Editorial

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Genetic biomarkers and occupational epidemiology-recollections, reflections and reconsiderations

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Genetic biomarkers and occupational epidemiology—recollections, reflections and reconsiderations

> *"We are under no illusion that preventive strategies will be easy to implement. For a start, the costs of prevention have to be paid in the present, while its benefits lie in the distant future. And the benefits are not tangible—when prevention succeeds, nothing happens. Taking such a political risk when there are few obvious rewards requires conviction and considerable vision."*
>
> Kofi Annan, Secretary General of the United Nations (1)

The objective of epidemiologic investigations is to estimate the distribution and determinants of disease in populations, with the ultimate goal of disease prevention. Use of biomarkers in occupational epidemiology requires a multidisciplinary approach in which molecular genetics, cell biology, toxicology, biochemistry, statistics, and bioethics are incorporated into a traditional research framework. Recently, both genetic and epigenetic abnormalities have been detected in lesions in people clinically free of disease, and these abnormalities could be used in assessing the risks to and monitoring of the health of working populations. Paul A Schulte, in this issue of the *Scandinavian Journal of Work, Environment & Health* (2), elegantly discusses the implications of using genetic biomarkers in occupational epidemiology and practice. As he puts it, "... sequencing of the human genome is the greatest opportunity for epidemiology since John Snow discovered the Broad Street Pump [p 76]". Can we seize this opportunity?

Biomarker use in monitoring exposure in a work environment was pioneered in the 1970s, first with respect to metals and organic solvents, then gradually expanding to a larger, more varied spectrum of exposures. This use expanded with the availability of techniques to measure effects at the molecular level, for instance, structural chromosome and gene damage, gene variation, and gene products in cells and body fluids (3). Use of these biomarkers improved our ability to understand causality by allowing more direct and more accurate measurement of exposure and outcome. The aim of occupational epidemiology is to study the causal relations between exposure to exogenous agents and the development of clinical disease. The mechanisms by which exposures lead to disease are still, however, often unknown. Direct observation of a relationship between disease and exposure was considerably easier when exposure levels were high, such as in the 1960s and the beginning of the 1970s. With changing environments and decreasing exposure levels, we need to evaluate subtler exposures and smaller risks.

It has also been suggested that biomarker use also enhances quantitative risk assessment, by providing more accurate data for establishing dose–response relationships and measuring exposure and by facilitating the extrapolation of results from experimental animals to human populations. Individual susceptibility to a particular exposure can also theoretically be mapped genetically. Such studies have progressed quickly because of the rapid advances that occurred in relation to methods for molecular genetics in the 1980s and 1990s. Information about the distribution of "preclinical" lesions or markers of susceptibility has also contributed to the characterization of high-risk populations (4).

The early detection of disease in occupational settings remains a priority for occupational medicine. The detection of early warning signs, at preclinical stages, can be facilitated by a variety of

genetic and epigenetic approaches that allow the identification of DNA (deoxyribonucleic acid) alterations that can be detected with robust, validated assays. The most successful approaches include microsatellite analysis for the diagnosis of bladder cancer from urine samples and oral cancer from saliva. Promotor hypermethylation is a promising method that can be used to detect various types of cancer. Its particular attraction is that cancers can be detected by a simple analysis of serum or plasma DNA. The finding that aberrant methylation can be detected in epithelium of the upper aerodigestive tract from cancer-free heavy smokers (5) suggests that aberrant methylation is an ideal biomarker for assessing lung cancer risk and for monitoring in chemoprevention trials. Moreover, it has been shown in vitro that methylation can be reversed by demethylating agents and thereby result in gene re-expression.

The role of polymorphic genes in the metabolism of xenobiotics has been the subject of extensive research during the past 30 years. Of primary concern in occupational and environmental studies are genes that have multiple alleles, sometimes referred to as "metabolic polymorphisms". They generally do not themselves present a risk, but do so only in combination with an exposure. Helmut Bartsch and his colleagues (6) summarized the results of studies on the relationship between several cytochrome P450 (CYP) genotypes and tobacco-related cancers in the upper aerodigestive tract, urinary tract, and breast. They reported that certain CYP variants were associated with increased risks of cancers of the lung, head, and neck in smokers.

Alcohol is also a risk factor for head and neck cancers. The mechanism by which ethanol acts is, however, unclear. It may act by forming acetaldehyde, as the enzymes involved in acetaldehyde production are polymorphic and, therefore, result in between-person variation in ethanol metabolism. If this is the mechanism of ethanol-induced cancer risk, the effect of alcohol would be greater among persons who metabolize rapidly. The potential relationship between exposure to acetaldehyde and head and neck cancer would appear to be a good subject for studies of "Mendelian randomization", using genetics to test hypotheses about nongentic exposures (7). Mendelian randomization studies must meet the following preconditions if they are not to be flawed: the gene should not have other functions that influence the risk (pleiotropy), it should not influence behavior (drinking), and there should be no linkage disequilibrium with other genes that may influence the disease (8).

Unlike most environmental exposures, which can be altered if proved to cause disease, inherited gene variants cannot be changed and can be passed on to subsequent generations. Given the number of xenobiotic-metabolizing enzymes and the wide variation in their inducibility and expression, it is probably too simplistic to consider examining one gene at a time in relation to cancer risk. Future studies should consider the roles of other genes in the pathways, and several genes should be examined at the same time in relation to disease risk. Techniques that provide simultaneous assessment of tens to hundreds of genetic variants in large numbers of samples will soon become available.

It is, however, unrealistic to anticipate the incorporation of a large number of genes into current studies until the appropriate statistical methods are available. Researchers should also be concerned about the use and misuse of genetic information. Proper informed consent and confidentiality for study participants, as well as careful evaluation of subgroups of patients and gene–environment interactions, are imperative.

In order to design a successful disease prevention program, we should ideally understand the natural history of the disease. Use of molecular markers in toxicology and epidemiology holds promise for elucidating the mechanisms of disease development and progression. Many of the factors in gene–environment interactions are modifiable and would provide a good starting point for primary prevention. It appears inevitable that various genetic polymorphisms will be identified at an increasing pace. Whether the identification will improve our ability to control occupational diseases is unclear. The number of genes that contribute to susceptibility to many diseases is likely to be large, and the effects of each gene on an allele will be weak. For example, if there are a dozen or more genes that contribute to myocardial

infarct or to lung cancer, attempting to identify susceptible subgroups for public health intervention would be too complex to be of practical value. Thus, for myocardial infarct and lung cancer, and for most other chronic diseases, it is likely that more persons will benefit from modifications in their life-style or environmental factors than from knowledge about their genotypes.

If scientists conduct a comprehensive search for the genetic basis of every health outcome and ignore environmental exposures and attributable risks, we are likely to miss opportunities to prevent disease. Undoubtedly, overoptimistic expectations about the ability of genomics research to solve chronic disease problems emerged in the period of excitement that followed the sequencing of the human genome. This overoptimisim stemmed in part from a lack of understanding of the complexity of disease causation and in part from a tendency of some scientists to overemphasize the immediate medical importance of their work to the media and granting agencies.

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