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Commentary

# Lung Cancer Risk, Genetic Variation, and Air Pollution

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Large-scale multinational genome-wide association studies (GWAS) of the genetic variation associated with lung cancer initially found that the 5p15.33, 6p21.33, and 15q25 regions were associated with risk of lung cancer among smokers (Amos et al., 2008; Hung et al., 2008). Interestingly, unique regions including 10q25.2, 6q22.2 and 6p21.32 were associated with lung cancer risk in those who had never smoked (Lan et al., 2012), suggesting that the risk variants for non-smoking related lung cancer were distinct from those for smoking related lung cancer. Given that tobacco smoking is the leading risk factor for lung cancer, it stands to reason that lung cancer in those that abstain from tobacco use would have additional novel risk factors which might include genetics or environmental exposures. Some of the main non-tobacco exposures associated with lung cancer are household air pollution, radon, occupational exposures, and outdoor air pollution (Alberg and Samet, 2003). Among the a priori regions identified by Lan et al.'s GWAS of never smokers, significant gene–environment interactions with household air pollution (*HLA Class II* rs2395185, $p = 0.02$; *TP63* rs4488809 (rs4600802), $p = 0.04$) were identified, thus suggesting that the risk of lung cancer associated with household air pollution exposure varied with the respective alleles for these regions. This study and other similar genetic studies provide evidence that the relationships between airborne exposures and genetic variation may contribute to lung cancer among non-smoking individuals.

In the current issue of *EBioMedicine*, Yu et al. (Yu et al., 2015) extend the literature by helping to explain how novel molecular signatures may be present in lung cancer attributed to air pollution. Yu et al. sought to dissect lung carcinogenesis attributed to air pollution by characterizing somatic genomic mutations in tumor and adjacent normal lung tissues and peripheral blood samples from 164 patients with previously untreated Non-Small Cell Lung Cancer (NSCLC) in Xuanwei, Yunnan Province, China. The use of the novel population in Xuanwei is a strength of Yu et al.'s study because the lung cancer incidence in Xuanwei is among the highest in China and it is attributed to substantial levels of combustion related byproducts generated by domestic smoky coal use for heating and cooking (Lan et al., 2002), an established risk factor for lung cancer (IARC, 2010). Based on genomic sequencing, Yu et al. compared subjects from Xuanwei to control regions (CR) where smoky coal was not reported. NSCLC tumors from each region were tested using exome sequencing. The tumors from Xuanwei had a mean of 68 mutated genes per tumor, while the CR tumors had a mean of 22. Significantly higher mutation frequencies were observed in 167 genes (i.e., *TP53*, *KRAS*) in Xuanwei patients compared to CR patients. Mutations in air pollution related lung cancers were three times as high as lung cancer from the CR cases and 70 genes were associated with subjects' lifetime benzo(a)pyrene exposure.

Previous work, on a limited scale compared to Yu et al.'s, has also sought to explore the mutational spectrum of lung cancer tissues in Xuanwei. A small exploratory study among 40 never smoking females who had NSCLCs from Xuanwei had *EGFR* mutations detected in 35% of tumors (Hosgood et al., 2013). *KRAS* mutations were observed in 15% of tumors, and *EGFR* and *KRAS* mutations were mutually exclusive. Most *EGFR* and *KRAS* point mutations were transversions and were also found in tumors from patients who used coal in their homes. The observed high mutation frequencies in *EGFR* exon 18 and *KRAS* and low mutation frequency in *EGFR* exon 21 were strikingly divergent from those in other smoking and never smoking populations from Asia, suggesting a unique signature of lung cancer attributed to coal smoke.

Overall, it appears that populations who have unique environmental exposures, such as burning coal indoors, may be susceptible to lung cancer attributed to unique underlying mechanisms of pathogenesis. Although household air pollution has been classified as a Group 1 human carcinogen, little is known about the underlying mechanism of tumorigenesis. Yu et al.'s findings are an important step in uncovering the mutation spectrum of air pollution-related lung cancers. The genes associated with lung cancer that were observed by Yu et al. provide mechanistic evidence as to what biological pathways are involved in the relationship between air pollution and lung cancer. Additionally, this research provides evidence for the pollution exposure-genomic variation relationship at a large scale, potentially providing a spring board for future research analyzing genomic variants in never smoking patients who are exposed to vast amounts of inhalable pollution. As with many genomic applications, however, researchers should replicate these findings in additional populations prior to considering translation to the clinic. Given that roughly 50% of all lung cancer cases reported in women and 15% of lung cancer cases reported in men throughout the world are not attributable to tobacco use (Sun et al., 2007), understanding the underlying mechanism of lung carcinogenesis related to exposures other than tobacco may have a large impact on the global burden of disease.

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## Authors' Contributions

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