



Lung cancer susceptibility beyond smoking history: opportunities and challenges

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Lung cancer remains the top cancer killer worldwide. While association of smoking with lung cancer is well recognized, the contribution of smoking to lung cancer incidence and mortality is projected to diminish substantially. Identifying other risk factors associated with lung cancer, particularly among never smokers, remains an important public health issue for prevention and early detection. Several risk factors have been linked to lung cancer in never-smokers. They include radon exposure and domestic fuel smoke (1-4). Infections, notably with *Mycobacterium tuberculosis* and Human Papilloma Virus have been linked in some studies to lung cancer risk (5,6).

Substantial effort has focused on genetic predisposition to lung cancer. A number of germline variants have been associated with lung cancer risk, particularly with the lung adenocarcinoma subtype (7). Some are associated with risk for multiple cancer types, notably the Li-Fraumeni syndrome associated with variants in the *TP53* tumor-suppressor gene (8). Others, notably epidermal growth factor receptor (*EGFR*) variants, are associated with risk largely limited to lung cancer (9). A multitude of studies of the association between single nucleotide polymorphisms (SNPs) and lung cancer risk have been published. One review of published studies singled out 15 SNPs on or near 12 genes and one miRNA as having strong evidence of association with lung cancer risk. They consist of *TERT*, *CHRNA3*, *AGPHD1*, *CLPTM1L*, *BAT3*, *TRNA*, *ERCC2*, *miR-146a2*, *CYP1B1*, *GSTM1*, *SOD2*, *IL-10*, and *TP53* (10). Additional SNPs were given moderate or weak ratings.

A study published in this journal addressed the identification of genetic factors with a particular focus on individuals with lung cancer presenting with ground-glass nodules (GGNs) in an East Asian population, given the rise in incidence of lung adenocarcinoma in this population group (11). Often these individuals have a family history of GGNs. However, the extent of genetic predisposition in these individuals has not been assessed. The authors carried out germline mutations analysis in 50 patients with early-stage lung adenocarcinoma (LUAD) presenting as GGNs with a first-degree family history of lung cancer from 34 independent families and compared findings with age- and sex-matched 39 patients with sporadic lung cancer and 689 local healthy subjects.

The findings from the study are quite interesting. Heritable, potentially deleterious, and rare candidate variants were identified that were associated with early-stage LUAD presenting with GGNs. In particular *MSH5*, *MMP9* and *CYP2D6* were significantly associated. These findings contribute to our understanding of genetic predisposition to lung cancer. The conclusion from this study that non-smoking individuals likely have a higher genetic predisposition to this type of cancer than smoking-affected patients seems reasonable. The number of rare damaging germline variants in non-smoking patients was significantly higher than that of smoking-affected patients. The broader significance of the findings needs to be further assessed, First, it remains to be determined if the genetic predisposition and the loci identified are limited to the population investigated which consisted of East Asians.

Second, even if restricted to this population, would it be cost effective to screen the general population for risk based on genomic profiling. An additional factor for consideration goes beyond incidence of cancer in this particular risk group and concerns the issue of mortality, namely to what extent is this genetic predisposition predictive of mortality due to lung cancer, as opposed to incidence of lung adenocarcinoma, given the association with GGNs.

From a cancer prevention point of view an understanding of risk factors due to genetic predisposition and environmental exposures on the one hand and the availability of biomarkers predictive of risk in blood or other biospecimens would allow for preventive interventions early on. An example of intervention would be the application of vaccines that may become available in the foreseeable future not only for therapy but also as a preventive intervention (12). If lung cancer could not be prevented, implementation of screening for subjects at risk, with low dose CT would detect lung cancer at an early stage with a better prospect for survival as demonstrated in the NLST and Nelson trials (13-15).

At the present time eligibility for lung cancer CT screening is primarily based on age and smoking history. Lung cancer risk models that include genetic predisposition as well as other types of biomarkers have the potential to increase the effectiveness of lung cancer screening. A case in point is the recent validation of a biomarker panel based on four proteins (16). This blinded validation study was performed in combination with a lung cancer risk prediction model based on subject characteristics, using prostate lung colorectal ovarian (PLCO) Cancer Screening Trial data. The findings were compared to current US Preventive Services Task Force (USPSTF) screening criteria. Among PLCO participants the model would have identified for annual screening 9.2% more lung cancer cases and would have reduced referral by 13.7% among non-cases compared with USPSTF2021 criteria.

Besides proteins there is a wide world of potential biomarkers that may be relevant to risk assessment and early detection of lung cancer (17,18). Such markers can be found in various biological fluids notably blood, urine, saliva or sputum (19-21). Exhaled breath has also been explored as a source of biomarkers (22) as well airway brushing (23).

Much work remains to be done to fully elucidate risk factors associated with lung cancer among both ever smokers and non-smokers. However progress is being made toward the goal of assessing lung cancer risk with hope for effective preventive intervention strategies and for early detection.

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