

NUTRITIONAL EPIDEMIOLOGY

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Summary

This chapter provides an overview of the study designs and methods used to learn about the relationship between dietary patterns and chronic disease risk. The strengths and weaknesses of animal experiments, population comparisons, analytic epidemiologic studies, and dietary intervention trials are reviewed both for nutritional epidemiology hypothesis generation and for hypothesis testing. This leads to some perspectives on future research needs and opportunities. Data pertinent to the controversial topic of dietary fat and postmenopausal breast cancer are described in some detail to elucidate the issues and challenges in this important research and public health area.

1. Introduction

The quality and quantity of the food supply is a key determinant of human health and world development. Aspects of food production, safety testing and distribution are critically important to public health, international trade, and economic development. Guidelines for the food and nutrient consumption of individuals and groups are developed by various scientific bodies in various parts of the world, with myriad

nutritional and international health and welfare policy implications. For example, in the United States the Food and Nutrition Board of the National Academy of Sciences periodically conducts a nutrient by nutrient review of the literature to update such dietary reference indices as estimated average requirement, recommended daily allowances, adequate intake, and upper levels. Much of this work focuses on the intakes needed to avoid deficiency diseases, specific to age and sex, but there is also a developing emphasis on nutrient intakes that may reduce the risk of prominent chronic diseases.

More generally the topic of nutrient and food consumption patterns that may reduce chronic disease risk has been a substantial epidemiologic research focus for the past few decades, with selected cancers and cardiovascular diseases receiving the most attention. While diet and disease prevention hypotheses have often arisen from population comparisons or animal experimentation, the testing of hypotheses has almost uniformly centered on traditional epidemiologic case-control and cohort study designs. However, following a quarter century of extensive investigation rather few consistent diet and chronic disease associations have emerged from these studies, and associations that have emerged have tended not to be supported by randomized controlled intervention trials in the few instances where pertinent RCT's have been conducted. Hence, one is obliged to think that either the dietary elements or patterns that have been studied are not particularly important determinants of chronic disease risk, or that the study methods that are being employed may not be able to reliably identify important associations.

There are a number of reasons for thinking that diet and nutrition, presumably in conjunction with physical activity, may have a major role in determining the risks of a broad range of chronic diseases. For example,

1. The pattern of consumption of macronutrients is related to established chronic disease risk factors.
 - Fat intake by degree of saturation relates strongly to blood cholesterol, a strong risk factor for coronary heart disease.
 - Energy consumption, and energy balance, relate to obesity and various aspects of body mass and shape, which in turn relate to the risk of many chronic diseases including prominent cancers, vascular diseases, diabetes and fractures.
2. Controlled feeding experiments, mostly over the past 60 years, have revealed many strong diet and disease associations in inbred strains of laboratory animals.
 - Some of the most impressive observations have concerned the risk reduction that follows from energy restriction. However, both macronutrient distribution and micronutrient content of the diet can be important.
3. International variations in disease rates and trends over time in national disease rates often correlate strongly with national dietary consumption patterns.
 - Good information is available on chronic disease rates for various populations worldwide. For example the Cancer Incidence in Five Continents series coordinated by the International Agency for Research on Cancer is comprehensive with good quality control. Many human cancers have ten fold or greater variations in incidence around the world, and cancer incidence patterns in many countries

have changed dramatically over the past few decades, presumably due primarily to changes in modifiable risk factors.

- The Food and Agriculture Organization of the United Nations provides estimates of the per capita ‘disappearance’ of various nutrients in countries throughout the world. The strong correlation between chronic disease incidence and mortality rates and these nutrient disappearance data helped to generate diet and disease hypotheses, for example concerning fat consumption and such diseases as breast, colorectal and prostate cancer.
4. The chronic disease experience of migrant populations strongly suggests that lifestyle factors and exposures are important determinants of chronic disease risk.
- Studies of mortality patterns indicate that migrant groups tend to adopt the (usually higher) mortality rates that prevail in their new location, usually within a generation or two of migration. This seems impressive since acculturation may extend over several generations.
 - There have been few analytic epidemiologic studies of migrant groups. One fairly recent breast cancer case-control study estimated the incidence rates of Asian migrants to the United States to increase by about 60% within a decade of migration.

Beyond these motivational and hypothesis generating data sources is a substantial body of analytic epidemiologic studies over the past 25 years. For example, a 1997 volume summarized these data as they relate to food, nutrition and cancer from a global perspective. While some fairly consistent associations have emerged from these studies, most notably concerning lower rates of several cancer with greater consumption of fruit and vegetables, it seems fair to summarize that overall such studies have been disappointing in that most suggested associations have been weak and inconsistent between studies. This state of affairs motivates a careful scrutiny of the study methods that are used to test diet, nutrition and chronic disease hypotheses, which in turn has implications for future research needs and trends in this important research area.

2. Research Designs and Methods

2.1. Hypothesis Development

As noted above nutrition and chronic disease hypotheses have frequently been generated by animal experimentation or by the comparison of disease rates among populations having differing dietary habits. Another source of hypotheses is analytic epidemiologic studies themselves. For example, dietary assessment in a cohort study context typically leads to individual consumption estimates for a lengthy list of foods, and hence to consumption estimates for various nutrients through the use of nutrient databases that provide estimates of the nutrient content of foods. Hence a single cohort study can potentially examine a large number of food and nutrient associations with a large number of diseases, given sufficient size and study duration, potentially yielding many nutritional epidemiology leads.

Each of these study design and data sources has important limitations, even for hypothesis development. Animal experiments are excellent for providing motivation for this research area, but the disease experience of inbred strains may have unclear

relevance to human health, and the dietary contrasts that may be necessary to control experimental costs and logistics (e.g., 25-50% energy restriction) may not be practical for free living humans. On the other hand pertinent animal models for a given dietary prevention hypothesis could yield much insight into mechanisms and hence contribute to hypothesis strengthening and refinement.

Population comparisons and time trend analyses, as they are typically conducted, suffer from a limited ability to control for both dietary and non-dietary confounding. The readily available nutrient and food supply (disappearance) data, even though objective, are rather crude. For example, these data are not age or sex specific, and they are restricted to per capita averages which do not allow estimation of the consumption distribution of foods or nutrients within each population group. There is potential for migrant studies to contribute substantially to hypothesis identifications and development. However, there have been very few analytic epidemiologic migrant studies to date, and those few studies have mostly not attempted to assess the dietary patterns of the study subjects.

As noted above, exploratory analyses in the context of cohort or case-control studies within populations have been an active source of diet and chronic disease hypothesis. The large number of associations that can be examined in such contexts, corresponding to the large number of foods and nutrients estimated, and to the many ways the distribution of each nutrient can be sliced or corrected for other nutrients, can lead to many spurious hypotheses. Beyond this multiple testing limitation are a number of important issues that apply to analytic epidemiologic studies in this diet and chronic disease research area, as will be elaborated in the next subsection.

Concerns about the relevance and/or reliability of the standard sources of information for hypothesis identification and development suggest that additional approaches and data sources may be needed to identify dietary intervention hypotheses that merit full-scale human testing. This topic will be returned to in Section 4.

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Biographical Sketch

Ross Prentice is a scientist in the Public Health Sciences Division of the Fred Hutchinson Cancer Research Center in Seattle, and is Professor of Biostatistics at the University of Washington, Seattle. He has longstanding research interests in statistical methods for biomedical research, and he is principal investigator of the Clinical Coordinating Center for the Women's Health Initiative. He received the COPSS award from the presidents of various statistical societies in 1986, was elected to the Institute of Medicine of the U. S. National Academy of Science in 1990, and he recently (2002) completed a six year term on the Food and Nutrition Board of the Institute of Medicine.