top four diseases with the highest mortality rate in China were stroke, ischemic heart disease, lung cancer, and chronic obstructive pulmonary disease (COPD). Two of these directly relate to the respiratory system. It is evident that there is an overwhelming pressure on the respiratory and related departments in China for the successful prevention and treatment of respiratory issues.

At present, the management of chronic respiratory diseases in China should shift from a focus on disease treatment to a focus on public health. This is necessary in order to establish a comprehensive health education system, promote health understanding, and guide the public in developing appropriate health awareness. We should improve early intervention strategies to assist the public in having healthy lifestyles within a healthy ecologic and social environment. This will increase life expectancy, enhance peoples' lives, create a solid foundation for the comprehensive protection of public health, and thus build a healthier China.<sup>1</sup> Medical work in tertiary grade A hospitals and that in township healthcare units should be directed by a model focused on public health. Article 13 of the Healthy China Initiative states that “implementing the prevention and treatment of chronic respiratory diseases” is a primary goal. This involves the following interventions: 1) guide key populations to detect diseases early, control risk factors, and prevent the occurrence and development of diseases; 2) assess lung function in high-risk populations during their first consultation and incorporate lung function tests into physical check-ups for people aged 40 years and older; 3) enhance the management of patients with COPD, and improve the capacity of primary healthcare institutions to perform lung function tests. Through these interventions, it is estimated that by 2022 the mortality rate of chronic

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respiratory diseases among people aged  $\leq 70$  years could be reduced to 9/100,000 and by 2030, to 8.1/100,000 or below.

For the management of chronic respiratory diseases, the shift from a focus on disease treatment to a focus on public health must be initiated from a prevention perspective and should be the result of public health initiatives (such as the prevention and containment of air pollution and control of tobacco use). Additionally, physicians should actively participate in the distribution of scientific knowledge regarding the prevention and treatment of chronic respiratory diseases. A focus of secondary prevention should emphasize what are known as the three early measures—early detection, early diagnosis, and early treatment. Tertiary prevention should involve slowing disease progression and promoting recovery. Below, we will elaborate on these suggestions with relevant examples.

Lung cancer

According to the data from the National Cancer Center of China released in 2018, lung cancer remains the malignant tumor with the highest rate of morbidity and mortality. Specifically, in men, lung cancer has the highest incidence and mortality rate, while in women, breast cancer has the highest incidence rate, and lung cancer has the highest mortality rate<sup>3</sup> (Table 1). These data indicate the immense responsibility put on pulmonologists for the prevention and treatment of chronic respiratory diseases. Further development of respiratory science and technology is extremely important to ensure the health of the Chinese population.

Early detection is crucial for the prevention and treatment of lung cancer. Detterbeck et al<sup>4</sup> investigated the relationship between the staging of lung cancer and

the 10-year survival rate, and found that the earlier the lung cancer was diagnosed, the higher the survival rate of the patients. The 5-year and 10-year survival rates for stage I lung cancer were 60%–70% and 80%, respectively, while the 5-year and 10-year survival rates for stage IV lung cancer were only approximately 13% and 2%, respectively. Therefore, early detection, early diagnosis, and early treatment are critical for improving the survival rates of lung cancer patients.

Lung cancer often manifests as small nodules in the early stages. Increasing public awareness about healthcare and improvements in imaging techniques, routine physical checkups, lung function screening, and artificial intelligence technology have resulted in higher rates of lung nodules detected earlier. For example, with the support of the Guangzhou Municipal Government, the Health and Family Planning Commission, the Civil Affairs Bureau, the National Clinical Research Center for Respiratory Disease, and the assistance of the First Affiliated Hospital of Guangzhou Medical University, the healthcare institutions in the Yuexiu District of Guangzhou provided free low-dose spiral computed tomography scans and tumor marker tests to eligible residents. This practice was initiated to increase the rate of early lung cancer diagnoses and reduce the total mortality rate of lung cancer. Thus far, more than 70 million residents have been screened, and the scope of the population that will qualify for screening may be expanded in the future.

For high-risk individuals, such as patients with a surgical history of lung cancer, it is advisable to undergo image screening. However, for the general population, image screening alone is not enough. In some regions, a false-positive rate as high as 30% with imaging studies alone was noted, suggesting the need for additional screening methods.

Table 1  
Leading cancers with the highest mortality rate in China (2014–2015).

| Rank                  | Male                     |                            | Female                |                            |
|-----------------------|--------------------------|----------------------------|-----------------------|----------------------------|
|                       | Disease                  | Mortality rate (1/100,000) | Disease               | Mortality rate (1/100,000) |
| 1                     | Lung cancer              | 41.34                      | Lung cancer           | 19.84                      |
| 2                     | Liver cancer             | 37.54                      | Gastric carcinoma     | 16.59                      |
| 3                     | Gastric carcinoma        | 32.46                      | Liver cancer          | 14.44                      |
| 4                     | Esophageal cancer        | 20.65                      | Esophageal cancer     | 9.51                       |
| 5                     | Colorectal cancer        | 8.19                       | Colorectal cancer     | 6.26                       |
| 6                     | Leukemia                 | 4.27                       | Female breast cancer  | 5.9                        |
| 7                     | Brain tumor              | 3.5                        | Leukemia              | 3.41                       |
| 8                     | Pancreatic cancer        | 2.94                       | Cervical cancer       | 2.86                       |
| 9                     | Bladder cancer           | 2.13                       | Brain tumor           | 2.74                       |
| 10                    | Nasopharyngeal carcinoma | 2.05                       | Uterine cancer        | 2.71                       |
| Total for the cancers |                          | 169.19                     | Total for the cancers | 98.97                      |

Mutations in circulatory DNA can be used as a biomarker. Early tumor cells in circulation have DNA mutations. Previously, DNA mutations have been commonly detected by testing somatic cells, which is time consuming and labor intensive. An alternate method is to detect DNA methylation, which can reflect DNA mutations with more sensitivity and can increase the rate of DNA mutation detection by a factor of 1000. This method has been used for the detection of liver tumors.<sup>5</sup> Some preliminary experiments on DNA methylation in lung cancer screening have been conducted.

Some of these studies have detected the methylation of circulatory DNA in more than 1000 patients with small pulmonary nodules. The sensitivity of diagnosis was 82.5% and the specificity was 83.3%, suggesting that a larger sample size was required.<sup>6</sup> An ongoing study with a larger sample size from 28 hospitals is currently testing circulatory DNA methylation in 10,000 patients with small pulmonary nodules. These patients would be followed up to assess test effectiveness and outcomes during the next 2–3 years, thereby determining whether high-throughput sequencing of DNA methylation can be used as a marker for lung cancer screening.

The decision to recommend postoperative chemotherapy for patients with early lung cancer is also challenging. Pignon et al<sup>7</sup> (the LACE study) found that the 5-year survival rates of patients with non-small cell lung cancer who received or did not receive adjuvant chemotherapy after surgery was 45% and 50%, respectively. Therefore, 45% of the patients with non-small cell lung cancer received sidekick chemotherapy, which lacks precision in selection, increases the toxicity of the chemotherapy, and adds to the financial burden on the patients. Therefore, the decision to prescribe chemotherapy requires the correct selection strategy, especially since reducing unnecessary chemotherapy is also part of the prevention strategy. In response to this, the First Affiliated Hospital of Guangzhou Medical University and the National Clinical Research Center for Respiratory Disease have combined the genotyping data (11 lung cancer-related genes) and clinical classification data (age, gender, smoking status, and tumor size) of more than 6000 patients with lung cancer. They have established a prognostic prediction model for surgery in early stage lung cancer, which has become the only lung cancer prognostic prediction model recommended for clinical use by the NCI (National Cancer Institute) in the United States.<sup>8</sup> This model divides lung cancer patients into three categories—high risk, intermediate risk, and low

risk. It can accurately screen and select individuals who require postoperative adjuvant chemotherapy. This considerably reduces unnecessary pain and expense for patients with lung cancer and follows the recommended strategy for prevention.

### Chronic obstructive pulmonary disease

The prevention and control of COPD in China is a difficult challenge. Currently, there are approximately 100 million patients with COPD. The prevalence of COPD among people aged over 40 years in China from 2002 to 2004 was 8.2% and by 2012–2014, this figure had increased to 13.7%.<sup>9,10</sup> Fang et al<sup>11</sup> found that patients with the global initiative for chronic obstructive lung disease (GOLD) stage I and II COPD accounted for 95.1% of all COPD patients. In this population, patients who were treated in outpatient clinics only accounted for approximately 5% of all COPD patients. A meta-analysis found that the lung function of patients with GOLD stage I and II COPD decreased more rapidly than patients with GOLD stage III and IV COPD.<sup>12</sup> Optical coherence tomography imaging technology can reflect changes in the airway at various levels in early stage lung cancer. Ding et al<sup>13</sup> found that in the bronchial tubes, the inner airway area and diameter in non-smokers were larger than those of heavy smokers at all levels, while those of heavy smokers were larger than those of COPD patients. As GOLD staging increased, the airway area and diameter of COPD patients gradually decreased, and the tube wall gradually increased. Patients with early stage COPD had clear lesions in the small airways, even though the patients were asymptomatic or had only mild symptoms at this stage.

GOLD 2019 states that the goal of COPD treatment is to “relieve symptoms and prevent disease progression.” However, this goal was proposed on the premise that there were symptoms. It may be too late to intervene once symptoms have emerged since most patients with COPD have no obvious clinical symptoms in the early stages. However, their lung function declines rapidly as the small airways have already changed. These conditions do not always receive the attention of patients and doctors and therefore, the efficacy of early intervention has never been studied prospectively. We conducted a Tie-COPD study to observe whether early intervention in COPD patients was effective. The Tie-COPD study was a randomized, double-blind, placebo-controlled, parallel-grouped, and multicenter clinical study, in which patients with GOLD stage I–II COPD (with no or mild symptoms) were treated with

tiotropium bromide (18 µg, once daily) for 2 years. The results demonstrated that compared with the control group, tiotropium bromide can continuously and significantly improve the lung function of patients with stage I–II COPD. This intervention can delay the rate of decline in the forced expiratory volume in the first second right after the administration of a bronchodilator (including patients with COPD assessment test <10 points). It can improve patients' quality of life, reduce acute onsets, and diminish medication use. This practice offers clinical benefits for patients with early stage COPD and provides more evidence that the early prevention and treatment of the disease can reduce the burden on both patients and society.<sup>14</sup> Fanny Ko<sup>15</sup> spoke highly of this study, noting that, “early intervention for diabetes and hypertension certainly leads to good effects, but is the strategy of early intervention also effective for patients with mild COPD? Zhou's research results are extremely important, because there is very little evidence for the treatment of patients with mild COPD.” This study has demonstrated that initially, early intervention in patients with COPD has a beneficial preventive effect. Although the US Preventive Services Task Force does not recommend screening for COPD in asymptomatic adults,<sup>16</sup> the prevalent conditions and specific circumstances in China (air pollution, firewood burning, and smoking) mean that screening for early stage COPD should be conducted as soon as possible, especially for people with long-term exposure to risk factors even if they are asymptomatic. The relevant questions are: could early intervention for COPD be done similarly to how high blood pressure and diabetes is carried out?, and why wait until the disease has progressed to a late-stage and become too severe to treat? These questions reflect the current situation and are quite thought provoking.

## Asthma

Epidemiological surveys illustrate that more than 70% of patients with asthma in China have a mild form.<sup>17</sup> Jeffery et al<sup>18,19</sup> found through histological studies of bronchial biopsy samples that patients with mild asthma undergo damage and shedding of their airway epithelium. Observation under electron microscopy revealed that in the early stage of the disease, the airway epithelial layer has already begun to disappear, the ciliated cells have begun to show damage, and early signs of airway remodeling such as submucosal vascular hyperplasia and bronchial smooth muscle hyperplasia have begun to emerge. Kicic et al<sup>20</sup> surgically collected bronchial brushing samples from seven

children with mild asthma, nine children with allergies but no asthma, and 12 healthy controls to analyze the changes in airway cell function. They found that the epithelial cells in children with mild asthma produced more pro-inflammatory cytokines (interleukin-6 and prostaglandin E2), more epithelial growth factors, and less transforming growth factor-β. This suggests that there is airway inflammation in patients with mild asthma. Optical coherence tomography tests illustrated that there were changes in the wall and lumen at all levels of the airways in patients with various degrees of asthma. The changes in the airway due to asthma were partially similar to those due to COPD, although not exactly the same.

Although patients with severe asthma have narrow airways, the airway lumen of patients with mild asthma is not that much different from that of healthy people. However, the airway wall is significantly thickened in mild asthma, mainly due to inflammation and smooth muscle hyperplasia. The lesions are primarily located in the 3rd to 7th level bronchi. Bronchodilators may not necessarily be effective, although currently the short-acting beta2 agonist (SABA) bronchodilators are commonly used to treat early stage asthma.

According to the treatment plan recommended by the current asthma management guidelines, low-dose inhaled corticosteroids (ICS) should be used in combination with SABA bronchodilators as required in the management of patients with mild asthma. However, most patients with mild asthma use SABA alone to relieve the symptoms and rarely use ICS in combination. This failure to comply with the standardized management of airway inflammation causes further aggravation of the disease. In 2018, *The New England Journal of Medicine* published the results of the SYGMA1 multicenter clinical study,<sup>21</sup> which analyzed the effect of using budesonide/formoterol to treat mild asthma based on patients' needs. These results demonstrated that in the management of patients with mild asthma, the combined application of budesonide/formoterol based on patients' needs can quickly reduce inflammation and relieve symptoms. This combination can not only provide beneficial results, but also offer a feasible and optimized treatment plan for patients with mild asthma who have poor adherence to treatment. The results of the Chinese subgroup of SYGMA1 have not yet been released, but the current data illustrate this intervention can have a beneficial effect. Need-based use of budesonide/formoterol significantly increased the number of weeks of well-controlled mild asthma than the need-based use of terbutaline. The effect of the continuous use

of budesonide is not necessarily inferior. From the perspective of an individual, once a diagnosis of mild asthma is given, it is best to continuously use ICS to eliminate allergic inflammation of the airway, regularly monitor lung function, and control the occurrence of asthma symptoms. This would lead to additional patients that may achieve a “clinical cure” and this process may also be used as a clinical strategy.

In summary, chronic respiratory diseases represent a significant component of the burden of disease affecting public health in China. These diseases should receive attention from all sectors of society. In the future, early detection, early diagnosis, and early treatment should become our focus in order to prevent and control lung cancer, COPD, asthma, and other diseases in healthcare institutions across all levels. We believe that under the guidance of the prevention and treatment strategy, with a focus on public health, the management of chronic respiratory diseases in China will achieve a greater success.

## Conflicts of interest

None.

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