INTRODUCTION

Many epidemiologic studies of disease causation include food intake and nutrition variables (1, 2). Epidemiologic research is also an established component of nutrition and food science endeavors to identify optimal dietary patterns and to improve the quality and potential health benefits of the food supply (4). Manipulation of eating patterns and/or food content is a core health promotion and disease control strategy. However, the process of translating nutritional epidemiologic study findings into health advice or policy is quite complex.

There is much debate on diet and health issues; however, the general inference that modern eating and physical activity patterns are ill-suited to the hunter-gatherer genetic predispositions of our species is sound (5, 6). Given the limits of our biologic adaptability, diet and physical activity are thought to be critical determinants of the major causes of death and disability—cardiovascular disease, cancer, diabetes, and obesity—worldwide (4, 7-13). Studies carried out in diverse populations have converged to suggest that avoiding or moving away from the high fat, low fiber, and high salt diets and sedentary activity patterns typical in western societies will usually decrease the occurrence of chronic diseases (4).

Food is a universal and indispensable human exposure, and the foods we eat are deeply rooted in and defended by cultural beliefs and practices (14-16). Therefore, the study findings suggesting a need to change dietary patterns have a unique salience and sense of urgency for policy-makers, clinicians, and consumers. It is commonly understood that a synthesis of such studies, as well as their reconciliation with laboratory and animal evidence, is needed. However, the social relevance of such studies often motivates excessive media attention at the moment of publication, with frequent overstatement of the meaning of specific findings and insufficient attention being given to the larger picture (17, 18).

This review identifies some major challenges that will affect the conceptualization and methodology of future nutritional epidemiologic studies. Types of nutritional epidemiologic studies are described, followed by a review of issues in the contemporary literature. Particular attention is given to the societal and paradigmatic contexts in which nutritional epidemiology is conducted. Concluding comments relate to nutrition monitoring and policy development.

THE EXPANDING DOMAIN OF "NUTRITION"

In a narrow sense, "nutrition" refers to those components of food that are necessary for growth, normal functioning, and the maintenance of life—i.e., proteins, minerals, carbohydrates, fats, and vitamins (19). However, nutrition science now also incorporates artificial ingredients and nonnutritive food constituents that may relate to health (20-22). Variables of interest include: high doses of antioxidant vitamins and minerals; hydrogenated fats as sources of trans-fatty acids; phytochemicals such as indoles, isothiocyanates, sulforaphanes, allylic sulfides, and isoflavonoids that are thought to have protective properties; "functional foods," which may refer to natural or modified foods with health-protective properties; and "dietary supplements." Dietary supplements are defined as anything taken to supplement the diet, including various forms, extracts, and metabolites of vitamins, minerals, amino acids, and botanical products (21).

NUTRITIONAL EPIDEMIOLOGIC STUDIES

Nutritional epidemiology is a hybrid of nutrition science and epidemiology. Descriptive nutritional epidemiology characterizes qualitative (i.e., the relative mix of foods or dietary constituents) and quantitative (i.e., the absolute quantities of foods or dietary constituents) aspects of food intake. Such studies are important for assessing dietary exposures, finding points of leverage for effecting dietary modifications...
to meet health objectives, and tracking dietary changes in (sub)populations in order to assess and understand changes in the population dietary risk profile. Figure 1, which shows food supply and food and nutrient intake variables currently monitored in the United States (7), illustrates the breadth of factors to be considered.

Observational studies linking food intake and nutrition variables to risk factors and health outcomes have a major role in informing nutrition policy (figure 2) (4, 7, 10). Epidemiologic studies are superior to animal experiments in their direct relevance to humans, and they are more relevant to the broad experiences of human populations than are small-scale human studies. Prospective studies can address questions about long term effects of various dietary exposures on morbidity and mortality that are not feasible or ethical to address experimentally. Such studies are especially important for examining interactions of dietary factors with other behavioral and environmental exposures and with host factors such as genetic predisposition.


FIGURE 2. Decision-making process used to categorize food components by monitoring priority status. Source: Federation of American Societies for Experimental Biology (7).
and physiologic state (1, 2, 23). Nutritional epidemiology also involves trials about effects, on health risks or outcomes, of dietary changes such as reducing fat or sodium intake, increasing fiber or fruit and vegetable intake, or reducing weight (24–30). Such trials may last for weeks, months, or years. They may be conducted at one site or multiple sites and in community settings or clinical settings. Various types of behavioral interventions are used in such trials; double-blind supplementation of nutrients or dietary constituents in pill form is less common (24–28). Behavioral trials are plagued by problems of incomplete adherence, particularly if they are long term. The “feeding study” approach, in which standardized meals are provided (29, 30), obtains high adherence; however, this approach is expensive and is not behaviorally relevant to lifestyle change.

**CHANGES IN THE CONTEXT FOR DESIGNING AND INTERPRETING NUTRITIONAL EPIDEMIOLOGIC STUDIES**

Nutritional epidemiology is carried out in societal and scientific contexts that influence the conceptualization, collection, and interpretation of evidence about how what we eat relates to health and disease. Several changes in these contexts that may impinge on the validity of inferences made from some existing data sets and that will determine how future data should be collected are outlined below.

**Food supply and consumer behavior**

The food intake component of health status and disease risk involves numerous interrelated factors that are changing continually and sometimes rapidly. Many of these changes are incidental to other societal factors, and some are counter to extant dietary guidance. For example, an increase in the amount of food eaten away from home has been linked to higher fat, calorie, and sodium intakes (31). Other changes within the food supply that are potentially noteworthy from a health perspective include those related to bioengineering, new formulations of packaged foods, fortified foods, new products (e.g., fat and sugar substitutes), and levels of microbiologic or chemical contaminants (7, 32). Food distribution and marketing variables include advertising, price structure, food labeling and other regulatory factors, packaging and serving sizes, and supermarket shelf space allocations for more healthful or less healthful foods (32, 33). Changes may be driven by market forces independently of health concerns, or they may exploit health concerns. Epidemiologists need to track the net effects of these food supply changes over the long term, while retaining the ability to isolate effects of specific factors.

Consumer behavior both determines and responds to food supply trends. Food purchases also reflect economic and lifestyle trends and health motivations, some of which are based on misinformation or on beliefs that are not science-based (7, 31, 34–38). The marketing and use of vitamin and mineral supplements, herbal products, and “functional foods” have outpaced the development of related scientific evidence, consumer guidance, and policies (20–22, 39).

**Transitions in dietary patterns and disease patterns**

The term “nutrition transition” is used to describe the complex changes that are occurring in the global food supply and in the mix of nutrition problems observed in economically transitioning societies (13, 40). These changes are altering relations between income and food intake and increasing the prevalence of “overnutrition” (i.e., problems associated with excess food intake and dietary imbalances) relative to undernutrition (40). Nutrition transitions are linked to the demographic and epidemiologic shifts associated with urbanization, longer life spans, decreased fertility rates, less infectious disease, and more chronic disease (40–43). Patterns and slopes of change differ across countries and among ethnic and socioeconomic status subgroups within countries. However, these transitions are generally associated with increased consumption of calories and fats (plant or animal) and decreased consumption of dietary fiber, even in low income countries. In developing countries, diet-related chronic diseases emerge as public health problems in addition to whatever nutritional deficiency diseases persist (9, 12, 13, 44). Addressing both types of problems requires a combination of studies, some in which deficiency diseases are studied as direct outcomes of inadequate intake and others in which absolute or relative dietary intakes are studied as risk factors or protective factors for multifactorial chronic conditions (7, 45).

**Scientific knowledge and paradigms**

Both the potential for and the complexity of nutritional epidemiology increase with knowledge gains in several relevant domains. Many of the aforementioned food supply changes are tied to advances in the field of food science (32). In addition, the interpretations given to food-related risks evolve as we focus on different biologically active compounds in foods.

Effects of diet on a range of outcomes other than cancer and heart disease—the traditional foci (2)—are now recognized. These outcomes include birth defects,
Modifiers of nutrition needs, such as nutrient-nutrient interactions, have evolved considerably since the early 1900s (51–53). Many exceptions to and interpretations of the earliest principles of nutritional adequacy have arisen that the principles themselves have been reframed (51, 52). The concept of "conditional essentiality" has emerged with respect to nutrients that do not ordinarily need to be provided through diet but which become dietary essentials when normal metabolic processes are underdeveloped or impaired (51). *Modifiers* of nutrition needs, such as nutrient-nutrient and nutrient-drug interactions, have also been identified. These two new perspectives suggest a need for more attention to the possibility of interactions in the design and analysis of diet and health studies.

"Optimum nutrition" is defined on the basis of chronic rather than acute effects—effects that go beyond mechanisms and doses of nutrients related to essentiality. In countries like the United States, public health monitoring for suboptimal nutrition (figure 2) (7) assumes that nutritional deficiencies, in the classical sense, are being addressed by current policies and programs. However, there is surveillance for scenarios in which gaps persist or might emerge. Concerns about iodine deficiency are now in this category (54).

Changes in models of disease causation also influence the way diet and disease questions are framed. For example, theories of carcinogenesis, atherosclerosis, bone formation, or obesity development have implications for particular cellular functions, metabolic pathways, developmental periods, or stages of pathogenesis when nutrients can have effects, and for the reversibility of these effects. The advent of alternative or complementary medicine as a mainstream health issue introduces paradigms that conflict with the allopathic models used by most nutrition scientists and epidemiologists (55–57). The ultimate outcome of the paradigm expansion needed to accommodate these views of food intake and health has yet to unfold.

Joseph and Kramer (58) and Rivelli et al. (59, 60), who have linked chronic disease risks in adult life with nutrition during gestation, have redirected thinking about how and when nutritional factors can influence health across the life span and about relations between undernutrition and overnutrition (60). Their studies underscore the importance of differentiating genetic and environmental effects from environmental effects in utero. It is difficult to imagine that genes will be determining factors for multifactorial conditions that respond rapidly to societal changes (13, 40–43). Nevertheless, where relevant genes have been identified, the potential for increasing the statistical power of nutritional epidemiologic studies by sampling or analyzing data based on diet-responsive genes (62) should be exploited.

**Social policy climate**

Dietary variables potentially explain some of the striking disparities in chronic disease morbidity and mortality between ethnic groups—e.g., between African Americans and White Americans (63)—as well as gender differences in disease patterns (64). Race/ethnicity and gender may reflect various genetic or biologic factors but may also be markers for behavioral, cultural, or socioeconomic factors that affect both dietary practices and health outcomes (41, 65–68). The use of theoretical models to explore race or gender effects has been strongly advised (65–67, 69), particularly to avoid making inappropriate conclusions about predetermined genetic differences. Attributing unexplained differences between US minority and White populations to genes may seem scientific, but it has a lesser basis in fact than explanations based on social disadvantage (65, 69, 70). The latter may suggest a need for social or political action that may be deemed inappropriate for scientists (35). New genetic technology should make it less acceptable, methodologically, to derive inferences about genes from studies in which genes have not been assessed.

Differentiation between risks that can be addressed through individual behavior change and those that require social structural solutions is of critical importance in policy formulation. However, attempts to do this may be biased toward prevailing social constructions (69, 71). The ideology that a person's health lifestyle is primarily a matter of individual choice may hinder recognition by epidemiologists of the need to assess structural aspects of lifestyle that are beyond the individual's control. Explanations that "blame" health risks on an individual's behavior may be particularly inapplicable to socially disadvantaged groups (72–74). For example, neighborhood food availability is a contextual factor within which many individual food...
selections are determined (75). Multilevel statistical analytic approaches that can incorporate such group-level variables have been proposed (76, 77).

OTHER METHODOLOGICAL ISSUES

Dietary assessment

Dietary assessment methodology, while inherently imperfect, has progressed impressively during recent years (1, 2). Nevertheless, the validity of dietary assessment using existing food frequency questionnaires or food databases may be compromised by the increasing diversity of foods being consumed and by the increasing number of potentially relevant food constituents for which analyses are needed. Reexamination of serving sizes used for quantification is critical, given marketing practices that involve offering very large servings or packages (33). Analyses based on summary dietary pattern scores are needed to evaluate net effects of adherence to multiple, interrelated dietary recommendations (78–80). However, the periodic updates to dietary guidance policy add complexity to the interpretation of dietary quality scores over time.

Biologic markers

Objective measures of energy needs (assessed with doubly labeled water) or protein intake (assessed with urinary nitrogen excretion) have revealed the serious problem of underreporting of food intake (1, 2), and this is differential according to body size and other respondent characteristics (81). This issue is clearly relevant to analyses in which total rather than relative intakes of energy or nutrients are of interest. The full implications of this source of bias for nutritional epidemiologic analyses and interpretation are still being explored. In addition, the availability of noninvasive measures such as dual energy x-ray absorptiometry have markedly improved the potential for characterizing body composition (e.g., bone status and fatness) (1, 2). In general, the increased use of biologic markers in nutritional epidemiology (1, 2) emphasizes the need for specialized knowledge of nutrient metabolism and partitioning to inform the appropriate selection and interpretation of such markers.

Study designs

Given the numerous and nonlinear secular changes in food intake, single-baseline prospective study approaches with long follow-up periods may be appropriate only for dietary factors hypothesized to have irreversible effects of long latency. Other circumstances may require repeated dietary assessments that can capture significant variations in exposures over time.

In shaping future nutrition policy, the role of clinical trials needs careful consideration (82). Such trials can offer rigorous tests of specific questions but usually involve study samples that are highly selected with regard to motivational and health characteristics and may involve artificial dietary circumstances (e.g., isolation of one particular type of dietary modification). Short feeding studies like the Dietary Approaches to Stop Hypertension study (28) raise questions about long term effects and replicability. Very long trials, such as the decade-long fat reduction trial in the Women’s Health Initiative (25), may be challenged by interim findings (e.g., the Nurses’ Health Study report indicating no effect of dietary fat on risk of breast cancer (83)). Secular changes in diet among controls in long trials may lead to crossovers and may reduce power. Long term trials cannot easily be modified midcourse to take advantage of new knowledge or to keep ahead of population trends.

Dependence on trials as the final requirement for policy formation raises potentially insoluble issues. Does carrying out a long term study like the Women’s Health Initiative mean that all changes in related dietary guidance will be placed “on hold” until it is completed? What is the appropriate approach to setting policy when a relevant trial can probably not be done for ethical or feasibility reasons—e.g., a long term trial of sodium reduction with mortality as the outcome (84)?

Food-to-nutrient credibility gap

One of the critical challenges for nutritional epidemiologists is to determine whether the evidence supports recommendations to change intake of a specific dietary constituent as opposed to certain foods and beverages. People report what foods and beverages they consume, and those who change their dietary patterns usually do so by changing their food selections. When associations with health outcomes are observed, a leap to assumptions about which constituent(s) of food is (are) responsible for the effect must be made. There are vivid examples, such as the paradoxical increase in lung cancer risk among heavy smokers given β-carotene supplementation, of the cases in which the inferences about specific food constituents that explain diet-health associations were not borne out (85).

CONCLUSION

Epidemiologic evidence has a major influence on what people eat. Nutrition policy must rely partly on...
epidemiology because of the limited ability to study optimum diet experimentally. This pressure to formulate policy will probably increase because of conflicting commercial, scientific, and consumer interests. Even when other environmental risk factors such as cigarette smoking, air pollution, or radiation exposure are well controlled, the need to identify and manage dietary risks will endure. The question will never be whether to eat but will always be what to eat.

What safeguards and initiatives are needed? Clarification of standards of good epidemiologic practice with respect to a wide range of issues is essential (86). Better media reporting of nutritional epidemiologic findings has also been suggested (17, 18). Comprehensive dietary assessment—sometimes viewed as an unaffordable luxury—should become routine in chronic disease epidemiology. This means that creative ways to work around the associated expense and response burden will be needed. One approach might involve the creation of exposure data registries with routine, repeated collection of the dietary intakes of defined populations for whom health outcomes could also periodically be characterized. Creative computerization of dietary assessment has also been proposed (87).

The role of government agencies in nutritional epidemiology also deserves clearer articulation. The constant flow of new evidence, inherent uncertainty, vested interests and, in some cases, political sensitivity (88) leave room for continuing debate on many food and nutrition policy issues, but policy development must still go forward. The amount of resources devoted to the development and analysis of public-use survey data versus the amount available for creation of "investigator-owned" research cohorts needs review. More attention must be given to data collection at a regional level, to elucidate nutritional aspects of geographic variations in health. Mechanisms for periodic reviews of the evidence supporting food policy can become more broad-based and more systematic (89). Perhaps the greatest responsibility of nutrition policy-makers will be to ensure the tracking of net effects of adherence to dietary recommendations on morbidity and mortality, i.e., to ascertain whether the presumed favorable benefit:risk ratio is correct (90-92). Linking recommendations to outcome measures in a systematic way can help us avoid some of the pitfalls of the inevitable debates about what people should be eating to protect their health.

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Epidemiol Rev
Vol. 22, No. 1, 2000

What to Eat in the 21st Century


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