One Screening for Ischemic Heart Disease, Lung Cancer, and Chronic Obstructive Pulmonary Disease: A Systems Biology Bridge for Tobacco and Radiation Exposure

In light of the emerging information by following a cohort of more than 7000 nuclear weapons workers, how should we be thinking about lung cancer screening? From the participants' perspective, what is most important is the information shared by the clinician as a basis for making an informed decision on whether to undergo thoracic computerized tomography (CT) screening.[1] Considerable evidence has emerged about reducing both the rate of false-positive CT scans and overtreatment.

However, evidence from early evaluation thoracic CT screening of a population of heavily tobacco-exposed individuals suggests that considering the primary etiological agent—tobacco—could have a greater public health benefit regarding imaging analysis. Is it time to critically consider a more comprehensive approach to more reliably establish relevant health information available through thoracic CT imaging, not only for heavily tobacco-exposed individuals but also for individuals with radiation and inhaled chemical exposures as well?

THE THREE MOST LETHAL DISEASES

A comprehensive analysis of diseases, injuries, and risk factors across the United States from 1990 to 2016 was recently reported by a jointly sponsored consortium from the National Institutes of Health and The Bill and Melinda Gates Foundation, as a guide to investment for research, care, and public health policy in the United States.[2] According to that report, lung cancer—including cancer of both the trachea and the bronchi—was and remains the second leading cause of years of life lost across the 26-year time interval of that study, during which the number of lung cancer deaths increased by 26.8%. In that analysis, the most lethal disease process was ischemic heart disease (IHD), which accounted for more than 544 000 deaths in 2016. Although there has been a 15% reduction in IHD mortality since 1990, it still results in over 2.84 times more deaths than lung cancer. The third leading cause of death is now chronic obstructive pulmonary disease (COPD); over that same 26-year interval, deaths from COPD rose by 86.9%. Collectively, these three diseases—IHD, lung cancer, and COPD—accounted for more than 44% of the mortality from the top 25 causes of years of life lost in 2016. In the United States, CT screening is currently being implemented in individuals older than 55 years who are current or former smokers with more than 30 pack-year exposure to tobacco combustion products. Their life expectancy is limited by these same three most lethal diseases.

A MORE INCLUSIVE EVALUATION

Considerable progress has been made in developing predictive risk models for lung cancer in the screening setting. However, from a potential screening patient's perspective, a lung cancer–only risk analysis misses the risk of death from IHD and COPD. Therefore, when considering the benefit of CT screening for those exposed to tobacco—and also to radiation inhalation and toxic chemicals—a more inclusive evaluation of health outcomes that considers the full range of knowable thoracic consequences of toxic exposures is needed.[3,4]

In the United States, IHD, lung cancer, and COPD cumulatively account for more than 13 500 000 years of lost life annually. However, from a heavily tobacco-exposed individual's perspective, lung cancer accounts for only 26% of this mortality burden. A thoracic CT scan may also provide actionable risk information for not only tobacco-related but also radiation and chemical causes of death. Given where we are with the cost of health care and the burden of major chronic disease on our aging population, why would we not be looking for a systematic approach to intervene in the consequences of heavily exposed individuals?

SHARED INFLAMMATORY PATHOGENESIS

The case for biological plausibility of shared pathogenesis of inflammatory mediated disease was recently highlighted by the CANTOS study, a large phase III trial of an antibody to IL-1B used to treat patients with evidence of a previous myocardial infarction. This study showed that suppression of this inflammatory mechanism not only ameliorated cardiovascular endpoints but also significantly reduced lung cancer mortality.[5,6] This finding from the CANTOS study was suggested to be caused by the shared inflammatory pathogenesis of these two major chronic diseases.[5,6] We and others have long postulated a pathogenic contribution of chronic inflammation in lung cancer.[7]

Therefore, as this new CT-based lung cancer screening service is being responsibly implemented, it is already

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evident that in this target screening cohort of heavily tobacco-exposed, elderly individuals, approximately 25% of the asymptomatic screened individuals will be found to have significant radiological findings consistent with COPD, and nearly as many will have objective evidence for elevated risk of IHD.[3,4] About 15% to 20% of screening participants will be found to have evidence of significant coronary calcification, which is currently the most reliable biomarker of near-term cardiovascular risk.[4] Should we be looking for long-term consequences of nuclear exposure with the same broad prism?

USING A BROADER PRISM

Of note, the full cost for a low-dose CT image and reading will typically range from $300 to $500, depending on the setting. With this current reimbursement for lung cancer screening, we are presented an economical opportunity to systematically detect and monitor three of the most significant causes of tobacco-related death. Efforts are already under way to optimize the reliability and cost in quantitatively characterizing the detection and monitoring of major intrathoracic disease with CT with the national implementation of lung cancer screening, which may also be leveraged to sustainably address health issues with the imaging of nuclear workers. In clinical practice, the radiologist's reports on lung cancer screening studies already frequently comment on COPD and cardiovascular status found on the screening CT. Professional societies have already published guidelines for

managing discreet amounts of reported coronary calcification, including with the use of lifestyle interventions based on the report of the CT scans done for lung cancer screening.[4]

In the setting of lung cancer screening for nuclear weapons workers, these important results are similar to the favorable stage shift that was reported with the National Lung Screening Trial. At the same time, with the same scan and the same cost, additional important information may be available about the two other leading causes of death. Will there be evidence that interventions such as more systematic and personalized implementation of smoking cessation or modification of diet or physical activity can mitigate all three CT-detected diseases in a population of nuclear workers? Considerations regarding health equity and efficiency are critical topics for the public health community. As the national implementation of lung cancer screening efforts matures, CT imaging of the thorax may be a resource for other relevant populations subjected to the pathogenic consequences of chronic inflammation. AJPH

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