

*Editorial***Nutrition and Cancer Prevention: Small-scale Human Studies for the 21st Century****Johanna W. Lampe**

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At the beginning of the 20th century, dietary deficiency diseases were at the forefront of nutritional and medical research. A new paradigm was becoming widely accepted, notably that minor constituents of food were essential for life. From 1915 to the 1950s, some 40 essential nutrients were identified and characterized and their functions were explored (1). Among the approaches used to study these essential compounds were dietary studies in humans, which bridged the gap between the human population-based studies of deficiency and the animal studies of essentiality.

Controlled feeding studies in healthy humans were used to establish the quantitative requirements and confirm essentiality of nutrients in humans. Typically, these studies had small sample sizes, were intensively controlled, and often focused on restriction and refeeding of specific nutrients or nutrient sources. They evaluated the acute effects of food deprivation (2), showed experimentally the effects of dietary restrictions on development of deficiency diseases (3), established specific amino acid requirements (4), and described vitamin metabolism (5). They were crucial in identifying the recommended daily dietary allowances. Nonetheless, Carpenter et al. (1) make the interesting observation that this emphasis on nutritional essentiality may have distracted attention from investigation of the nonnutritional components of food and from the ancient paradigm that foods contain nutriment, medicines, and poisons. This more reductionist approach undoubtedly slowed scientific progress in understanding the totality of diet in relation to health.

At the beginning of the 21st century, the paradigm has shifted once again: now, a whole host of other nonessential minor constituents of food are recognized by the mainstream scientific community as important for maintenance of health and prevention of disease. Furthermore, the number of minor constituents receiving research attention has grown considerably. A laundry list of phytochemicals, diet-derived carcinogens, and other dietary constituents are receiving some of the same attention the vitamins and minerals did a century ago. With the onslaught of interest in all these additional compounds and in the quest for new magic bullets for chemoprevention, it seems that, in the 21st century, we still run the risk of shunning the ancient and relevant paradigm and of not enabling understanding of the effects of the totality of diet. Observational data regularly

show that dietary patterns and the consumption of foods within a range that is behaviorally possible and culturally normative affect disease risk; we still need to retain this as a focus of experimental human studies (6, 7).

The tools to evaluate effects of diet are changing rapidly. In less than a decade, we have gone from a reductionist pursuit of single biomarkers to a holistic approach, in which a significant fraction of all regulated genes and metabolites has the potential to be quantified concurrently (8). The “omics”—genomics, transcriptomics, proteomics, and metabolomics—approaches will improve our understanding of the interactions of the various systems that are often studied in isolation and have the potential to revolutionize many aspects of our study of nutrition and cancer prevention. Despite the excitement, at this stage, the technologies still require rigorous evaluation and validation. Controlled feeding studies are a perfect approach in which to validate and test the robustness of these technologies with the goal of ultimately being able to use them to evaluate the effects of totality of diet on totality of response in humans.

With increased understanding of the mechanisms of carcinogenesis and identification of biomarkers of cancer risk and the cancer process, the small-scale dietary trial approaches of the 20th century remain well suited to evaluate the role of diet in cancer susceptibility and prevention. There are more tools to use and more hypotheses to test, including those related to genetic and epigenetic control of response to diet. It has long been recognized that, even in the setting of a controlled feeding study, there is a wide range of responses to certain dietary treatments. Functional genetic polymorphisms have been identified as some of the sources of variation. Polymorphisms in genes encoding for proteins that metabolize and transport dietary chemopreventive agents as well as carcinogens affect cancer risk. Polymorphisms that influence receptors and transcription factors that interact with these compounds affect the impact of the agents on transcriptional regulation. Controlled feeding studies are a useful venue in which to test genotype-diet interactions as well as genotype-phenotype interactions. In the latter case, evaluating the relationship between genotype and phenotype on the background of the same dietary exposures (i.e., a controlled diet) phenotypes can be better characterized.

Small-scale human studies of nutrition have been a part of *Cancer Epidemiology, Biomarkers & Prevention* since the journal's inception in 1991. Over the past decade, we have tested nutrition and cancer prevention hypotheses born of observational studies and evaluated biological

effects established in animal models and cell systems; we continue to bridge the gap. With the advent of new tools, new hypotheses, and the well-recognized role of small-scale interventions in cancer prevention research, *Cancer Epidemiology, Biomarkers & Prevention* looks forward to welcoming the results of the feeding studies of the 21st century.

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