

# Symposium: Interactions of Diet and Nutrition with Genetic Susceptibility in Cancer

## Overview<sup>1</sup>

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There is considerable evidence from observational epidemiology indicating that nutrition is of importance in the etiology and prevention of cancer (Trichopoulos and Willett 1996, World Cancer Research Fund 1997). Dietary factors appear to contribute to the etiology of the major cancers including lung cancer (Ziegler et al. 1996), colorectal cancer (Potter 1996), breast cancer (Hunter and Willett 1996) and prostate cancer (Kolonel 1996). However, the mechanisms underlying these associations and the specific nutrients or other food components responsible for the observed effects are far from clear. The inclusion of biological markers of exposure and of disease and predisease conditions in epidemiologic investigations of cancer is allowing for some elucidation of mechanisms and of relevant active agents. In addition, an understanding of the role of endogenous factors, particularly genetic factors, is of importance in our growing understanding of the role of diet and nutrition in carcinogenesis and cancer prevention.

Increasingly, there is evidence that genetic variation may lead to intraindividual differences in metabolism. That evidence has led to interest in understanding the potential effect of genetic variability in relation to susceptibility to cancer. Carcinogenic and anticarcinogenic effects of environmental exposures including dietary factors may be modified by genetic differences. Enzyme activity, receptor activity and the action of other factors important in carcinogenesis may vary among individuals who have similar exogenous exposures and significantly affect their cancer risk. Unlike the single-gene mutations that have been identified for some cancers, which are rare but when present greatly increase the probability of cancer, these genetic polymorphisms are much more common and generally contribute to only a moderate variation in risk. However, the

public health implications of these weaker common genetic factors may be considerable because of the commonness of their occurrence.

There is considerable potential for better understanding the role of dietary factors in carcinogenesis when these interindividual differences in metabolism are taken into account. Identification of subgroups with greater susceptibility to dietary factors is of interest both in terms of prevention strategies for that subgroup and also because such findings may illuminate the underlying disease etiology.

The inclusion of measures of genetic susceptibility in the epidemiologic study of diet and cancer is relatively new. The papers included in this symposium provide some insight into the beginning efforts in that field. There is rapid growth in the field as genetic variants are described and hypotheses are generated regarding potential interaction of the genetic factors with dietary factors and risk. These papers review the current state of knowledge in the field. In addition, specific hypotheses regarding the interaction of diet and nutrition with genetic susceptibility are addressed.

Although there is some consensus that diet is likely to play a role in the etiology of chronic diseases, there is unexplained variation in response among individuals with apparently similar exposures. Some of this variation may be explained by error in the measurement of the exposures and by other unmeasured exposures. Additionally, these commonly occurring genetic factors may explain some of the observed variation. Identification of genetic susceptibility factors can provide insight into the mechanism of disease and perhaps into disease prevention. Much work remains to advance this field. Recently there were recommendations published regarding the directions that future research should take (Sinha and Potter 1997). It was emphasized that such research entails the use of an ensemble of approaches, with study designs extending from the molecular to the population level, integrating evidence from cell models, tissue studies, animal studies, small intensive human studies and population-based studies, requiring the collaboration of laboratory and population scientists. There are basic biologic questions that need to be addressed. These include structure/function relationships of genetic variants and the relationship role of genotype to phenotype. There is the need for research to focus on the identification of genetic variants

<sup>1</sup> Presented at the symposium "Interactions of Diet and Nutrition with Genetic Susceptibility in Cancer" as part of Experimental Biology 98, April 18-22, 1998, San Francisco, CA. The symposium was sponsored by the American Society for Nutritional Sciences. Published as a supplement to *The Journal of Nutrition*. Guest editors for the symposium publication were Jo L. Freudenheim, State University of New York, Buffalo, NY and Rashmi Sinha, National Cancer Institute, Bethesda, MD.

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in candidate pathways, particularly variants in rate-limiting steps, rather than focusing research on the known polymorphisms. Finally, there needs to be consideration of not only genetic variation in enzymes of carcinogen activation and detoxification but also of other variants including those in receptors, DNA repair enzymes, cell cycle regulators and transcriptional factors. Many of these factors may be of significance in understanding the role of nutrition in carcinogenesis. Understanding the role of genetic susceptibility as a contributing factor in interaction with dietary and other environmental exposure holds considerable promise for contributing to the understanding of cancer etiology. The work is now in embryonic stages and needs to be pursued both systematically and with vigor.

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