Editorial

Circulating mitochondrial DNA as a biomarker for lung cancer screening

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Because advanced stage at diagnosis drives poor outcomes in lung cancer, for decades investigators have sought to detect early-stage, clinically silent lung tumors through radiographic screening (1). Based on a clear reduction in lung cancer mortality, annual low-dose computed tomography (LDCT) is now approved in at risk populations, currently defined as individuals ages 50–80 years who have smoked at least 20 pack-years (2,3). The procedure is relatively straightforward. Radiation exposure is less than 25% that of a standard diagnostic chest CT; lack of contrast eliminates requirement for vascular access and risk of kidney toxicity and allergic reaction; and the imaging study is completed within a single breath hold. Furthermore, LDCT appears to be highly efficient. The number needed to screen (NNS) to prevent one death from lung cancer is 320, which compares favorably to more than 700 for mammography for breast cancer and more than 1,800 for Pap smears for cervical cancer (4-6).

Despite these apparent advantages, lung cancer screening remains remarkably underutilized, with fewer than 15% of eligible individuals currently undergoing LDCT (7). A number of concerns may contribute to this limited uptake. Pulmonary nodules are highly common among adult smokers, occurring in approximately 40% of participants in the National Lung Screening Trial (NLST). When these radiographic abnormalities are sufficiently concerning to warrant biopsy, the procedure—whether bronchoscopy or percutaneous—is generally more complex and riskier than tissue sampling in other cancer screening modalities (8). Endoscopically detected polyps may be sampled and even removed at the time of screening colonoscopy. Near-term, even same-day, ultrasound-guided breast biopsy may be available at mammography centers. Separately, while the stringent eligibility criteria for lung cancer screening increase the likelihood of identifying malignancy, they leave a substantial population without screening options, including the 15% of lung cancer patients who are never smokers. Additional information about the risk of a person developing lung cancer or the risk of a nodule found on a CT scan being malignant would be of significant benefit. As part of this, there is large field of research to use computational analyses of CT images ("radiomics") to assess the likelihood of a nodule being malignant (9). It is in the context of these concerns that blood-based biomarkers have received growing attention.

Blood-based biomarkers may be able to improve lung nodule risk stratification, potentially resulting in improved decision making for intermediate nodules and improved outcomes for patients (10). Additional benefits of blood-based markers include patient acceptance, relative non-invasiveness, and cost and time efficiency. Several different categories of blood-based biomarkers have been studied to

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date, including DNA germline variants, circulating tumor proteins, anti-tumor antibodies, microRNAs, and DNA methylation (11-17).

Mitochondrial DNA (mtDNA) levels have emerged as a potential biomarker associated with lung cancer risk (18-20). Although there is considerable variability in the literature, in general lower levels of circulating white blood cell (WBC) mtDNA appear to be associated with increased risk for lung cancer (18-20). Kennedy and colleagues evaluate peripheral blood WBC mtDNA content in a case control study comparing patients known to have lung cancer versus healthy controls (21). They showed that after multivariate analysis controlling for race, age, gender, and smoking history, peripheral blood WBC mtDNA content was lower in patients diagnosed with lung cancer compared to controls. Because of disparities for screening efforts in African American and other underserved populations it was important that, while there were differences in mtDNA by race (higher WBC mtDNA levels in African Americans), the risk of developing lung cancer by mtDNA content was found in both Caucasian and African American populations. Correctly, the authors indicate that large populations need to be studied to make sure this finding is validated. Equally important, we need methods to identify risk of developing lung cancer in lifetime never smokers. They found that mtDNA were higher in never smokers. Thus, it will be of great interest in future expanded studies to evaluate if never smokers with low mtDNA content also have a higher risk of developing lung cancer compared to their never smoking peers with high mtDNA levels.

There was a stronger effect size for the lowest versus highest quartiles of mtDNA content and the effect reduced in a stepwise fusion, indicating there may be a biological explanation underpinning the differences in mtDNA content and lung cancer risk. This study did not specifically evaluate a biological mechanistic understanding for the result, but previous studies indicate that exposure to high levels of reactive oxygen species may overwhelm compensatory mechanisms of mtDNA stability, leading to lower levels of mtDNA upon exposure to high levels of carcinogens (22). Additionally, mutations in the D-loop of mtDNA which can impair mtDNA replication, or abnormal p53 expression (often altered in lung cancer due to carcinogen exposure) may alter mtDNA replication, leading to lower levels of mtDNA (23,24). As the authors note, these potential mechanisms have been found in tumor cells and need to be studied to see if they also take place in WBCs. In this regard, we need information on the relationship of clonal hematopoiesis of indeterminant potential ("CHIP") and mtDNA levels particularly in those cases with identified mutations such as TP53 (25). Equally important, for lung cancer pathogenesis we know there can be a variety of molecular changes in the normal lung epithelium at risk ("field effect") in patients with lung cancer, and if these could be identified they could be used, albeit with invasiveness required for tissue sampling, to provide risk assessment (26). In this regard, it would be of great interest to compare WBC mtDNA levels with those in lung epithelium to determine if they were correlated.

It is important to note that this study found that low mtDNA levels still predicted for risk of developing lung cancer even after controlling for age and smoking history, which are two clinical variables used to determine eligibility for low dose CT lung cancer screening. This indicates that circulating WBC mtDNA levels have additional risk assessment benefit after assessing standard clinical data. Interestingly, they also evaluated clinical outcomes in the lung cancer cases according to quartile of peripheral blood WBC mtDNA quantity, showing that there were no associations between mtDNA and clinical outcomes. Thus, mtDNA levels predict risk of developing lung cancer but not outcomes.

The authors provide both an excellent summary of the prior literature with regard to mtDNA levels and lung cancer risk (see their *Tab. 5*), and importantly, a table summarizing the key issues surrounding using mtDNA levels for lung cancer risk assessment (see their *Tab. 6*). We agree with their summary and note two key issues they identified: "reverse causation" (for example, when people change their diet or other lifestyle habit after being screened for or developing a disease); and longitudinal studies (for example, are mtDNA levels, high or low, stable over repeated testing?). The next logical steps are to validate WBC mtDNA as a biomarker for lung cancer screening in a larger diverse prospective cohort study. Generation of receiver operator characteristic curves in a prospective study will be crucial to determine clinical utility. The authors point out prior work related to mtDNA levels that is inconsistent with their findings may be due to differences in laboratory measurement of the biomarker and standardization of this approach would be required for a clinically useful biomarker. Finally, with mtDNA levels as a promising blood-based biomarker for lung cancer screening, there is the need for studies integrating mtDNA level assays with other blood-based biomarkers to develop a combined biomarker score.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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