The role of epidemiology in developing nutritional recommendations: past, present, and future[1,2]

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ABSTRACT Observations of the relations between food choices and health have been made since ancient times, but epidemiology, which can be regarded as the science of systematically studying these relations, has played a key role in official nutritional guidance only in recent years. In the past 20 y the principal goal of nutritional guidance has changed from the prevention of nutritional deficiencies to the prevention of chronic diseases. This evolving purpose of nutritional guidance has demanded that nutritional epidemiology play an increasingly important role. Although no other type of nutritional science can equal epidemiology in the relevance of either the dietary exposures or the health outcomes, substantial problems limit the ability of nutritional epidemiology to convincingly prove causal associations. The classic criteria for causation are often not met by nutritional epidemiologic studies, in large part because many dietary factors are weak and do not show linear dose-response relations with disease risk within the range of exposures common in the population. The most important problem in nutritional epidemiology in the past has been the inaccuracy of dietary assessment. In the future, an additional problem will be the proliferation of hypotheses that can be tested in multiple ways among the many subgroups of the population that can be defined by factors such as age, sex, and genotype. Future progress in our understanding of the relations between diet and health will necessitate improved methods in nutritional epidemiology and a better integration of epidemiologic methods with those used in the clinical nutritional sciences. *Am J Clin Nutr* 1999;69(suppl):1304S–8S.

KEY WORDS Epidemiology, nutrition, diet, dietary guidelines, nutritional recommendations, dietary assessment, chronic disease risk, public health, disease prevention, health promotion

INTRODUCTION

The best basis for recommendations on how people should eat to stay healthy is an understanding of how healthy people eat. To that end, nutritional epidemiology studies the right species in the right environment. The rest of nutritional science, ranging from laboratory animal manipulations to the descriptions of molecular dances in flasks, though much more elegant and precise than epidemiology, contributes less to the decision about what we should have for lunch than do studies of the simple associations between food choices and health in free-living people.

This supplement examines the role that nutritional epidemiology should play in formulating nutritional recommendations and how the various types of studies can best contribute to our understanding of the relations between nutrition and health. The decisions as to which epidemiologic study should carry more weight for any particular recommendation and how epidemiologic evidence can best be balanced with experimental evidence will always need to be predicated on 3 assessments: the nature of the question at hand, the strengths and weaknesses of various study designs, and, perhaps most importantly, the quality of individual studies as carried out. The purpose of this article is to frame our discussions at this workshop by reflecting on the roles that nutritional epidemiology has played in the past, commenting on the current controversies in interpreting findings from nutritional epidemiology, and speculating on roles that nutritional epidemiology will likely play in the development of future nutritional recommendations.

Although recommendations for research priorities in nutritional epidemiology may emerge from our discussions here, our attention will focus primarily on the question of the best use of nutritional epidemiology in setting nutritional recommendations. As we begin to consider this, it is important to consider the alternatives—if not nutritional epidemiology, then what? Animal experimentation, in vitro laboratory studies, and human experimentation are the only alternatives. Animal and laboratory studies are useful for understanding mechanisms of nutrient effects but have limited ability to guide us directly on either our individual food choices or our national nutritional policies. Studies in humans are more informative but they are often severely limited by cost, compliance, ethics, and time. Consequently, few experimental studies on nutritional factors affecting disease endpoints have been completed, and most of our inferences about the roles of foods and nutrients in the prevention of chronic diseases must be based on observational epidemiology.

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DEFINITIONS

To clarify the title and purposes of this article, I will set the following definitions. *Nutritional epidemiology* includes all studies of the relations between diet and health in human populations. The term *recommendation* refers to any reasoned conclusion derived from scientific studies about nutrition that is transmitted to the general public for purposes of health promotion and disease prevention. Hence, this definition includes both those recommendations that might be made informally, as by a scientist or journalist writing for the public, or formally, as by an officially appointed expert panel. The *past* includes everything before 1996, the *present* includes everything from January 1996 until now, and the *future* is the remainder of time.

THE PAST

Nutritional recommendations are not new. The ancient writers of Leviticus passed on a litany of recommendations about foods to be avoided, relying heavily on the concept of "abomination" in recommending against certain choices (1). Subsequently, nutritional guidelines have become increasingly scientific while also decreasingly compelling. In the fourth century BC, Hippocrates observed a relation between health and food choices, noting that "…to the human body it makes a great difference whether the bread be fine or coarse; with or without the hull, whether mixed with much or little water, strongly wrought or scarcely at all, baked or raw….Whoever pays no attention to these things, or, paying attention, does not comprehend them, how can he understand the diseases which befall man?" (2). The ancient recommendations were not based on science, yet they were almost certainly derived from insightful observations of the relations between diet and health that were passed down over centuries of oral tradition.

The modern era of nutritional guidelines began in the early 20th century with public health campaigns to eradicate diseases caused by vitamin deficiencies by promoting variety in the diet, particularly the eating of vegetables and fruit. These campaigns were based on the observations of nutritional epidemiologists who followed the sequence from ecologic observation to case-control studies to intervention trials to confirm the relation between food choices and vitamin deficiency disorders. One of the residuals of these campaigns may have been the oral tradition of nutritional guidelines first passed on to most of us by our mothers when we were young children in the middle of the 20th century: "Eat those peas—they're good for you."

General recommendations for nutrient intakes were formalized in 1943 with the first recommended dietary allowances (RDAs), which were based largely on clinical and experimental studies of nutritional deficiency states (3). The scientific studies used in the development of the current RDAs are specified by the Food and Nutrition Board of the National Research Council as being of 6 types: "*1*) studies of subjects maintained on diets containing low or deficient levels of a nutrient, followed by correction of the deficit with measured amounts of the nutrient, *2*) nutrient balance studies that measure nutrient status in relation to intake, *3*) biochemical measurements of tissue saturation or adequacy of molecular function in relation to nutrient intake, *4*) nutrient intakes of fully breast-fed infants and of apparently healthy people from their food supply, *5*) epidemiologic observations of nutrient status in populations in relation to intake, and *6*) in some cases, extrapolation of data from animal experiments" (3). This description of the role of epidemiologic studies in the development of the RDAs is general, but it implies that the consideration of epidemiologic studies is limited largely to ecologic studies in which nutritional deficiency states are related to measures of low nutrient intake.

The ways in which both the RDAs and the dietary guidelines were developed and the philosophical and political forces at play in guideline formulation were well discussed recently by Kunkel (4). Guidelines that addressed more directly food choices for Americans for chronic disease prevention than did the RDAs did not appear until the Senate Select Committee on Nutrition and Human Needs report of 1977 (5). That report, which encouraged Americans to move toward a more plant-based diet lower in fatty foods, was based largely on data about the relation between diet and heart disease. Those data included findings from a strong set of ecologic and longitudinal epidemiologic studies complemented by clinical studies confirming the relation between diet and serum cholesterol concentration, which is a strong intermediate marker of the relation between nutrition and heart disease.

Cardiovascular disease was the first chronic disease to be shown to have a dietary etiology and that discovery is still perhaps the best example of the proper fusion of epidemiology with experimental nutritional science. The difference between the nutritional-epidemiologic approaches to heart disease and to cancer is interesting. For heart disease, case-control studies were difficult to perform, both because of sudden death and because incident disease can cause changes in physiologic risk factors. Therefore, prospective studies were used almost exclusively. Early on, the nutritional causation of heart disease was thought to be mediated only by serum cholesterol concentrations. Consequently, full and systematic investigations of the diet–heart disease relation did not occur until recent years when the roles played by other aspects of diet, such as fiber, antioxidant micronutrients, and folate, in heart disease risk were uncovered. In contrast to this reliance on longitudinal studies with a strong intermediate factor, the initial approach to studying diet and cancer was to use case-control designs until the mid 1980s, when cohorts were assembled. Cancer studies have not yet identified strong intermediate markers for cancer that are analongous to cholesterol as a marker for heart disease.

In contrast to the focus on nutritional deficiency in the RDAs, and more consistent with the intent of the Senate Select Committee report (5), the 1989 *Diet and Health* report focused on the role of optimal nutrition in the prevention of chronic diseases (6). The Committee on Diet and Health of the National Research Council considered all sources of information including in vitro studies and animal experiments but placed considerable emphasis on studies in human populations, which were nearly exclusively observational epidemiologic studies. The committee adapted the Hill (7) criteria for causality to interpret the diverse nutritional literature, qualitatively judging whether the totality of evidence pointed to an association that was strong, showed a dose-response relation, was temporally correct, was consistently observed, was specific, and had biologic plausibility. Even the committee recognized, however, that these criteria are of limited use in nutritional epidemiology. Not all meaningful associations are expected to be strong (hence a set of studies will not necessarily show either a dose-response relation or consistency), nutritional factors are not specific because they may affect several diseases similarly, and biologic plausibility is a product of the state of knowledge at any given time and subjective imagination. The Hill criteria for causality are therefore of limited practical

utility in nutritional epidemiology, in which many findings of public health relevance will produce relative risks that are small, nutritional dose will not necessarily be expected to relate to disease outcome across the range of exposures measured, and biologic plausibility can be thin ice. The limitations of the Hill criteria are discussed by others in more detail in this supplement.

The various types of epidemiologic studies are shown according to their classic sequence and hierarchy in **Figure 1**. The strengths and weaknesses of these types of studies as applied to nutritional epidemiology will be discussed in detail during this workshop. Although this classic sequence suggests an inherent hierarchy of strength and accuracy among epidemiologic studies, for many nutritional hypotheses ecologic studies perform better than studies of individuals, and case-control studies perform better than prospective studies. Randomized, controlled trials, although theoretically supreme, do not offer a practical approach to answering many nutritional questions. In formulating its 1989 report, the Committee on Diet and Health recognized that "there is no universally valid hierarchy or weighting of categories of studies and hence no comprehensive procedure for leaping from results to conclusions." (6) The classic sequence from ecologic study to randomized trial to conclusion and recommendation (Figure 1) is rarely followed. In practice, the various studies contribute to a conclusion and recommendation in a less linear fashion, as shown in **Figure 2**. Prospective and case-control studies differ in many ways but provide essentially the same information and so are grouped together in Figure 2. Many of the more strongly held conclusions and recommendations are derived mostly from ecologic studies; these conclusions include the ideas that cereal fiber prevents colorectal cancer and low-fat diets prevent breast cancer (8, 9). In fact, the strongest rationale for a trial even as large as the Women's Health Initiative seems to come from ecologic studies (10).

The US Preventive Services Task Force (11), in writing the *Guide to Clinical Preventive Services*, established criteria for judging the diverse set of studies on the effectiveness of various options for clinical disease prevention. These criteria were then used to grade a large set of possible clinical procedures according to effectiveness based on a 5-point scale. The hierarchy of evidence generally followed the classic hierarchy displayed in Figure 1 in that large, randomized, controlled trials were weighted heavily on quality but findings from uncontrolled trials, prospective studies, case-control studies, and ecologic studies were weighted progressively less heavily. The Food and Drug Administration adapted similar criteria for judging the evidence supporting health effects of nutrients in the process of responding to requests for approval of health claims for nutrients (12).

THE PRESENT

For the purposes of this article, the present began in January 1996, shortly after the publication of the fourth edition of *Dietary Guidelines for Americans* (13, 14). The first edition was published in 1980, and it is mandated by Congress that the guidelines be updated about every 5 y. Because the dietary guidelines are intended to be useful to the general public, they focus more on foods than on nutrients and are developed largely by considering epidemiologic studies. Epidemiologic studies are therefore supportive of most of the recommendations, although the scientific origin of the recommendation on dietary variety ("Eat a variety of foods") seems to be difficult to trace (13).

Nutritional epidemiology does a better job of describing the relation between foods and health than of assessing and quantifying nutrient effects. The example of β-carotene and lung cancer, which is discussed in more detail elsewhere in this supplement, is a reminder of the limitations of nutritional epidemiology in drawing inferences about the specificity of effects of particular nutrients from data that are food-based. Nonetheless, the practice of using crude information on food intake to make inferences about the relations between specific nutrients and health will undoubtedly continue. Nutrient databases for specific carotenoids, flavonoids, and phytoestrogens, for example, can now be used to generate effect estimates for many different types of compounds from a single set of food measures. Therefore, we can now create at least the illusion of being able to separate the effects of different nutritional chemicals from data that are based on crude estimates of the intakes of various foods by using statistical methods to separate chemicals that may in fact be difficult or impossible to separate in the laboratory.

In 1996 the American Heart Association (AHA) (15) and the American Cancer Society (ACS) (16) both released revised statements on dietary guidance for disease prevention. The AHA guidelines are more nutrient-based, mostly in aspects of the quantification and separation of dietary fats, and are based more on clinical feeding studies than are the ACS guidelines, which are and more food-based and generally avoid nutrient recommendations. The major difficulty in formulating the ACS guidelines concerned the issue of dietary fats and red meat. There was considerable debate about whether total dietary fat, a specific type of fat, or red meat per se was most relevant to cancer risk. The question of relevance was difficult to resolve due to the paucity of well-conducted studies in which these effects were analyzed separately and the uncertainty about the biological independence of nutritional factors that were separated statistically.

Important questions remain about the role of dietary fat in heart disease as well as cancer. In particular, serious questions remain about the independent effects on heart disease risk of total fat intake, specific types of fatty acids, and the specific food sources of fats (17, 18). This continuing controversy seems to derive from 4 sources: *1*) imprecision in dietary assessments, *2*) different assumptions about the implications of changes in an intermediate marker of disease (reductions in HDL cholesterol concentrations), *3*) lack of data on the behavioral responses of the public to alternative recommendations, and *4*) different assumptions about the effects of dietary fats on energy intake and obesity.

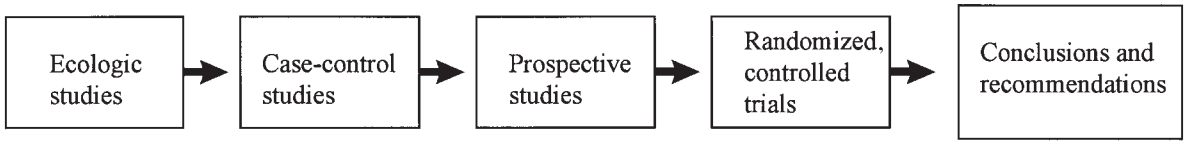

FIGURE 1. The classic sequence of hypothesis testing in nutritional epidemiology leading to nutritional recommendations.

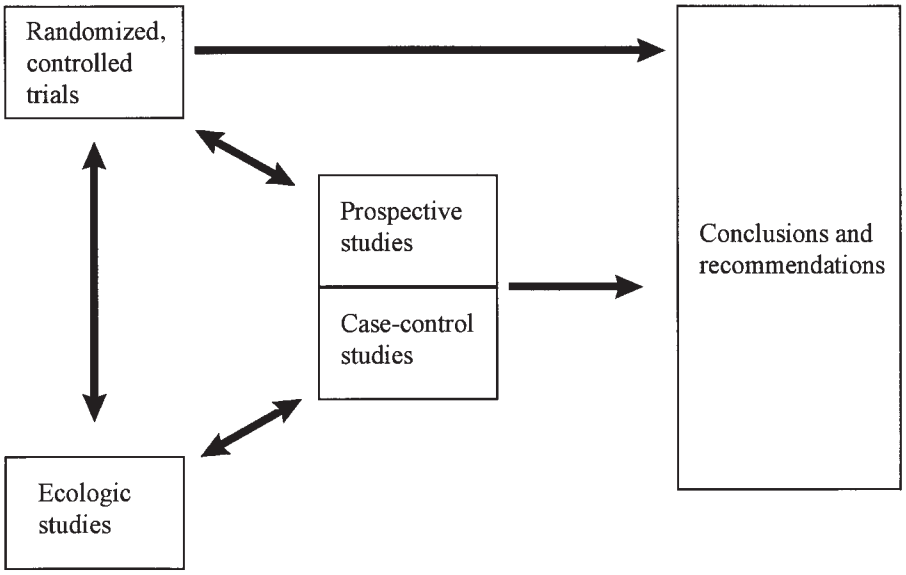

FIGURE 2. The currently practiced sequence of hypothesis testing in nutritional epidemiology leading to nutritional recommendations.

It is interesting to examine the alcohol guidelines of both the AHA and the ACS because alcohol may be one of the rare foods or nutrients for which there is a possible conflict between the recommendations for heart health and the recommendations for cancer prevention. The AHA guidelines, although recognizing a possible benefit from moderate alcohol intake, stop short of recommending alcohol consumption. The ACS guidelines, also acknowledging a possible benefit for heart disease, point to the epidemiologic evidence suggesting that breast cancer risk increases with even moderate alcohol intake. Both sets of recommendations fall back on the time-honored position of moderation for people who choose to drink alcohol. The conclusion that there is a lower risk of both cancer and heart disease with higher fruit and vegetable intake comes entirely from epidemiologic studies. The belief that high intakes of fruits and vegetables benefit health seems to be common ground for most nutritional epidemiologists, even those who disagree on other issues (17, 18). However, even within this safe territory (where even apple pie resides, but only in the opinion of some) there are those who remind us that our recommendations should not overstate the certainty of our understanding (19).

Several controversies are active in nutritional epidemiology. These controversies are fed by imprecision and bias in nutritional assessment methods, uncertainty about the ability of statistical methods to identify meaningful independent effects of nutrients, and difficulty in choosing among the many hypotheses that could be tested. Estimates of food intake can be analyzed and presented in several ways—as individual food frequencies, food groups, nutrient indexes, and food-group-specific nutrient indexes. Any of the preceding can be presented with or without various adjustment factors, including other, correlated foods and nutrients. Therefore it can be difficult to interpret studies featuring findings from only a single nutrient index, or for only one food item, and studies featuring associations between diseases and dietary factors that are adjusted for several other factors included in the same dietary measure. In the present, therefore, we are struggling to come to grips with the problems in dietary assessment and the analytic technologies that we can now apply to nutritional data.

THE FUTURE

In the future we will need to develop better ways to conduct nutritional epidemiologic studies and a better understanding of how to analyze and interpret dietary data. With apologies to Hippocrates (2), it could now be said that …to epidemiology it makes a great difference whether the data be fine or coarse; with or without error, whether mixed with many or few covariates, strongly wrought or scarcely analyzed at all, baked or raw….Whoever pays no attention to these things, or, paying attention, does not comprehend them, how can he understand the diseases which befall man?

The future will provide many more data from nutritional-epidemiologic studies on which to base recommendations. The proliferation of cohort studies, both in the United States and around the world, will provide the basis for more analyses and meta-analyses in the future. Studies of how dietary effects may differ among subgroups defined by characteristics such as age, sex, race, or genotype will be common in the future. As difficult as the challenge has been in the past to achieve consensus on nutritional recommendations for the general public, the problem will only be compounded when we consider recommendations for subgroups of the population, defined by factors such as age, sex, and genetic subtypes.

Epidemiology has always been a strong contributor to nutrition recommendations, and it always should be. However, in the future epidemiologists should not feel compelled to make too many recommendations or to state them with more certainty than they deserve (20). Better systems are needed for the translation of new research findings for the general public to avoid the confusion we have seen in the past (21). As we learn more about the relations between diet and health, however, we need to be open to new interpretations and to be prepared to change our minds occasionally. Advances in science are not always linear or predictable. For example, superbly reasoned arguments for why the human body needs only ≈70 μg Se/d (22) can be turned upside

down by a single study showing lower cancer rates among those given 3 times that amount (23). Although nutritional guidelines cannot flap in the wind with every new study, our understanding will certainly change in the future. We need to be prepared for that change. Firmly held opinions can create ethical belief systems that can cloud our interpretations (4). If in the future we should find that peas in childhood are important for long life, then we can thank our mothers. If, however, in looking more closely we should find that peas are not particularly good for us, we can simply forgive our mothers and stop eating them.

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