Health claims and observational human data: relation between dietary fat and cancer[1,2]

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ABSTRACT The US Food and Drug Administration review that provided the basis for authorizing a food-label health claim linking the risk of cancer to dietary fat intake illustrated several considerations in the use of epidemiologic data, and observational data in particular, to support dietary recommendations. The review suggested the need for clear and established criteria for judging the quality of observational human data as well as the importance of making the evaluation process for individual studies transparent and organized. The review, which provided for a claim in the absence of controlled human studies, also suggested that observational data may play a greater role when the nature of the relation to be described by a health-claim statement is broad and general rather than targeted and specific. Of particular importance was the relevance of available data to the questions inherent in showing a diet-disease relation, the need to consider the totality of the evidence, and the key role that existing authoritative reports must play in establishing the basis for relation. *Am J Clin Nutr* 1999;69(suppl):1357S–64S.

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INTRODUCTION

Health claims are statements on food labels that link a food substance, food, or category of foods to a disease or health-related condition. Such statements, such as that linking calcium to a reduced risk of osteoporosis, characterize a diet-disease relation. Congress recognized the increasing evidence that diet affects chronic diseases and provided for such statements with the 1990 Nutrition Labeling and Education Act (NLEA) (1). Health claims were viewed as having the potential to both assist consumers in maintaining healthful diets and to encourage manufacturers to develop healthful foods. The US Food and Drug Administration (FDA) was charged with the responsibility of implementing health claims along with other NLEA provisions requiring changes in the listing of nutrients on food labels and in the criteria for nutrient content claims.

The 1990 legislation permitted the FDA to authorize a health claim if the totality of publicly available scientific evidence supported the claim and if there was significant scientific agreement that the claim was supported by such evidence. According to the NLEA, scientific evidence includes results from well-designed studies conducted in a manner consistent with established scientific procedures and principles. The act did not stipulate the type of study that may be used, only that the studies used be of good quality. Moreover, health claims focus on the reduction in risk of a disease or health-related condition; they do not specify prevention or treatment of a disease.

Emphasis on a rigorous standard for health claims results in claims that are likely to be enduring. This, in turn, avoids consumer confusion and the undermining of consumer confidence that could occur if such claims were based on emerging science that may be subject to frequent changes in conclusions about the nature of the association. Congress identified 10 diet-disease relations for initial consideration for health claims on foods labels (1). The process for evaluating and, as appropriate, authorizing these relations for use on food labels involved evaluation of observational and controlled human studies as well as data from animal and laboratory studies. In addition, existing recommendations and consensus reports from authoritative bodies, including the National Institutes of Health, the Office of the Surgeon General, the National Academy of Sciences, and the Life Sciences Research Organization, were considered.

The authorization process highlights several issues important to this supplement, particularly the role of observational data in establishing a link between a dietary component and a disease or health-related condition. For the purposes of this article, controlled studies, sometimes called intervention, experimental, or clinical studies, reflect a study design in which the researcher controls the intervention or exposure. Observational human studies, which include a substantial amount of available epidemiologic work, are based on exposures or other interventions that are not within the control of the researcher.

This article focuses specifically on issues related to authorizing a health claim for the relation between dietary fat and cancer. The authorization of claims based on this relation, which was well acknowledged by several major authoritative reviews, is noteworthy for the absence of controlled human studies showing the link between the substance and the disease. Rather, the relation is based on an array of epidemiologic evidence.

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TABLE 1
Health claims authorized by the US Food and Drug Administration in 1993–1997

Substance and disease	Health claim statement
Calcium and osteoporosis	Regular exercise and a healthy diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis.
Saturated fat and cholesterol and heart disease	While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease.
Dietary fat and cancer	Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers.
Fruit, vegetables, and grains and cancer	Low-fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a disease associated with many factors.
Fruit, vegetables, and grains and heart disease	Diets low in saturated fat and cholesterol and rich in fruits, vegetables, and grain products that contain some types of dietary fiber, particularly soluble fiber, may reduce the risk of heart disease, a disease associated with many factors.
Fruit and vegetables and cancer	Development of cancer depends on many factors. Eating a diet low in fat and high in fruits and vegetables, foods that are low in fat and may contain vitamin A, vitamin C, and dietary fiber, may reduce your risk of some cancers. (Name of food, eg, oranges) are a good source of (name: fiber, vitamin C, vitamin A).
Sodium and high blood pressure	Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors.
Folate and neural tube defects[1]	Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect.
Sugars and alcohols and dental caries[2]	Frequent between-meal consumption of foods high in sugars and starches promotes tooth decay. The sugar alcohols in (name of food) do not promote tooth decay.
Soluble fiber from certain sources and cardiovascular disease[2]	Soluble fiber from foods such as (name fiber source), as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.

[1] Authorized in 1995.
[2] Claim authorization process was initiated by petition.

AUTHORIZATION PROCESS FOR A HEALTH CLAIM

The evaluation of data and the resulting decision by the FDA to authorize or reject a health claim for a food label is an open process known as *notice-and-comment* rule making. The process may be started by the FDA or, more likely, initiated in response to a petition submitted to the FDA by an interested party. The FDA first publishes the review and conclusions as a proposal, and a written comment period follows during which any interested person or organization may submit comments and requests for corrections or changes to the proposed findings to the FDA. Then, all comments are considered by the FDA, the proposal is modified, and a final rule is published. Furthermore, because the scientific review process associated with authorizing health claims requires considerable and diverse scientific expertise, the data supporting the 10 diet-disease relations identified by Congress were evaluated in conjunction with scientists from Public Health Service agencies, including the National Institutes of Health and the Centers for Disease Control and Prevention. Additionally, the health-claim authorization process was the subject of a 2-y dialogue among representatives from academia, industry, consumer groups, and government. The dialogue and resulting report affirmed the principles and approach used to authorize health claims (2).

Of the 10 original relations, significant scientific agreement was determined to exist for 8 (**Table 1**) and the FDA provided for the use of health claims describing these relations on food labels in January 1993. The 2 claims not authorized were for the link between n−3 fatty acids and cardiovascular disease and the link between zinc and immune function in the elderly. To date, 2 additional health claims, one concerning the relation between sugar alcohols and tooth decay and another concerning β-glucan soluble fiber from oats and the risk of heart disease (Table 1), have been added through the petition process.

General criteria for health claims

Several elements characterize the nature of both the relation that can be considered for a health claim and the scientific review process. The entire authorization procedure involves a series of checks not only for the scientific basis for the claim but also for a range of factors including required components of the label message and the qualifications of the foods that may bear the claim (2–4). As an overall principle, health claims reflect an effect on the general population. The food substance must be associated with a disease or health-related condition for which the general US population or an identified subgroup is at risk. Moreover, the beneficial and estimated intakes must be safe as well as effective in realistic amounts within the context of the total daily diet.

The scientific review process for health claims is comprehensive and focuses first on the review of individual studies. After

relevant studies of good quality are identified and their strengths and weaknesses are summarized, a more comprehensive review can be conducted based on the body of evidence as a whole. The review of individual studies is standardized as much as possible and generally follows the approach outlined in the *Guide to Clinical Preventive Services* (5). The individual reviews are summarized for the comprehensive review through the use of summary tables. Study design is addressed, including the sample size, subject and control selection, measurement modes, confounders and bias, attrition and follow-up, statistical measures, and external validity. Particular attention is given to the modes of measurement of both the substance and the disease endpoint. To show that a particular substance or food component has a benefit relative to a disease, the disease must be specified and measurable and the benefit must be attributed specifically to the substance of interest, which in turn is characterized and measured.

The creation of such summary tables not only organizes and guides the comprehensive review, it assists in making the process of authorizing a health claim more transparent. Although there is usually some subjectivity along with the scientific opinion in the final decisions concerning weight of evidence and significant scientific agreement, the existence of detailed summary tables supports such decisions. The summary tables are published as part of the proposed conclusions about the various diet-disease relations and thus are open for review and comment.

The comprehensive review focuses on determining the strength and consistency of the relation for the purposes of determining significant scientific agreement. As established by Congress through the NLEA (1), significant scientific agreement exists when there is agreement among experts, qualified by scientific training and experience to evaluate such claims, that the claim is supported by the available evidence. Recently, Congress enacted a revision to the health-claim authorization process that allows authoritative statements currently in effect that were issued by federal government bodies targeted to public health and nutrition, as well as by the National Academy of Sciences, to serve as evidence of significant scientific agreement (6). In the case of such statements indicating the existence of a particular diet-disease relation, the basis for the relation need not be subjected to an independent FDA review.

Significant scientific agreement is a point in the process of scientific discovery and can be viewed as occurring beyond the state of emerging science but usually before the final endpoint of consensus. It is important to recognize that significant scientific agreement is not consensus, but is considerably more than an initial body of emerging evidence (2). The strength of evidence associating a nutritional exposure with a health outcome depends not only on the quality of the individual studies but on the overall grade of the evidence taken together: the number of studies, the consistency of results, and the size of the effects.

Finally, if a proposed diet-disease relation meets the standard for a health claim, there are specific regulatory requirements that set out criteria that a food must meet to bear a health claim and the approach to crafting the specific wording of the health-claim message. For example, to bear a health claim about the benefits of consuming a substance at reduced dietary amounts, a food must be sufficiently low in the substance to meet the definition of the term low as provided by federal regulations. For claims about consuming a substance at other than decreased dietary amounts, a food must be sufficiently high in that substance to meet the definition of high. Moreover, there is special status associated with a health claim in providing information for the public about diet and health. Therefore, provisions for health claims stipulate that not only are they to be authorized for scientifically valid and meaningful relations, but that foods bearing health claims cannot contain any nutrient in an amount that increases the risk of a disease or health-related condition. For this reason, foods eligible to bear a claim based on the presence or absence of a certain food component must also contain less than a certain amount of total fat, saturated fat, cholesterol, and sodium.

Scientific standard and observational data

The scientific standard for health claims as specified by Congress (1) is clear in that the relations are to be authorized on the basis of high-quality studies and good science. Observational data, if of good quality, can play a role in supporting the authorization of a health claim, depending on the specificity of the claimed relation as well as the existing body of evidence supporting the relation. The types of studies evaluated for the 10 original relations during 1990–1992 are shown in **Figure 1**. Observational data predominated in some cases.

Although controlled studies are generally considered more reliable than observational studies for determining cause-and-effect relations (7), there are frequently reasons why such studies are not feasible or ethical. These factors have been discussed in detail by others and are summarized in *Diet and Health: Implications for Reducing Chronic Disease Risk*, published by the National Academy of Sciences (7). Diet-disease relations have been built on a body of evidence that consists of a variety of different types of data, depending on the nature of the relation and the types of data that can be collected. Moreover, diet-disease relations have often been studied indirectly using studies designed for other purposes. Therefore, the relevance of available data to the health-claim review is a complicated issue and study results are often difficult to apply.

During the initial health-claim authorization process, some people making comments mistakenly believed that the possibility of weighting controlled human studies more heavily than other types of data (4) meant that the agency was imposing a drug standard for health claims on foods. Controlled studies can be as essential to showing an association between a dietary component and a disease as they are to showing efficacy for drugs. Instead, the scientific standard for health claims is to contain more flexibility than the standards established to support a claim for a drug, which specify well-controlled interventions and clinical trials. If significant scientific agreement were to be assessed under any quantitative or rigidly defined criterion, the associated inflexibility could cause some valid claims to be disallowed where the disagreement, although present, is not persuasive (3, 4). Given the reliance on overall strengths and weaknesses of the totality of the evidence, it is not possible to specify in advance the type or number of studies needed to support a health claim or for that matter dietary recommendations. Such reviews do not lend themselves to prescribed and predetermined protocols as might be the case to prove the efficacy of a new drug.

The approach to establishing diet-disease relations has generally been to look for congruence among observational, clinical, and laboratory research findings (8). The health-claim standard must be flexible to take into account the complicated and varied nature of the data that are used to show a relation between food substances in the diet and the reduction of disease risk. The health-claim standard is, however, based on established scientific

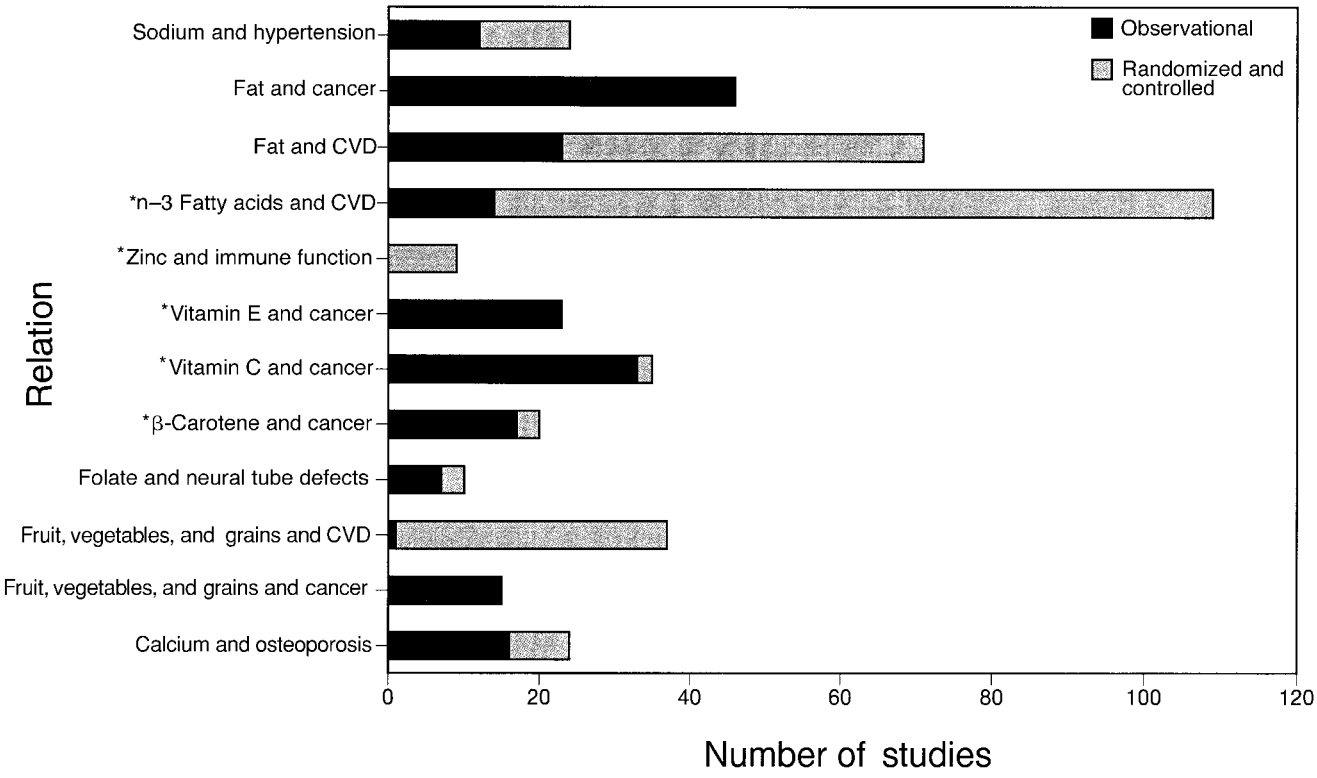

FIGURE 1. Comparison of numbers of observational and controlled human studies reviewed during the initial health-claims authorization process in 1990–1992. Reviews for β-carotene, vitamin C, and vitamin E constituted the review for the relation between antioxidant nutrients and cardiovascular disease. *Reviewed but not authorized. CVD, cardiovascular disease.

principles; poor-quality studies cannot be used to authorize a health-claim relation regardless of whether the studies are controlled or observational. Criteria for the quality of observational data exist, based largely on the early work of Hill (9), and can serve to sort flawed studies from well-designed studies. Each relation brings a unique set of confounders and measurement issues. The goal is to evaluate individual studies on their merits by using rigorous evaluation screens and then to review the combined evidence in its entirety to determine the plausibility and strength of the proposed association. The basic questions associated with the relation must be clearly defined at the beginning of the review and checked to see if they are answered at the end of the review.

As described below, the health-claim review experience suggests that although controlled studies are likely essential for establishing relatively specific diet-disease relations, in some cases more broadly defined relations may be supported with little or no evidence from controlled human studies. Significant scientific agreement was judged to exist without current evidence from controlled human studies for the association between fiber-containing foods and cardiovascular disease as well as for that between dietary fat and cancer. The Public Health Service review groups supported authorizing such health claims because the available human observational data complemented existing authoritative reports. They were also supported by high-quality and relevant animal studies. In addition, the described relations were of a relatively general nature and targeted widespread dietary characteristics (eg, dietary fat and fruits, vegetables, and grains) and broad disease endpoints (eg, cancer).

DATA SUPPORTING THE RELATION BETWEEN DIETARY FAT AND CANCER

Basis for a relation in existing data

The starting point for health-claim authorization reviews is the consideration of the conclusions to be found in the reports from authoritative bodies. These bodies include the Office of the Surgeon General, the National Academy of Sciences, various federal agencies, and the World Health Organization. The conclusions of the authoritative documents are considered to reflect the best scientific agreement at the time of their publication (3, 4). Because the 1990 legislation indicated that the basis for a health claim was the determination of significant scientific agreement, such reports were weighted heavily within the review processes. The authoritative reports related to dietary fat and cancer were both numerous and consistent (**Table 2**). This fact played a key role in determining the nature and conclusions of the health-claim review.

The National Academy of Sciences made the observation in the early 1980s that fat had probably been studied more thoroughly and been associated with various cancers more frequently than had any other dietary factor (16). By the end of the 1980s, several major documents and thus, the public health community, had come to the conclusion that excess intake of fat was linked to several adverse consequences for the American population (7, 10–12, 17). The authoritative reports indicated that existing evidence was suggestive of a relation between fat intake and the risk of some types of cancers. The 1989 report, *Diet and Health: Implications for Reducing Chronic Disease Risk* (7), concluded that although there was

TABLE 2
Reports from authoritative sources on the relation between dietary fat and cancer[1]

Source	Report	Type of data	Conclusion
DHHS	*Surgeon General's Report on Nutrition and Health*, 1988 (10)	Observational and animal	Weight of the studies is strongly suggestive of a role for dietary fat in the etiology of some types of cancer.
NRC, National Academy of Sciences	*Diet and Health: Implications for Reducing Chronic Disease Risk*, 1989 (7)	Epidemiologic and experimental animal	Weight of the evidence suggests that dietary fat may influence the risk of some types of cancer, particularly those of the breast, colon, and prostate.
US Department of Agriculture, DHHS	*Nutrition and Your Health: Dietary Guidelines for Americans*, 1990 (11)	Observational and animal	Dietary fat should be limited to 30% of energy intake, in part to reduce the risk of cancer.
World Health Organization	*Diet, Nutrition, and the Prevention of Chronic Diseases*, 1990 (12)	Observational and animal	High intake of total fat, and in some case-control studies also saturated fat, is associated with increased risk of cancers of the colon, prostate, and breast.
NRC, Life Sciences Research Office	*Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 10. Lipids and Cancer*, 1991 (13)	Observational and animal	The risk of developing cancer is increased by high fat intakes. Data relating dietary fat to cancers of the breast, colon, and prostate are substantial but not conclusive.
Food and Drug Administration, DHHS	*Food Labeling: Health Messages*; *Dietary Lipids and Cancer*, 1991, 1993 (14,15)	Animal (rodents)	As a whole, a high-fat diet resulted in a significant increase in tumors; no dose-response was delineated. Mammary, colon, pancreas, and liver were affected by the diet. Studies were limited most commonly by limited linoleic acid in diet.
		Correlational	Dietary fat intake, independent of energy intake, is associated with tumors of the breast, colon, and prostate.
		Cohort	The association between dietary fat and cancer is equivocal.
		Case-control	Although not conclusive, data support a relation between dietary fat and cancer; colon cancer was the only site to be affected consistently.

[1] DHHS, US Department of Health and Human Services; NRC, National Research Council.

less persuasive evidence for the relation between fat and cancer than for that between fat and cardiovascular disease, the weight of the evidence from epidemiologic and experimental animal studies suggested that dietary fat may influence the risk of some types of cancer, particularly cancer of the breast, colon, and prostate.

Several authoritative reports were critical to the health-claim review for dietary fat and cancer. In *The Surgeon General's Report on Nutrition and Health* (10), the potential relation of dietary fat to cancer risk was evaluated by reviewing results of a range of different types of studies. The report concluded that although not yet conclusive, epidemiologic and animal data supported an association between dietary fat and the risk of cancer, especially breast, colon, and prostate cancer. The report stated that the effects of different types of dietary fat (ie, saturated compared with unsaturated) have not been separated in most human studies and considerable uncertainties remained. However, the report did conclude that the weight of the studies was strongly suggestive of a role for dietary fat in the etiology of some types of cancer. Also, in the federal report *Nutrition and Your Health: Dietary Guidelines for Americans* (11), available evidence supporting the association between dietary fat and risk of some types of cancer, particularly breast, colon, and prostate, were reviewed. The review resulted in the recommendation that <30% of energy intake be from fat. Discussions in the supporting text found in the 10th edition of *Recommended Dietary Allowances* (17) also highlighted the association between dietary fat and cancer and the benefits of reducing fat intake. As highlighted above, the report *Diet and Health: Implications for Reducing Chronic Disease Risk* (7) indicated that the weight of the evidence supported a role for high-fat diets in the risk of several types of cancer. It also included the recommended goal to reduce total fat intake to ≤30% of energy.

The World Health Organization study group report *Diet, Nutrition, and the Prevention of Chronic Diseases* (12), in which the collective views of an international group of experts was presented, concluded that even though the relations between dietary components and cancer were less well established than those between diet and cardiovascular disease, a review of the evidence indicated that a high intake of total fat, and in some case-control studies also saturated fat, is associated with an increased risk of cancers of the colon, prostate, and breast. The report, based on epidemiologic data, indicated that such data were not totally consistent but were generally supported by laboratory data from studies in animals. The report recommended fat intakes of <30% of total energy to lower the risk of fat-related cancers.

At the time that the proposed authorization for a health claim relating dietary fat and cancer was being developed, an indepen-

dent report from the Life Sciences Research Office entitled *Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 10. Lipids and Cancer* (13) was published. This report concluded that high fat intake increases the risk of developing cancers. The report stated that there is substantial but no conclusive evidence that high-fat diets increase the risk of developing cancers of the breast, colon, prostate, and possibly other sites compared with low-fat diets. The report also pointed out that there was a critical gap in knowledge because of a lack of direct evidence that cancer risk can be reduced by decreasing the fat content of the diet and that this gap can only be filled by data from intervention trials.

In none of these reports did available data include controlled human studies. Rather, the nature of the disease had precluded the practical development of clinical or intervention data. Thus, the evidence was derived from observational data. Although not essential for the acceptance or rejection of human data, animal studies provided support for the observational conclusions in the case of dietary fat and cancer. Moreover, the conclusions from the various bodies were independent and consistent.

Other evidence

After consideration of the authoritative reports, the health-claim review process focused on identifying studies made available after the publication of the existing reports. Given the conclusions of the authoritative reports, the most prudent approach was to review in detail the data published after 1988 to judge whether agreement had continued to build or whether newer data were inconsistent with earlier conclusions. This post-1988 review examined ≈30 human observational studies published after 1988 as well as >20 animal studies (14, 15). No controlled human studies were identified. As described in detail in the preamble to the proposed regulation to authorize the health claim (14), each study was critiqued for appropriateness and relevance to the association. The general criteria used to evaluate the studies were provided in the preamble along with the evaluation summary table (14, 15). As discussed below, 2 factors played a predominant role in the review. These were the relevance of the study to the association between dietary fat and cancer and the nature of the totality of the evidence.

At the time of the 1991 proposal (14), the results of animal studies were not entirely consistent, but taken as a whole they showed that high-fat diets enhanced carcinogen-induced tumor development. Additionally, as described in the FDA review (14, 15), animal studies supported the site-specific nature of the effect relative to the mammary glands, colon, pancreas, and lungs. These findings were independent of energy intake. The effects of different types of fat on tumorigenesis were not widely studied in animal models and the results were inconclusive. The animal studies had not provided a mechanism by which fat affects tumorigenesis.

International correlational studies of human populations suggested that dietary fat intake, independent of energy intake, was associated with tumorigenesis of the breast, colon, and prostate but not with the incidence of cervical or lung cancer (14, 15). Cohort studies provided mixed results, with 2 finding no association, although 1 was not adjusted for energy intake. Two cohort studies concluded that there was a relation, the first finding a relation with breast cancer and the second with colon cancer but not breast cancer (14, 15). Total fat intake was associated with risk of breast cancer in most but not all case-control studies. Six studies found a significant relation, 1 study found a borderline association, and 2 studies found no relation. As in the animal studies, no specific effects of different types of fat were evidenced.

Considering the totality of the evidence, the proposal indicated that the conclusions of the authoritative reports that dietary fat had an important influence on cancer incidence and mortality, particularly at sites such as the breast, colon, and prostate, were supported by the results of recent ecologic and animal studies (14). Results of human prospective and case-control studies were less supportive, in part because of limitations in the experimental design. However, most case-control studies were consistent with the conclusions that fat intake was associated with breast and colon cancer risk (14, 15). The FDA therefore proposed that the health-claim message indicate that eating a low-fat diet may help reduce the risk of some cancers, including those of the breast, colon, and prostate.

Although no new human or animal studies meeting the criteria for selecting studies to be included were submitted with comments written in response to the proposal, the FDA conducted a review of studies that became available after publication of the proposal (15). This evidence supported the initial conclusion that there was an association between dietary fat and cancer risk. However, the evidence for specific types of cancer was not clarified and in fact appeared to be increasingly equivocal. Several comments to the proposal had suggested that the FDA exclude the designation of specific cancers for the sake of simplicity and because of the inconclusiveness of the relevant scientific evidence (15). Some comments stated that the size of the association between dietary fat and the risk of various cancers varied so widely that it was misleading to presume that strong evidence supports each site. It was suggested that the claim should therefore not be site specific. The FDA (15) agreed with these comments and changed the health-claim message to refer to an association between dietary fat and "some types of cancer" or "some cancers." References to specific sites were omitted.

Relevance of available studies

Questions to be addressed when investigating a relation between a dietary component and a disease are specific and targeted. However, the evolution of the database to answer these questions often, as described earlier, evolves indirectly and without regard to the specific questions. Therefore, relevance to health-claim questions is a major criterion in the early step of evaluating the quality and usefulness of individual studies.

Relevance pertains to several factors. First is how well the study designers measured the substance of interest. For instance, there are considerable differences between measuring total fat, specific types of fatty acids, or total dietary intakes as compared with test-product compositions. Second is how well the investigators measured the disease endpoint. Some studies may evaluate only bile acid secretion whereas others measure adenomatous polyps or colon tumors. Finally, there is the issue of total dietary context. It is important to determine whether the amounts of known effective intakes are within the range of what is feasible and practical in the daily diet.

Several issues raised in the FDA review targeted the relevance of available studies to address questions specific to a health-claim relation. One was the importance of separating the effect of fat intake from that of energy intake. More precisely, it was important that available data address the concern that the association of fat intake with cancer risk was the result of the higher

energy intake normally associated with high fat intake. For this reason, studies that controlled for energy rather than those that merely measured fat intake were considered more relevant. Also, a question of considerable interest was whether the effect of fat on cancer was site specific. Measurement and reporting of these were especially problematic with correlational and other observational data. Another key issue was the effect of total dietary fat as compared with specific types of fat. Studies were weighted differently depending on their measurement of intake of either total fat or specific types of fat.

Relevance also pertains to the expected benefit of the substance in amounts feasible within the normal diet. Data from studies that examined the relation by using amounts that reflected realistic dietary intakes were obviously weighted more heavily, eg, studies that included intakes at 30% of energy compared with 15%. There is an interesting footnote to concerns about dietary context that illustrates a role that observational data, particularly ecologic data, may play in delineating a diet-disease relation. When the threshold effect has been surpassed within the population of interest, such as the case for dietary fat and cancer within the US population, observational studies may provide a recourse for clarifying the dose-response relation. No clinical trials had examined the quantitative relation between reduction in fat intake and altered cancer risk in populations. It was therefore not possible to conclude how much reduction in fat intake would be necessary to realize the benefit, although available data supported that a diet low in total fat was associated with lowered risk. Consequently, data from a national survey were used to examine relations between dietary fat and the risk of cancer at certain sites in >13 000 persons (18). No evidence of increased risk with increased intake was found. This suggested that a threshold effect had occurred because the difference in fat intake between the US survey groups with the highest and lowest fat intakes, 37% of energy compared with 32%, was not as great as the known differences in fat intakes between countries, many of which had average intakes <30% of energy and for which ecologic data were suggestive of a lower risk of cancer. This, in turn, indicated that a reduction in fat intake to <30% of total energy may be needed to observe any reduction in cancer risk in the United States. Moreover, it supports the suggestion of Greenwald (19) that cross-cultural case-control studies that measure wider ranges of nutrient intake may increase the usefulness of further epidemiologic investigations, particularly in the study of cancer.

Totality of evidence

Totality of the evidence was a critical concern because of the lack of controlled human studies relating dietary fat to cancer. Given that controlled studies are to be considered more compelling than observational studies, it is apparent that for a relation to be shown, these observational studies must be numerous, be consistent, and fit within the totality of existing evidence such as animal studies. Furthermore, there must be an explanation for the lack of clinical evidence. In short, given all the data available, is there a comfort level of a causal relation between the food substance and the disease outcome? Will changing the intake of the food substance have a high probability of having the desired or expected effect on the disease risk? For the review described here, the authoritative reports established significant scientific agreement for the relation. The fact that no controlled studies were available was a component of the review; furthermore, it was well acknowledged that intervention studies targeted to the development of cancer are problematic on many levels. The role of the health-claims review was to update the state of the agreement to determine whether it had been eroded and, if possible, to more appropriately define the association.

The review concluded that the totality of the evidence was consistent with these reports in specifying an association between total dietary fat and cancer; but additional observational studies had only muddied the relation between fat and cancer for certain sites. Thus, because observational studies are most appropriately used for more generalized relations, the final conclusion was that the association was limited to some cancers but that the specific types could not be clearly identified.

IMPLICATIONS

The authorization process for the health claim relating dietary fat with cancer illustrates some of the principles that are important to use when interpreting epidemiologic data, particularly observational data, to support dietary recommendations. The evaluation of individual studies to see that they were well designed and appropriately addressed the questions at hand ensured not only that that good science drove the evaluation but also that the conclusions were not based on the presence or absence of certain types of studies, but rather on the weight of the evidence as balanced against the specificity of the claim. The health-claim review experience suggests that the identification and consistent use of evaluation criteria for individual studies makes the process of incorporating observational data into considerations of diet and health relations more acceptable to the scientific community at large and encourages a transparent, open review. Although such criteria cannot be exacting or applied without some scientific judgment, the evidence of rigor in evaluating the body of evidence is a constructive and important first step in judging support for relations that, by nature, must rely heavily on observational data. Moreover, although a basic body of evaluative criteria exists, some have suggested that the formation of health policy in general will benefit from more and updated articulation of these standards (20).

The health-claim experience further suggests that the specific role of observational data is tempered by both the existing authoritative conclusions and consistency with animal and laboratory data. Most importantly, observational data may be able to play a greater role when the nature of the relation, that is, the claim, is less targeted and relatively nonspecific. Highly specific or targeted relations are more likely to require controlled studies to show the association. Relations that focus on a category of foods or a widespread dietary component and that are linked to a broadly defined disease or health-related condition may be sufficiently supported by observational human studies in the absence of controlled studies if other available data and conclusions are consistent with the observational data.

Finally, an important consideration that was not addressed here and is separate from the scientific review for health claims and other dietary recommendations is how consumers pay attention to, interpret, accept, and implement a label claim or dietary recommendation. Given that such messages must be based on scientific evidence and reflect the science accurately, there is much to be learned about the most effective approaches to presenting such information to the public as well as the paradigms consumers use to judge such information and make behavioral changes.

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