Genetic variants, tobacco exposure and lung cancer risk

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There is an association between the rs1051730-rs16969968 genotype and objective measures of tobacco exposure, which indicates that lung cancer risk is largely, if not entirely, mediated by level of tobacco exposure, according to a study published April 25 in the *Journal of the National Cancer Institute*.

The rs1051730-rs16969968 genotype is known to be associated with heaviness of smoking, lung cancer risk, and other smoking-related outcomes. Prior studies have generally depended on self-reported smoking behavior, which may have underestimated associations and masked the contribution of heaviness of smoking to the associations of these polymorphisms with lung cancer and other health outcomes.

In order to determine the association between the rs1051730-rs16969968 genotype and self-reported cigarette consumption and plasma or serum cotinine levels, Marcus R. Munafò, Ph.D., of the School of Experimental Psychology at the University of Bristol and colleagues, examined data from six independent studies that looked at self-reported daily cigarette consumption and plasma or serum cotinine levels among cigarette smokers and conducted a meta-analysis of pooled per-allele effects. In addition, the researchers looked at the link between the genotypes and lung cancer risk using published data on the association between cotinine levels and lung cancer risk.

The researchers found that the rs1051730-rs16969968 genotype is strongly associated with tobacco exposure measured through cotinine levels, and that the association is strong even after adjustment for self-reported cigarette consumption. "These data therefore support the conclusion that association of rs1051730-rs16969968 genotype with lung cancer risk is mediated largely, if not wholly, via tobacco exposure," the researchers write.

The researchers point out certain limitations of the study, however, namely that the data were drawn from disparate studies from various populations. The data also relies on current smoking measures, rather than lifetime exposure, which is more strongly associated with lung cancer risk.

However, they have confidence in their results, which show that phenotype precision is important to uphold in GWAS studies, rather than ever-larger sample sizes, they say. "The use of objective measures of smoking behavior in genome-wide studies may reveal novel variants associated with these outcomes, which would be undetectable using conventional self-report measures."

In an accompanying editorial, Margaret R. Spitz, M.D., MPH, of the Department of Molecular and Cellular Biology at the Dan L. Duncan Cancer Center at Baylor College of Medicine, writes that these findings "confirm that cigarettes per day is an imprecise measure of nicotine consumption, and favor the interpretation that the association between these variants and lung cancer is mediated by smoking. But the degree to which the association is mediated by smoking is yet to be determined." They add that more studies, including mouse and cellular models, along with emerging metabolic markers, "may help tease apart the direct and indirect associations of these variants with lung cancer risk."

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