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Commentary

Genetic Risk for Lung Cancer and the Benefits of Quitting Smoking

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Smokers are very often told that quitting smoking will produce substantial health benefits, even after decades of smoking. This advice is based upon an abundance of evidence that would seem to establish these facts with certainty (Fagerstrom, 2002). In this issue of *EBioMedicine*, the paper by Chen et al. (2016) addresses a very important question: Does quitting smoking improve the health of all smokers equally? More specifically, it addresses the question of whether similar benefits are obtained with high- and low-risk variants for the well-established CHRNA5 variant 16969968. They find that although the high-risk variant has a rather large impact on lung cancer risk, developing cancer 4 years earlier than those with the low-risk variant, the same benefits can be obtained by quitting smoking independent of genotype. Indeed, quitting can reduce the risk of developing lung cancer by 50% and delay its onset by 7 years.

This is an important finding, but the deeper impact of this paper involves the question of the nature of the causality of the high-risk CHRNA5 variant that is linked to the risk of developing lung cancer, nicotine dependence, and heavy smoking (Bierut et al., 2007; Bierut et al., 2008; Amos et al., 2008). In efforts to combat smoking and reduce the incidence of smoking related diseases it is important to understand the nature of genetic contributions to disease risk. This will help guide medical advice, patient decisions, and even public policy. One indication of the nature of this genetic risk allele is that the high-risk allele is related to other smoking-related diseases in addition to cancer (Thorgeirsson et al., 2008). This combination of associations would seem to suggest that the effects of the gene are primarily mediated through effects on behavior, contributing to heavier smoking, a greater degree of dependence, and, consequently, a reduced ability to quit smoking (Baker et al., 2009). If this is indeed the case, then one would predict that quitting would have equal benefits in individuals with either the high-risk or low-risk allele, providing they can manage to quit. On the other hand, CHRNA5 variants might have an influence on lung cancer risk that is independent of behavior, and therefore, not influenced by quitting.

The authors addressed this question using a meta-analytic approach involving 15 studies that examined more than 12,000 smokers (Chen et al., 2016). The study found that there were no differences in the benefits of quitting based on CHRNA5 allelic status. Consistent with many previous studies the benefits of quitting smoking, even for individuals with a long history of smoking, were quite large, much larger than the risk associated with CHRNA5 variant alone. Of course, this study addressed variation in only one risk locus, which by itself is likely to contribute only a small percentage of the overall risk, as appears to be the case for addiction genetics generally (Hall, 2016). Nonetheless, it tells a rather important tale about the relationship between lung cancer risk and the underlying genotype-phenotype relationships that are important for understanding health outcomes associated with genetic risk in smoking.

It will be important in future studies to address the nature of the greater, collective genetic contribution to lung cancer risk. Is the majority of this risk due to genetic influences on smoking behavior and psychological processes as opposed to a more fundamental biological predisposition to the development or progression of lung cancer? This question has important implications for the overlapping fields of lung cancer research/treatment and nicotine dependence research/treatment. If the majority of the genes involved in the predisposition to lung cancer are behavioral, then lung cancer treatment and prevention approaches need to take this into account. In the broadest sense this has public policy implications for governmental spending on research and treatment efforts in this area. A few years ago there was a suggested merger of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. There were certainly reasons for and against the potential merger (Grabowski, 2010; Meyer, 2010), that eventually weighed into the decision not to merge the institutes. One of the issues that came out in the debate, however, surrounded the large research portfolio dedicated to lung cancer research within the National Cancer Institute, and whether future directions in lung cancer research/treatment efforts (and funding) might be more profitably directed a bit more towards the research and treatment of nicotine dependence. The present findings would seem to suggest that addictive behavior really lies behind genetic contributions to lung cancer, at least for this "lung cancer" locus, although certainly more remains to be done to assess the nature of the wider genetic contributions to lung cancer risk.

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Disclosure

The author declared no conflicts of interest.

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