Editorial

Lung cancer recurrence epigenetic liquid biopsy

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Lung cancer is the third most prevalent cancer after prostate and breast cancer in the US, having over 400,000 people diagnosed with the disease (1,2). It is the fifth overall leading cause of death in the world [after ischemic heart disease, stroke, lower respiratory infections and chronic obstructive pulmonary disease (COPD)] (3), and it is the primary cause of cancer-related death worldwide. Lung cancer accounts for almost 27% of all cancer-related deaths; and its 5-year survival does not reach 20% (1,2). Most of cases are diagnosed at late stages. Very recently, the National Lung Screening Trial (NLST) demonstrated that mortality reduction of lung cancer can be achieved by performing screening with low-dose computed tomography (CT) scans (4). The NLST enrolled 53,454 persons at high risk for lung cancer, current and former smokers, (30 pack-years) age 55 to 74 years old, from 33 US medical centers to undergo three annual screenings with low-dose CT compared to chest radiography. The trial reported a 20% mortality rate reduction in 26,722 participants randomized to low-dose CT scan screening as compared to 26,732 participants randomized to chest radiography screening. However, the enthusiasm of low-dose CT screening has been diminished by a serious concern about its high false positive screens and low positive predictive value leading to additional radiographic or diagnostic procedures, as well as the morbidity and mortality associated with further invasive testing (5,6). The false positive rate in the NLST was over 94% in all annual screenings, leading to a substantial number of benign nodules classified as positive with only 4% them resulting in lung cancer diagnosis (4,6). In spite of increasing nodule size threshold up to 10 mm false positive rate remains 78% (7). Therefore, complementary non-imaging-based screening techniques need to be studied and validated. In this regard, epigenetic molecular markers for early detection of lung cancer have been in study and development for years (8-12). However due its technical difficulties, cost-performance effectiveness and low yield of detected DNA in circulating plasma, its application has been far from its use in clinical practice and its approval by scientific societies and guidelines. In the recent years, the development of new methylation specific PCR techniques allowed to study DNA from sources that previously had extremely low yield for DNA methylation detection (13). As a result, we are living a "renaissance" of biomarker research with increasing interest by the scientific community on the latest advancements on molecular biomarkers with circulating DNA and liquid biopsy. In this context, there is a blossoming of studies on early detection of lung cancer and risk of recurrence by analyzing biomolecular epigenetic signatures. As a consequence of these findings, epigenetic studies are extending beyond screening to prognostic and recurrence risk. From Dr. Herman's group, Brock *et al.* showed that some epigenetic changes from tumor and lymph nodes samples could predict lung cancer recurrence on a study involving 167 subjects studying the promoter gene methylation of *p16*, *MGMT*, *DAPK*, *RASSF1A*, *CDH13*, *ASC*, and *APC* with a 40-month follow-up period (14). Recently Belinsky *et al.* published the largest epigenetic study investigating the risk of lung cancer recurrence using

sputum and plasma including 535 subjects studying the promoter gene methylation of *CDKN2*, *MGMT*, *DAPK1*, *RASSF1*, *GATA4*, *GATA5*, *PAX5*α and *PAX5*β with a median follow-up of 6 years (15).This study was part of the Eastern Cooperative Oncology Group prevention trial (ECOG-ACRIN5597) that enrolled resected stage I non-small cell lung cancer patients who were randomized 2:1 to receive selenized yeast versus placebo for 4 years. This most recent epigenetic study showed that detection of methylation in both sputum and plasma was predictive of lung cancer recurrence. Interestingly showed that methylation in plasma is associated with time of recurrence in spite of the known fact that the methylation prevalence in plasma is significantly lower than in sputum. These findings further endorse that we will soon see emerging biomolecular epigenetic techniques for early detection of lung cancer and recurrence risk prediction. In addition, it further highlights the fact that despite the current revolution in the management of advanced lung cancer therapies, primary prevention and screening continues to be important to focus on. Lung cancer screening is a great opportunity to encourage smoking cessation. Several studies showed that the odds or smoking cessation are higher among individuals who undergo screening, which indirectly further improves mortality reduction (16,17).

In summary, we are living exciting scientific times and we are looking forward to see the use of fingerstick in the community by primary care physicians, like the ones used for diabetes follow-up, but using them instead to profile the epigenetic signature of patients in the community to characterize the risk of lung cancer and recurrence and to personalize the adjuvant treatment with the recent advances in immunotherapy or targeted therapy such as the ones targeting specific gene mutations or rearrangements for *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, and *BRAF* mutations (18,19). However, given the heterogeneity of lung cancer subtypes and individual responses, it is unlikely that a single biomarker modality will provide robust diagnostic and screening tools, but rather a panel of biomarkers or biomolecular signature. Much work still needs to be done and these questions can only be explored through prospective clinical trials and broad collaborative research to further validate and generalize its results for different population ethnicities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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