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Expanding the Reach of Lung Cancer Screening: Risk Models for Individuals Who Never Smoked

Lung cancer represents a substantial portion of the overall burden of cancer and resulted in an estimated 2.2 million new cases and 1.8 million deaths worldwide in 2020, representing approximately 1 in 10 (11.4%) cancers diagnosed and one in five (18.0%) deaths (1).

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In 2011, the U.S. National Lung Screening Trial demonstrated a 20% relative reduction in lung cancer mortality with annual low-dose computed tomography (LDCT) among individuals at high risk based on age and tobacco use criteria (2). The NELSON trial (Dutch-Belgian lung cancer screening trial) recently confirmed a mortality benefit to annual LDCT screening among high-risk populations (3).

However, current screening criteria exclude a substantial proportion of individuals who will go on to be diagnosed with lung cancer. The proportion of lung cancers diagnosed in individuals who have never smoked is increasing over time, accounting for 25% of all lung cancers. If considered as a distinct disease entity, non–smoking-related lung cancer would rank as the seventh most common cause of cancer-related death worldwide (4). In Asia, 30–40% of all lung cancers and 60–80% of lung cancers in women occur in never-smokers, considerably higher than the proportion observed in the United States and Europe (5, 6). The observed increase in lung

cancers diagnosed among never-smokers in Asia likely reflects exposures to environmental factors, including outdoor air pollution and household burning of solid fuels for heating and cooking (7). Of note, outdoor air pollution is estimated to cause 20.5% of lung cancer deaths in China, compared with 4.7% in the United States (8).

Given these observations, further development of risk prediction tools to estimate lung risk among never-smoking individuals may lead to a benefit from LDCT screening in this underrecognized population. In this issue of the *Journal*, Wang and colleagues (pp. 77–88) develop lung cancer risk prediction models (termed NCC-LC_{m2021}) for individuals who currently or previously smoked and a separate model for never-smokers using two large prospective screening cohorts in China (9). The models were developed using the NLCS (China National Lung Cancer Screening) program, a study of one-off LDCT screening (10). The final model for never-smokers included five variables that were associated with increased lung cancer risk: age, female sex, body mass index, family history of lung cancer, and chronic respiratory disease; the final model for individuals who currently or previously smoked included two smoking variables (cigarettes per day and years smoked) as well as age and body mass index. Among individuals with a prior smoking history, NCC-LC_{m2021} identified slightly more screening-eligible females and was more efficient overall in identifying incident lung cancers than recently revised 2021 United States Preventive Services Task Force screening criteria (age 50–80 yr, ⩾20 pack-years; quit ⩽15 yr) (11). Among individuals who never smoked, the performance of NCC-LC_{m2021} was only marginally better than $PLCO_{all2014}$ (a prior model developed by Tammemägi and colleagues that is analogous to the $PLCO_{m2012}$ model but configured to include never-smokers) (7, 12). Wang and colleagues also demonstrate that NCC-LC_{m2021} 3-year lung cancer risk thresholds of ⩾0.47% for never-smokers and ⩾0.51% for ever-smoking individuals would result in screening eligibility for 18% of the Chinese population aged 40–74 years, while identifying 44% of all incident lung cancers. When considering just the population that has never smoked, an NCC-LC_{m2021} threshold of ⩾0.47% would result in screening eligibility for 11% of the Chinese never-smoking population and identify 27% of all incident lung cancers in this population (9).

The results of this study by Wang and colleagues are consistent with other recent efforts to estimate the impact of new risk prediction models and screening in populations with low smoking prevalence. Preliminary findings reported from the TALENT (Taiwan Lung Cancer Screening for Never-Smoker Trial), a multicenter single-arm cohort of LDCT screening among 12,011 never-smoking individuals aged 55–75 years with at least one risk factor (family history of lung cancer within a third-degree relative, passive smoking exposure, history of tuberculosis or chronic obstructive pulmonary disease, and exposure to cooking fumes), demonstrate an overall lung cancer prevalence of 3.2% at baseline screening (13). The cancer stage data (78% diagnosed at stage 1A/1B) are encouraging; however, the results from the TALENT also raise some concern regarding the potential for lung cancer overdiagnosis. Although the cancer detection rate of 3.2% at baseline was higher than baseline cancer rates in the U.S. National Lung Screening Trial or NELSON, 18% (57 of 311) of cancers were diagnosed at stage 0 (i.e., carcinoma *in situ*). The NLCS data, on which the NCC-LC_{m2021} models are based, had a high rate of missing stage information (32%) but reported a stage 0–1 lung cancer prevalence of 63% (244 of 389) in the screened group (10). However, rates of stage 0 were not separately provided.

Additional evidence for overdiagnosis from screening of low–smoking-prevalence populations was recently provided in an analysis by Gao and colleagues that assessed stage-specific lung cancer incidence using data from the Taiwan National Cancer Registry (13). After the introduction and marketing of LDCT screening in the mid-2000s, the incidence of stages 0–1 lung cancer in women increased more than sixfold (from 2.3 to 14.4 per 100,000) between 2004 and 2018; however, there was no change in the incidence of stage II–IV lung cancer. The pattern of increasing early-stage disease not accompanied by a decrease in late-stage disease suggests a substantial contribution of overdiagnosis. The likelihood of considerable overdiagnosis was further supported by a minimal decrease in lung cancer mortality (17 to 16 per 100,000) but a substantial change in 5-year survival from 18% to 40% during the same time period (14).

The findings from Wang and colleagues and the TALENT trial, as well as other studies in East Asia, suggest that screening can be effectively performed in lower–smoking-prevalence populations, including never-smoking individuals. Furthermore, these studies highlight the importance of identifying risk factors beyond age and tobacco consumption. Models that consider additional clinical and demographic variables are likely to have a place in clinical practice. However, the balance of benefits and harms of expanded screening remains uncertain, and further research will be required to elucidate the impact of risk factor– or model-driven approaches to patient selection for screening and the impact on lung cancer mortality, overdiagnosis, biopsy and complication rates, and cost. ■

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Seeing Premature Lung Disease: Hyperpolarized Xe Magnetic Resonance Imaging

Preterm birth impacts more than 15 million children annually worldwide and is the leading cause of death in children under 5 years of age (1). Complications related to premature birth, particularly in very preterm infants (less than 32 weeks gestational age), represent 30% of newborn healthcare costs in the United States, nearly $13.4 billion annually (2). Bronchopulmonary dysplasia (BPD), or chronic lung disease of prematurity, is characterized by small- and large-airway obstruction, alveolar simplification, pulmonary fibrosis, and pulmonary vascular abnormalities, which can be precisely quantified using advanced imaging technology (3–6). Pulmonary sequelae of premature birth extend well beyond the neonatal phase and manifest with reduced lung function, progressive lung function decline, and persistent respiratory symptoms (7). In recent years, the limit of viability has decreased to 22 weeks gestational age, and the incidence of lung disease associated with premature birth has increased with improved neonatal survival of the most vulnerable patients. Thus, it is ever more important to precisely define the long-term pulmonary changes that may result from premature birth.

A significant challenge in evaluating pulmonary complications of premature birth is that most existing definitions rely on defining the disease by respiratory support at 28 days of life or 36 weeks postmenstrual age (8). Although these definitions are useful for predicting clinical outcomes, they provide little insight into the underlying pathophysiology of premature lung disease. In this issue of the *Journal*, Chan and colleagues (pp. 89–100) made a leap forward by combining multiple breath washout and hyperpolarized Xe magnetic resonance imaging (MRI) to define ventilation abnormalities and lung microstructure in preterm-born children with different lung function phenotypes (9).

Children born preterm with obstructive lung disease had elevated ventilation defect percentage (VDP) on the basis of hyperpolarized Xe MRI as well as ventilation abnormalities on the basis of multiple breath washout; MRI also revealed a significant increase in ventilation heterogeneity that cannot be defined with other tests of pulmonary function. Furthermore, children with BPD, but not those born prematurely without BPD, had an elevated apparent diffusion coefficient, suggesting that alveolar simplification persists into school age, which differs slightly from a prior study using ^{3}He (10). Surprisingly, children with BPD did not demonstrate an elevation in VDP in this study compared with term control subjects despite a significant reduction in forced expiratory flow. This discordance is different than the relationship of VDP and spirometry seen in other pediatric obstructive lung diseases such as cystic fibrosis and obliterative bronchiolitis and may reflect a novel underlying pathology in BPD or the small sample size in this study, so these findings should be interpreted with caution (11, 12). Furthermore, the children enrolled tended to have a milder neonatal course, with few participants meeting the criteria for severe BPD who are most likely to have long-term respiratory sequelae related to premature birth. Consequently, the findings of Chan and colleagues may underestimate the full spectrum of changes in pulmonary structure and function from prematurity. Nevertheless, these findings provide significant new insight into the pathophysiology of respiratory outcomes in school-age children who were born prematurely.

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