Genetic Susceptibility to Lung Cancer: An Example of Gene-Environment Interaction.

David C. Christiani, MD,MPH, MS

Professor of Medicine, Harvard Medical School

Professor of Occupational Medicine and Epidemiology

Harvard Medical School

Physician, Massachusetts General Hospital

Boston, Mass,

USA

There are several significant challenges to understanding variation in an individual's or a population's susceptibility to an environmentally induced disease such as lung cancer.

Firstly, the genetic landscape of human susceptibility is complex. There are likely to be only rare instances in which mutations within a single gene convey significant sensitivity to typical levels of exposure. More likely, there will be many genes with moderate or small effects, which, in combination, result in disease susceptibility after exposure. Interactions among genetic variants, as well as gene-environment interactions and epigenetic processes, are likely to play a significant role in determining disease susceptibility to an exposure. This etiologic heterogeneity presents methodologic challenges.

Secondly, we are only beginning to understand the distribution of single nucleotide polymorphisms (SNPs) in the human genome and to type large numbers of SNPs accurately. Ideally, we would like to handle all known SNPs' measures in epidemiologic, clinical, or in vitro studies, eliminating the puzzle of whether unmeasured genetic variants contribute to observed variation in disease risk or progression. Currently, in population genetics, multistaged research strategies, such as linkage to identify potential genomic regions, followed by positional candidate gene studies or genomic scans using tag SNPs followed by fine mapping, are employed to identify a set of genes and their variants that are most significantly associated with disease susceptibility. These multistaged approaches typically assume that individual mutations have statistically significant and context-independent (ie, some disease association in different populations or other contexts) disease associations. However, true multigenic models of susceptibility to common (ie, complex) disorders have not been achievable to date.

Lung cancer remains the leading cause of cancer mortality in the Western world, and its incidence is increasing worldwide. Lung cancer is associated strongly with environmental exposures, with the highest population-attributable risk from cigarette smoking. Although smoking accounts for the majority of lung cancer cases, the fact that only a minority of smokers develop lung cancer in their lifetimes makes this disease an important model for assessing gene-environment interactions. Because of its clinically poor prognosis, which makes it difficult to conduct efficient family-based linkage analysis of pedigrees for polygenic inheritance, the predominant method used to date in lung cancer has been the candidate gene approach in case-control studies. The most common method to date of selecting candidates consists of what can be considered as forward selection on the basis of existing knowledge of toxicologic and carcinogenic pathways (eg, DNA repair, cell cycle, apoptosis) and from functional genomics. This presentation will present results of studies we have performed on the role of common genetic variation on lung cancer risk, as well as the role of common variants in lung cancer prognosis.