TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/Test/dose	Results	Assessment/comments
Wardlaw 1990 (Ref. 144).	Clinical study of effect of types of dietary fat on serum lipids. Double blinded, randomized, cross-over.	20 men, average 34.7 yr normal diet fat 37–43% calories	5 week diet phase; 7 wk/ washout; cross-over and repeat.	Diets..... 1. Butter—2 wk..... 2. Corn-PUFA..... 3. Sun-MUFA.....	Both vegetable oil diets (PUFA and MUFA) reduced chol 16–21%, LDL-C 21–26% and TG by 10–21% compared to butter diet. Serum chol falls within 1 wk on vegetable oil diets. Dietary chol raised from 190 to 500 mg/day while on vegetable oil diet did not change serum TC, LDL-C, HDL-C or TG. High Concentration of PUFA may have pharmacological effects on lowering HDL-C, however, diets containing 35% of calories from fat and P-S ratio < 1.5 are not likely to lower HDL significantly.	Well designed and executed study. Applicable to men who consume high SFA diet (did not include women). Consumption of low fat diet reduced serum lipids levels in young healthy men who had previously consumed high fat diet. Furthermore the authors suggest some risk may be involved as reduce SFA in diet, especially substitute PUFA for MUFA.
Wood 1991 (Ref. 145).	Clinical study of effect of diet and exercise on serum lipids. Randomized, controlled. Evaluation of diet and activity by clinical activity logs, 7 day diet records, and telephone interviews.	Moderately overweight, sedentary men and women (132 each), 25 to 49 yr old; 119 men & 112 women completed study; non-smokers, low alcoholic consumption.	1 year.....	Divided into 3 cohorts 44 men & 44 women in each cohort. 1. Control, habitual diet..... 2. Hypocaloric NCEP diet 3. Hypocaloric NCEP diet (+) exercise.	Both NCEP groups reduced body fat significantly and BP. In men: Diet (+) exercise increased HDL, while decreasing TG, apo B HDL increased significantly (13%) in men who exercised over diet alone. In women: Diet alone & (+) exercise significantly reduced BP, TC, apo B compared to controls. Women in diet alone group, had significantly lower HDL-2 and apo A-1 compared to control. Addition of exercise decreased the reduction of HDL-2 by low fat diet.	Well designed and well executed study. Suggests multifactorial approach for reduction CVD. Exercise is important in increasing level HDL. Diet is important in reduction of TC and LDL-C.

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21 CFR Part 101

[Docket No. 91N-0097]

RIN 0905-AD08

Food Labeling: Health Messages; Dietary Lipids and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize health claims on foods and food labeling that state that diets low in total fat may reduce the risk of some types of cancer, particularly colon, breast, and prostate, in the general population. The agency reviewed this topic under the provisions of the Nutrition Labeling and Education Act of 1990. The agency's conclusion is based on its review of the publicly available scientific literature. The strength and consistency of the scientific data supports such claims. Under this proposal, it also may not imply any particular degree of risk reduction. The proposed rule requires that to bear such a claim, the food or food product must meet the criteria proposed in § 101.62 for a "low fat" claim. FDA is proposing to permit foods that qualify to use a combined cancer-cardiovascular disease label statement and is requesting comments addressing scientific and compliance issues that may arise from the use of such combined health claims.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based on this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: He-Chong C. Lee, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW Washington, DC 20204, 202-485-0358.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (Pub L. 101-535) (the 1990 amendments), which amends the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary) (and by delegation FDA) to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule entitled "Food Labeling: General Requirements for Health Claims for Food," which establishes general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, and other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling. In that companion document, FDA tentatively determined that such claims would only be justified for substances in dietary supplements as well as in conventional foods if the agency determines, based on all of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

Sections 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x) of the 1990 amendments require that within 12 months of their enactment, the Secretary shall issue proposed regulations to implement section 403(r) of the act, and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including fats and cancer, meet the requirements of the act. In this document, the agency will consider whether a claim on food or food products, including conventional foods and dietary supplements, on the relationship between fats and cancer would be justified under the standard proposed in the companion document on general requirements for health claims.

B. Public Health Aspects

1. Prevalence and Economic Impact

The importance of cancer as a public health problem in the United States cannot be disputed. All forms of cancer taken together are ranked as the second leading cause of death in the United States and account for one in five deaths. Deaths due to cancer numbered more than 475,000 in 1987. The overall economic cost of cancer, including the direct health care costs and losses due to morbidity and mortality, was estimated to be $72.5 billion. The social impact of cancer can be measured in part by the potential years of life lost by death before age 65. Potential years of life lost were 18 million years for cancer compared to 15 million years for heart disease (Ref. 1).

Risk of occurrence differs markedly for various types of cancer. In 1990, the leading types of cancer in men in the U.S. were lung (35 percent of all cancer deaths), colorectal (11 percent), and prostate cancer (11 percent). For women, the leading types were lung (21 percent), breast (18 percent), and colorectal cancer (13 percent) (Ref. 1).

2. Dietary Lipids in the United States

Lipids (fat and oils) with dietary importance include fatty acids, phospholipids, and cholesterol. As dietary components, lipids are commonly referred to as "fats." Henceforth, the colloquial term, "fat" will be used in place of the more technically correct term "lipids."

The fatty acid components of fat are classified as short chain (less than 6 carbons), medium-chain (6 to 10 carbons), or long-chain (12 or more carbons). Fatty acids are also classified as saturated (lacking double bonds), monounsaturated (containing a single double bond), or polyunsaturated (containing more than one double bond). The polyunsaturated fatty acids are subdivided into those whose first double bond occurs either three carbon atoms from the methyl carbon (omega-3) or six carbon atoms from the methyl carbon (omega-6).

Dietary fats serve several major physiological functions, and only a brief overview will be given here. Fats facilitate the intestinal absorption of the fat-soluble vitamins. Small amounts of linoleic and linolenic acid, two polyunsaturated fatty acids, are essential in the diet as precursors of eicosanoids and phospholipids. Phospholipids, as well as cholesterol, are major components of all cell membranes and myelin, the coating around nerve fibers. Cholesterol is also the precursor of the steroid hormones and of bile acids.

Fat is the most concentrated source of dietary energy of all the nutrients, supplying nine calories per gram (g) as compared to four calories per g from either carbohydrate or protein. More than one-third of the calories consumed by most people in the United States are provided by fat. In 1985, estimated average intake of fat was as follows: 19 to 50 year old men, 36 percent; 19 to 50 year old women, 37 percent; 1 to 5 year old children, 34 percent of energy (calorie) intake. The largest contributors to total fat intake for all sex and age groups were meat, poultry, and fish as well as grain-products (including baked goods and cakes) and dairy products. For adults, meat, poultry, and fish contributed 32 to 38 percent of total fat intake, grain products contributed 19 to 22 percent, and dairy products contributed 13 to 15 percent. For children, from 1 to 5 years, dairy products (28 percent) was the largest contributor to total fat, while meat, poultry, and fish contributed 22 percent and grain products contributed 24 percent (Ref. 2).

3. Relation of Dietary Fats to Cancer

Fat consumption in the United States is in excess of that needed to meet the physiological needs for energy and essential fatty acids. Recent U.S. Government nutrition guidelines and goals recommend an American diet with lower fat (30 percent or fewer of the calories), saturated fat (10 percent or fewer of the calories), and cholesterol (less than 300 milligrams (mg) daily). The available evidence shows that this excess intake of fat has significant consequences for the American population. While the most convincing evidence supports a relationship between dietary fat intake and the risk of cardiovascular disease, high fat diets also appear to be linked to increased risk of some types of cancer and obesity. A recent National Research Council's (NRC's) Report, "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 3) concluded that although there was less persuasive evidence for the relationship between fat and cancer as compared to fat and cardiovascular disease, the weight of 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 and possibly the pancreas, endometrium, and ovary. Although the

precise quantification and the nature of the association between dietary fat and the overall risk of cancer has not been determined, all recent general dietary guidelines from the Federal Government and the NRC have recommended that lower fat intakes should be encouraged in the United States (Ref. 1, pp. 119-120).

C. Dietary Fat: Regulatory History

Because there was a lack of agreement on the relationship between fat and cholesterol and good health when the agency's current regulations were adopted, FDA limited the amount of information that could be provided on the food label about these food components. Current relevant regulations are § 101.9(c)(6) (21 CFR 101.9(c)(6)), which requires that the fat content of a food be included in the nutrition label (38 FR 2132, January 19, 1973; and amended at 38 FR 6951, March 14, 1973), and § 101.25 (21 CFR 101.25) (42 FR 14302, March 15, 1977), which provides for the voluntary listing of cholesterol and fatty acid content as part of the food's nutrition label. No other information on fat or cholesterol content is permitted.

In 1986, however, with the emergence of a consensus that limiting dietary cholesterol would contribute to good health, FDA published a proposal to define terms that describe the cholesterol content of foods (51 FR 42584, November 25, 1986) and also proposed to require that, whenever these or other terms describing cholesterol content are used on the label, the fatty acid content of the food must be declared on the nutrition label.

As part of the Secretary's food labeling initiative, FDA issued a tentative final rule on cholesterol labeling in the **Federal Register** of July 19, 1990 (55 FR 29456). In that document, the agency proposed to limit the fat and saturated fatty acid content of foods bearing cholesterol claims. FDA proposed to limit the use of "cholesterol free" and "low cholesterol" to foods which, in addition to containing the requisite cholesterol levels, contain not more than 5 g of fat and not more than 2 g of saturated fats per serving. On a dry weight basis, these foods could contain not more than 20 percent fat and not more than 6 percent saturated fat.

For a complete description of FDA's regulation of the fat and saturated fat content of foods, see the proposal on fat, saturated fat, and cholesterol descriptors published elsewhere in this issue of the **Federal Register**.

In response to industry initiatives in which health messages about the relationship of low fat diets to reduced risk of cancer were placed on labels of breakfast cereals, FDA proposed to define health messages on August 4, 1987 (52 FR 28843). In that proposal, a "health message" was described as a claim for a food that addressed the relationship between that food in a diet and health. That relationship included the linkage between certain health problems (e.g., heart disease) and certain food factors and dietary habits. Because of a number of comments suggesting that this proposal was vague and unworkable, after seeking comments in an advanced notice of proposed rule making on August 8, of 1989 (54 FR 32610), FDA published a reproposal for regulating health messages in February 13, 1990 (55 FR 5176). In that document, the agency stated that it intended to review available scientific evidence to address whether a claim may be made with respect to a number of different topic areas, including fats and cancer.

On November 8, 1990, as stated above, the 1990 amendments were enacted, and FDA was charged with reviewing 10 topic areas. This document presents the results of FDA's review of the relationship between dietary fats and cancer.

D. Evidence Considered in Reaching the Decision

The agency has reviewed all relevant scientific evidence on fat and its relationship to cancer. The scientific evidence reviewed included all conclusions reached in: "The Surgeon General's Report on Nutrition and Health" (Ref. 4) and the U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services (DHHS) report "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 6). It also considered documents from other recognized and scientific bodies, including: NRC's "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 3); NRC's "Recommended Dietary Allowances" (Ref. 5); The World Health Organizations (WHO), "Diet, Nutrition, and the Prevention of Chronic Diseases" (Ref. 7); and the Life Sciences Research Office (LSRO) report "The Role of Dietary Lipids in Cancer" (Ref. 8). FDA relied on these reports for a review of all evidence available before 1988.

The agency updated the conclusions reached by these reports by reviewing all human and animal studies released since these documents were completed.

To ensure that its review of relevant evidence was complete, FDA requested, in the **Federal Register** of March 28, 1991 (56 FR 12932), scientific data and information on the 10 specific topic areas identified in section 3(b)(1)(A) of the 1990 amendments. The topic of fat and cancer was among the 10 subjects on which the agency requested information.

E. Comments Received in Response to FDA Request for Scientific Data and Information

In response to the March 28, 1991 **Federal Register** request for scientific data and information on fats and cancer, FDA received 15 comments from the food and dietary supplement industries, a consumer advocacy organization, trade associations, a state health department, the Government of Canada, a private nutrition research foundation, an organization of public health professionals, and a consumer.

The comments dealt with the issues of fat and cancer and related food label requirements, as well as the general goals and requirements of the 1990 amendments. FDA reviewed all of the documents including letters, press releases, scientific articles, review articles, and recommendations included in submissions. FDA included the data submitted in scientific articles in its review of scientific literature which is discussed below.

The comments received from the food industry, the private nutrition research foundation, the consumer advocacy organization, and the consumer suggested that there was adequate scientific evidence and scientific agreement to justify claims for fat and cancer. The comments from the dietary supplement trade association and nutritional supplement manufacturers stated that the conclusions in several authoritative documents filed in the FDA docket on this topic are negative with respect to the role of nutritional supplements in providing the protective nutrients that are associated with disease. The dietary supplement trade association suggested that FDA exercise its independent judgment in reviewing the evidence on nutrient-disease relationships and not rely solely on conclusions drawn in the authoritative documents.

Comments from a state health department and an organization of professional public health nutritionists recommended caution in approving health claims and the need to prevent possible abuse of health claims or misinterpretation by the general public. These comments also expressed concern about the many topics that are candidates for health claims under the 1990 amendments.

A comment from a major grain food manufacturer suggested that one of the requirements for a fat and cancer health

claim should be that the food product contains a minimum amount of dietary fiber and a standard level of all other important nutrients commonly found in that food. Criteria for qualifying levels for fat were suggested as 10 percent of calories from food.

A major manufacturer of food oils and related food products suggested that fat intake should be reduced primarily by lowering saturated fatty acid intake. This comment raised questions about the possibility of increasing the risk of heart disease among consumers by reducing the relative proportions of polyunsaturated fatty acid intakes along with reductions in total fat intakes. It suggested that health claims for fat and cancer were justified only for foods especially low in saturated fat rather than total fat.

Finally, the Government of Canada submitted information that it considered helpful in the context of increased harmonization of regulations or standards affecting trade in specific products. The Director General, Food Directorate, Health and Welfare Canada, described the official position of Canada on the relationship of diet and nutrients to disease, including cancer, and the metabolic effects of nutrients, including fat, as stated in the volume "Nutrition Recommendations, the Report of the Scientific Review Committee—1990" (Ref. 9).

The conclusions of the Canadian Scientific Review Committee on fat and cancer were that "the present level of total fat, and particularly of saturated fat, in the Canadian diet constitutes a risk factor for cardiovascular disease and possibly for certain other diseases including some forms of cancer." The Committee recommended that total fat intakes of Canadians be no more than 30 percent of energy. The Director General also stated that food label health claims or messages regarding the role of fat in cancer risk could result in a food product being classified as a drug because the Food and Drug Act in Canada "prohibits the advertising and sale to the general public of a food that is represented either by label or in advertising as a treatment, preventative or cure for some 46 diseases, disorders or abnormal physical states including cancer."

II. Review of the Scientific Evidence

A. Federal Government Documents

In "The Surgeon General's Report on Nutrition and Health" (Ref. 4), the potential relationship 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, epidemiological and animal data support 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 (i.e., saturated versus unsaturated) have not been separated in most human studies and considerable uncertainties remain to be resolved.

The Surgeon General's report concluded that the weight of the studies are strongly suggestive of the role for dietary fat in the etiology of some types of cancer (Ref. 4, p. 194).

The conclusions of the other authoritative documents from the Federal government listed above support the positive relationship between dietary fat and the risk of some types of cancer, particularly breast, colon, and prostate. These conclusions were the basis, in part, for the "Nutrition and Your Health: Dietary Guidelines for Americans" report that recommended calorie intake from total fat be less than 30 percent (Ref. 6).

B. Other Documents and Statements

The NRC's report "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 3) included the recommended goal to reduce total fat intake to 30 percent or less of calories. It stated that although less persuasive than the data supporting the fat and cardiovascular disease relationship, the weight of the evidence indicates that high fat diets are associated with a high risk of several types of cancer, especially of the colon, prostate, and breast. This report reviewed epidemiologic data as well as supportive evidence from animal studies that examined the mechanism of carcinogenesis.

The WHO study group report, "Diet, Nutrition, and the Prevention of Chronic Diseases" (Ref. 7) that presented the collective views of an international groups of experts, concluded that—

> * * * even though the "relationship between specific dietary components and cancer are much 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 epidemiological evidence is not totally consistent, but is generally supported by laboratory data from studies in animals. * * * [I]ntakes of less than 30 percent of total energy will be needed to attain a low risk of fat-related cancers. * * * [M]ost expert groups now consider it prudent to reduce fat intakes in Western societies from the prevailing figure of about 40 percent of energy towards 20 to 30 percent figure.

C. Review of the Scientific Literature

1. Evidence Considered

To the extent possible, the agency evaluated data from studies in humans as well as in animals. The criteria that the agency used to select pertinent recent studies required that they have been published and conducted after NAS' "Diet and Health" was published (i.e., after 1988), and that they:

(1) Present primary data carried out in animal or in human studies;

(2) Be available in English;

(3) Include direct measurement of dietary fat intake as a single nutrient or as a component of foods; and

(4) Include direct measurement of risk of cancer (prognostic indicator, incidence, development, prevalence, or mortality).

FDA considered that experiments in different animal species can take genetic variability into account and permit more intensive observation under controlled experimental conditions. However, the agency believes that extrapolation of data from animal studies to humans is limited by the differences in metabolism and physiology between animals and humans.

Various types of epidemiologic studies in humans also have limitations in methodology. The strengths and weaknesses of different kinds of epidemiologic studies and the methodologies for dietary assessment relevant to risk of chronic diseases are reviewed elsewhere (Ref. 3, pp. 23–32). Despite the limitations in epidemiologic studies, repeated and consistent findings of an association between certain dietary factors and diseases are likely to be real and indicative of a cause-and-effect relationship. Studies in animals can be used to confirm findings in humans and to elucidate mechanisms involved.

2. Evaluation Criteria

The data in humans and animals have been evaluated against general criteria for good experimental design, execution, and analysis. The criteria used in evaluating studies in animals include:

(1) Whether experimental diets were within physiological ranges of intake, particularly whether levels of fish oil or total fat in the diet were within the range of current human consumption and whether the diet provided adequate linoleic acid for growth of the host and tumor cells (There is evidence to support a linoleic acid requirement for optimal tumorigenesis. In a dose-response study, O'Connor et al. (Ref. 27) tested

azaserine-induced pancreatic tumorigenesis by measuring the development of atypical acinar cell nodules (AACN) in rats. AACN development was not affected when the diet contained less than 5 weight-percent corn oil but was increased as the omega-6:omeg-3 fatty acid ratio increased if the diet contained more than 5 weight-percent corn oil. This result is consistent with the reports by Ip et al. (Refs. 20 and 71) that there is a linear relationship of linoleic acid intake to mammary tumor development in rats up to an intake level of 4 to 5 weight-percent.);

(2) Whether confounding factors were controlled, particularly whether isocaloric diets were used;

(3) Whether the animal species selected for study were sufficiently similar to humans in responses to dietary modification;

(4) Whether the number of subjects was large enough to produce reliable data;

(5) Whether duration of exposure and period of observation were appropriate; and

(6) Whether the methods used in the measurement of disease endpoints were reliable and accurate.

The criteria used in evaluating human epidemiological studies included:

(1) Reliability and accuracy of the methods used in food intake analysis and measurement of disease endpoints;

(2) Choice of control subjects (e.g., hospital-based versus population based);

(3) Representativeness of subjects;

(4) Control of confounding factors, particularly energy intake which has a high correlation with fat intake, in data analysis;

(5) Potential for misclassification of individuals with regard to dietary exposure or disease endpoints;

(6) Presence of recall bias and interviewer bias; and

(7) Degree of compliance and how compliance was assessed.

FDA evaluated the weaknesses and strengths of individual studies (see Tables 1 and 2, assessment column). The strength of the overall combined evidence (e.g., epidemiologic studies and animal studies) was then assessed taking into account the strength of the association, the consistency of findings, specificity of the association, evidence for a biological mechanism and presence or absence of a dose-response relationship. FDA's conclusions reflect the strength, consistency, and weight of the data.

3. Review of the Evidence

a. *Animal studies.* Twenty-one animal studies were reviewed and critiqued in Table 1. Most studies used rats or mice, and a few studies used hamsters. Most rodent studies used a known cancer initiator, promoter, or both in conjunction with fats. A few studies used the transplant technique of existing tumor cells or cell lines.

i. *Level of fat in the diet.* Fourteen of the reviewed animal studies examined the effect of levels of dietary fats on incidence or development of cancer at the following sites: mammary gland (Refs. 10, 11, and 12), colon (Refs. 13 through 16), pancreas (Refs. 17 through 19), lung (Refs. 12, 21, and 22), gallbladder and common duct (Ref. 19), and skin (Ref. 23). The range of fat level tested, in most studies, was 5 to 20 percent by weight. The major dietary fat source was corn oil or beef tallow. Eleven of the studies examined the effect of omega-3 fatty acids in the development of cancer at the following sites: mammary gland (Refs. 12, 24, and 25), colon (Refs. 15, 16, and 26), pancreas (Ref. 27), lung (Ref. 12), skin (Refs. 28 and 29), as well as lymphoma and thymoma (Ref. 30), and sarcoma (Ref. 31). The major omega-3 fatty acid sources tested were menhaden oil and maxEPA. MaxEPA contains both eicosapentaenoic acid and docosahexaenoic acid as its major fatty acids, while menhaden oil contains only eicosapentaenoic acid as its major fatty acid.

Although there were few studies that examined the effect of fat consumption with lung and skin cancer, their results are consistent. All three studies of lung tumorigenesis showed an adverse effect of high fat versus low fat diets (Refs. 12, 21, and 22). Similar results were observed for the single study of skin tumorigenesis (Ref. 23).

However, mixed results were observed for tumorigenesis at the mammary gland, colon, and pancreas. One study showed a high risk of mammary cancer with high fat intakes (Ref. 11). Two studies showed no significant relationship of mammary tumorigenesis with fat intakes (Refs. 10 and 12). Shao et al. (Ref. 10) also reported no association between intake of total fats and mammary tumorigenesis in mice. However, the very high nontumor-related death rate (26 of 60 total) observed among the experimental animals makes it difficult to interpret the findings.

For colon cancer, one study (Ref. 16) showed a high risk of colon tumorigenesis with high fat intakes. A second study (Ref. 15) showed a significant relationship of a high fat diet to tumor incidence, but not tumor multiplicity. A third study (Ref. 14), however, showed no association. Sinkeldam (Ref. 13) also reported a significant effect of high fat on N-methyl-N' -nitro-N-nitrosoguanidine-induced colon tumorigenesis in rats. However, the results might have been confounded by an inadequate provision of linoleic acid in the diet.

Similarly, for pancreatic cancer, one study (Ref. 17) showed a positive relationship, but another showed inconsistent effects, of fat intake on different lesions: adenoma, adenocarcinoma, or carcinoma in situ (Ref. 19). Appel et al. (Ref. 18) did not find a significant difference in azaserine induced pancreatic neoplasms in rats between a group of rats given the 20 percent by weight lard (20 percent of the diet as measured by weight, not calories) and a group receiving a combination of 4.5 percent by weight lard and 0.5 percent by weight safflower oil. However, the low lard diet might not have provided adequate linoleic acid for growth of tumor cells.

Although the results of the animal studies are not in complete agreement, taken as a whole, and considered in the light of the aforementioned criteria, rodents consuming a high fat diet experienced significant elevation in the occurrence of tumors as measured by incidence, multiplicity, or metastasis. As discussed above, some animal studies showed significant reductions in the risk of tumorigenesis by reducing fat intakes from 20 percent by weight to 5 percent by weight. However, there was no dose-response study that quantitatively delineated the level of fat reduction in the diet necessary to cause reduced tumorigenesis. Tumor yield was enhanced when a high fat diet was fed after, but not before, initiation of tumorigenesis, which suggests a promotional effect of dietary fat (Refs. 16 and 23).

ii. *Fat level versus energy (calorie) intake.* Intake of dietary fat is highly correlated with energy (in this document, energy is used in place of calorie) intake, and the question has been raised as to whether energy intake or fat intake is the major dietary factor affecting tumorigenesis. In many recent animal studies, researchers have tried to determine the independent effect of dietary fats on tumorigenesis by using isocaloric diets or by training experimental animals to consume similar energy. Most of these studies with similar energy provisions among test groups showed significant associations between dietary fat level

and cancer risk: mammary tumors (Ref. 11), pancreatic tumors (Ref. 17), and skin tumors (Ref. 23). One study (Ref. 19), however, with similar energy provisions showed inconsistent results in N-nitrosobis (2-oxopropyl) amine-induced pancreatic ductular tumorigenesis. In this study, high fat significantly increased multiplicity of carcinomas in situ but not multiplicities of adenomas or adenocarcinomas. In addition, from a Murine mammary tumor virus-induced mammary tumor study in mice, Shao et al. (Ref. 10) reported that energy consumption rather than fat level affects tumorigenesis. However, this study had severe limitations in its methodology and execution because of a high, unexplained, nontumor death rate (26 of 60 total mice) which was even higher than the tumor death rate (19 of 60 total).

Abundant data have shown that energy restriction itself significantly reduces cancer risk probably through different mechanisms than the one through which dietary fat exerts its effect (Ref. 11). Although both fats and energy have been shown to have independent effects, precise relative contributions of fat and calories to cancer incidence is beyond the scope of this document.

iii. *Types of fat.* The effects of different types of fat (saturated fat, monounsaturated fat, and polyunsaturated fat) on tumorigenesis have not been studied extensively, and the results that do bear on this issue are as yet inconclusive. Generally, both a high corn oil diet (Refs. 11, 12, 17, 21 and 23) and a high lard diet (Ref. 13) exerted tumor-enhancing effects.

iv. *Fish oil, omega-3 rich.* The relationship of omega-3 fatty acids to cardiovascular disease is addressed specifically as a separate topic area. Therefore, this text will discuss only scientific data relevant to the association of omega-3 fatty acids with cancer.

Most studies, although concluding that a diet high in fish oil suppresses tumorigenesis, are limited by flaws in methodology. The main limitation is that the testing dose of fish oil in the diet, from 10 to 20 percent by weight in most studies, is unrealistically high for the current U.S. diet. Another limitation is that the diets under study often contained fish oil as the sole fat source or contained very high amounts of fish oil with very low amounts of corn oil.

Those very high fish oil diets would not have provided adequate linoleic acid for growth of the tumor cells. There may be a dietary requirement of linoleic acid at 3 to 5 percent by weight to yield a maximum carcinogenesis at the mammary gland and pancreas in rodents. The amount of linoleic acid required for maximal tumorigenesis is higher than the linoleic acid requirement for growth of the rodents, exclusive of the tumor cells (1 to 2 percent energy, which means 1 to 2 percent of the total dietary intake as measured in calories). The linoleic acid requirement for tumorigenesis has not been examined for tumors other than mammary and pancreatic. However, it is not possible to rule out the possibility that linoleic acid deficiency, rather than fish oil, might have caused, at least in part, the observed tumor suppression in fish oil studies. Therefore, FDA did not include fish oil studies in which the animals received very limited linoleic acid provision in their diets in the following discussion.

There are few fish oil studies in which the linoleic acid provision seems adequate for growth of tumor cells as well as for the animal in which the tumor is present (Refs. 12, 15, 16 and 27). Reddy et al. (Ref. 16) reported that azoxymethane-induced colon tumorigenesis in rats was significantly suppressed by a very high level of fish oil (18.5 percent by weight) diet compared to high levels of corn oil in the diet. Unlike the effect of total fat on tumorigenesis, the effect of fish oil was evident during the initiation as well as the postinitiation period.

O'Connor et al (Ref. 27) studied the relationship of a linearly increased omega-3:omega-6 fatty acid ratio in the diet with azaserine-induced pancreatic AACN. In this study, test levels of fish oil and total fat included the level of current consumption by the U.S. population. An increased omega-3:omega-6 ratio at 0.01 to 7.0 significantly decreased AACN in number and volume. There was significant regression between an increased omega-3:omega-6 ratio and decreased AACN diameter.

Deschner et al. (Ref. 15) reported a biphasic response of fish oil on azoxymethane-induced colon cancer in mice. In this study, a 4.4 percent fish oil to 16 percent corn oil diet significantly enhanced the tumorigenesis while a 10.2 percent fish oil to 10.2 percent corn oil diet suppressed it. Because the corn oil level is not held constant as the fish oil concentration is varied, it is not possible to comment on the tumorigenic effect of fish oil alone, though this does suggest that an increase in the fish oil to corn oil ratio may cause a decrease in tumor production. Adams et al. (Ref. 12) reported a nonsignificant tumor inhibiting effect of high (15.5 to 20.5 percent by weight) fish oil on transplanted mammary tumorigenesis in rats.

Although most studies consistently concluded that there is a suppressive effect of fish oil on tumorigenesis, the results cannot be extrapolated to humans because of study design limitations described above.

v. *Biochemical mechanisms.* Although several mechanisms have been proposed, the biochemical mechanism by which fats affect tumorigenesis has not been definitely established. While the required level of linoleic acid intake for optimal expression of mammary and pancreatic carcinogenesis in rats has been determined to be 4 to 5 percent by weight in the diet, how linoleic acid affects tumor development is not yet clear.

Several hypotheses about the mechanism of enhancement have been debated. One suggestion is that eicosanoid synthesis and changes in the fluidity or microenvironment of cell membranes affect tumorigenesis (Ref. 32). Another proposed mechanism is that polyunsaturated fatty acids may promote fat peroxidation at cell membranes or subcellular sites such as deoxyribonucleic acid (DNA), mitochondria, or microsomes, leading to the initiation of carcinogenesis (Ref. 32). A third suggestion is that dietary fats alter immune function, gene expression, and metabolism of chemical carcinogens (Refs. 34 and 35). Fats may also increase levels of estrogen and androgen, thereby enhancing the risk of such endocrine-responsive tumors as cancer of the breast and prostate (Ref. 36).

With regard to colon cancer, the effects of free fatty acids and bile acids on the colonic epithelium have also been debated. The ionized forms of these substances may be irritating and toxic to colonic epithelial cells and may increase cancer risk by promoting or possibly initiating colon carcinogenesis. Bile acids, particularly those modified by intestinal enzymes, may also increase cancer risk by accelerating turnover of intestinal mucosal cells (Ref. 33). Omega-3 fatty acids found in fish oil may suppress tumorigenesis by an altering eicosanoid production.

b. *Human studies.* FDA considered the following kinds of human studies in this review of the role of dietary fats in cancer: (1) Correlational (ecologic) studies—correlational studies examine the relationship between the exposure and health outcome among populations using grouped data. Because these studies do not examine relations among individuals, they have been regarded traditionally as useful for generating hypotheses rather than definitively

testing such hypotheses; (2) analytic epidemiologic studies—studies that involve comparisons of individuals have been regarded as the strongest type of observational evidence in human populations. In case-control studies, the relationship of an attribute to the disease is examined by comparing persons who already are diagnosed with cancer (cases) to persons without cancer (controls). A potentially serious limitation of the case-control study is that diet is assessed in the cases after diagnosis, so that cases may unintentionally overestimate or underestimate fat intake. Cohort studies compare individuals who have been exposed to a risk factor to those who have not and observe the individuals over time to determine if disease develops. In cohort studies, diet is assessed at the beginning of followup, before cancer develops.

Two criticisms have been raised in regard to results of the analytical epidemiologic studies of dietary fats and cancer. Such studies are often carried out in populations with a fairly narrow range of fat intake. Thus, it is difficult to show a dietary fat effect, especially if the true protective effect of a low-fat diet emerges only at a level below the intake of most members of the study population. Also, because there is considerable error in the assessment of diet, there may be considerable measurement error resulting in misclassification of a substantial proportion of subjects. Homogeneity of dietary intake in populations, together with misclassification of dietary data, tends to weaken the observed association and limits the ability of epidemiologic studies to demonstrate a true direct relationship between dietary fats and cancer.

Thirty-one original epidemiological research articles published since 1987 were reviewed and are critiqued in Table 2.

i. *Breast cancer.* In relation to breast cancer, 2 ecologic studies (Refs. 37 and 38), 2 cohort studies (Refs. 39 and 40), 11 case-control studies (Refs. 41 through 51, and Refs. 87 and 89), 2 surveys (Refs. 52 and 53), and 6 studies examining prognostic indicators of breast cancer (Refs. 53 through 58), and 1 metaanalysis of 12 case-control studies (Ref. 73) are included in Table 2.

The Hursting, et al. correlational (ecologic) study (an international correlation study combining data from 20 countries (Ref. 38)) found significant associations between estimated total fat intake and the incidence of breast cancer. Energy intake, which is highly correlated with fat intake, was adjusted in the data analysis. Therefore, the effect of dietary fat on the cancer incidence was assessed independently of the effect of energy intake. When the results were adjusted for intake of other component fats as well as total calories, the intake of saturated fatty acids was significantly associated with the incidence of breast cancer. The intake of omega-6 polyunsaturated fatty acid was also associated with breast cancer incidence. However, intake of monounsaturated fatty acids or omega-3 polyunsaturated fatty acids was not associated with any cancer risk.

In another correlational study, Prentice (Ref. 37) also examined the relationship between estimated per capita fat intake and breast cancer in 21 countries. Dietary fat, but not protein or carbohydrates, was significantly associated with breast cancer incidence.

In conclusion, the correlational studies demonstrated a significant positive association between dietary fat and breast cancer. The effect of dietary fat on breast cancer risk seems to be independent of the effect of energy. No specific fat type was found to be responsible for the observed risk of breast cancer.

Most of the case-control studies found a significant association between dietary fat intake and breast cancer risk (Refs. 44, 46, 47, 50, 51 and 87). Among those six studies with positive results, three studies (Refs. 46, 50 and 87) adjusted energy intake in the risk estimation. Gerber (Ref. 43) reported a borderline ($p=0.07$) association but did not adjust for energy intake. Holm (Ref. 53) reported that patients with higher fat-energy intakes had larger tumors than patients with less fat-energy and higher carbohydrate-energy intakes. However, the authors did not consider the possible confounding effect of lead time (the period of time between start of tumor growth and clinical diagnosis of cancer) among individuals with different levels of fat intake. A case-control study investigating the relationship between diet and histologic types of benign breast disease among Canadian women (Ref. 89) found that severe atypias and borderline carcinomas in situ were associated with frequent meat fat consumption but the results were not statistically significant.

Two studies (Refs. 42 and 45) resulted in no associations. In one (Ref. 42), intakes of energy, protein, or carbohydrates were also not associated with the risk of breast cancer. However, dietary habits of the population may have been homogeneous, thus reducing the ability to detect variation in disease risk associated with variation in dietary intakes. In the other negative study by Pryor (Ref. 45), subjects (ages 20 to 54) were asked about their food habits during the adolescent period. Errors in recall of dietary intake up to 40 years before might have biased the results, because of a selective memory difference between the cases and the controls.

In a study of 85 Israeli women, Eid and Berry (Ref. 52) reported that fatty acid composition in breast tissue was not associated with the risk of breast cancer. In this study, the percent composition, but not the amount of fatty acids, was reported. Studies in rodents have demonstrated that after a requirement for linoleic acid is met, total amount rather than type of fat in the diet is responsible for tumorigenesis. Therefore, the results of Eid and Berry are not contradictory to the current fat and cancer hypothesis. On the other hand, Neoptolemos et al. (Ref. 59) found that tissue arachidonic acid was decreased in colon cancer patients whereas there was no difference in dietary intake. The authors suggested a possible disturbance in fat metabolism in cancer patients.

Howe (Ref. 73) performed a meta-analysis of 12 case-control studies of diet and breast cancer. He found a consistent, statistically significant positive association between breast cancer risk and saturated fat intake in post menopausal women. However, he was unable to adjust the results for total caloric intake.

Considered together, the case-control studies support the conclusion that there is a positive association between dietary fat and breast cancer. The effect of fat intake on the risk of breast cancer is independent of the effect of energy intake. The total amount of fat rather than any specific type of fat seems to be responsible for the elevated risk of breast cancer.

The Howe et al. cohort study, (Ref. 40) found a weak but significant association between total fat intake and the risk of breast cancer in a prospective study in a large cohort (56,837 women, 519 cases during a 5-year followup). The group that consumed the highest amount of fat demonstrated a risk of developing breast cancer that was 1.3 times as great as the group that consumed the least amount of fat after adjustment for other sources of energy. Intake of various types of fat (saturated, monounsaturated, and polyunsaturated fatty acids) showed a general pattern of increasing risk of breast cancer with exceptions in the lowest quartile for intake of saturated and monounsaturated fatty acids. On the other hand, in a 20-year prospective study with a smaller cohort (3,988

women, 54 cases) in Finland, Kneckt et al. (Ref. 39) found no association between energy-adjusted fat intake and risk of breast cancer. The strength of the association between fat intake and the breast cancer risk could have been underestimated in this study because of possible changes over time in dietary habits during the 20 years before diagnosis.

The results of these two prospective studies are contradictory regarding the relationship between dietary fat and cancer. To date, only a small number of prospective studies that have examined this association have been completed. Because of the long latency period of breast cancer, a suitable length of time for a prospective study is likely to be 20 years or more, which presents many difficulties in its administration. In addition, in order to demonstrate an effect, the fat intake of the population would have to show sufficient variation to detect an effect.

To test the feasibility of low-fat dietary maintenance over time, a 2-year intervention study by Insull et al. (Ref. 60) required that subjects maintain a diet comprised of only 20 percent of total calories for 2 years. Compliance was good, thus supporting the authors' inference that studies that requiring maintenance of a low-fat diet are feasible.

ii. *Colon cancer.* There have been few studies published on the relationship of dietary lipids to colon cancer since the authoritative documents. An overview of these studies is given in Table 2 and discussed below.

The Hursting, et al. correlational (ecologic) study (Ref. 38) found a significant association of energy-adjusted, estimated total lipid intake and the incidence of colon cancer. When the results were adjusted for intake of the saturated fat component of lipids as well as total calories, the intake of saturated fat was significantly associated with the incidence of colon cancer. The intake of omega-6 or omega-3 polyunsaturated fatty acids were not associated with the risk of colon cancer. (See Table 2 for detailed critiques for each study.) Morales Suarez Varela-et al. (Ref. 90) evaluated the relationship between Spanish diet and rectal or colon cancer and found a positive correlation between rectal or colon cancer and total fat consumption. However, the results were not adjusted for total energy intake or for lifestyle confounders such as tobacco smoking.

A case-control study in Utah (Ref. 61) also reported a significant association of total fat intake with the risk of colon cancer in both females and males. In females, the group consuming the greatest quantity of total fat exhibited 1.9 times the risk of colon cancer as the group consuming the lowest quantity. In males, the risk was 2.0 times as great. However, various lipid types (saturated fat, monounsaturated fat, and polyunsaturated fat) were not consistently associated with the risk. Energy intake, not adjusted in the risk assessment, may have confounded the results.

De Verdieu (Ref. 77) in a Swedish case-control study of colorectal cancer found an increased risk with increased energy intake and with increased total fat intake but only the trend of increasing risk with increasing consumption levels was statistically significant. None of the individual fat consumption levels was associated with increased risk of colorectal cancer. The results were adjusted only for fiber intake and not for total energy. Also, there was a high nonresponse rate among the cancer cases, 21 percent, which may have biased the results.

Slattery, et al. (Ref. 88) conducted a case-control study of colon cancer in Utah that found a nonsignificant increase in cancer associated with total fat intake. The results were not adjusted for total energy intake.

Cohort studies—a prospective study of 88,751 registered nurses was performed by Willett. et al. (Ref. 62). During a 6 year followup period, 150 colon cancer cases were identified. After adjusting for the difference in age and energy intake, a positive association was found between fat and colon cancer. Specifically, the group with the highest total fat consumption demonstrated a risk of developing colon cancer that was 2.0 times as great as the group with the lowest fat intake. The groups with the highest consumption of animal fat, saturated fat, and monounsaturated fat also showed a higher risk of developing colon cancer of 1.9, 1.4, and 1.7 times the groups with the lowest consumption, respectively. Intakes of linoleic acid, vegetable oil, and cholesterol were not associated with cancer risk.

A prospective study of 8006 Hawaiian Japanese men (Ref. 85) was conducted to assess the impact of fat and calcium intake on the risk of developing colon or rectal cancer. The cohort was followed for 22 years. The results, which were not adjusted for total energy intake, demonstrated that fat intake did not affect colon or rectal cancer risk.

Thus, recent human studies on fat and colon cancer show an inconsistent association between intake of total fat and the risk of colon cancer. Many of the studies are difficult to interpret because the results were not adjusted for the effects of energy.

iii. *Other cancer.* Correlational (ecologic) studies (Ref. 38) demonstrated a significant association of energy-adjusted, estimated total lipid intake and prostate cancer but not with the incidence of cervical or lung cancer. When the results were adjusted for intake of component fats as well as total calories, the intake of saturated fat and omega-6 polyunsaturated fat was significantly associated with the incidence of prostate cancer. The intake of monounsaturated fat or omega-3-polyunsaturated fat was not associated with of risk of cancer. See Table 2 for detailed critiques for each study.

Ghadirian et al. case-control studies (Ref. 63) found significant associations of total lipid and saturated fat intake with the risk of pancreatic cancer in a case-control study in Montreal; however, cholesterol was not significantly associated with risk. Age, sex, energy intake, response status, and cigarette smoking habits were adjusted in the data analysis.

Baghurst, et al. (Ref. 75) in a case-control study of pancreatic cancer found an increased risk with increased cholesterol intake but not with polyunsaturated fatty acids. Thus, the results are somewhat contradictory. A well done case-control study of pancreatic cancer (Ref. 78) found no increased cancer risk associated with consumption of total fat, saturated fat, cholesterol, or omega-3 fatty acids. The results were adjusted for total caloric intake as well as for all major risk factors for pancreatic cancer other than diet. Finally, LaVecchia, et al. (Ref. 82) also found no relationship between pancreatic cancer and indicators of dietary fat in a well-controlled case-control study.

A case-control study in Hawaii (Ref. 64) showed that male lung cancer patients consumed significantly more fats (total fats, saturated fats, and monounsaturated fats) compared to the controls after adjustments for age, ethnicity, and cigarette smoking. However, there was no significant association between lipid intakes and risk of lung cancer in females. Another case-control study of lung cancer (Ref. 79) found a borderline increased risk of lung cancer associated with high levels of cholesterol consumption but not with total fat consumption. A case-control study of laryngeal cancer found no association with indicators of dietary fat (Ref. 81).

Steineck (Ref. 65) reported a dose-response relationship between total fat intake and the risk of urothelial cancer

in a case-control study in Sweden. Gender, age, and smoking habits, but not energy intake, were adjusted in the data analysis. Maclure, et al. (Ref. 83) found a weak association between risk of renal cancer and fat consumption. (See Table 2 for detailed critiques of these studies.)

Slattery, et al. (Ref. 86) in a case-control study of prostate cancer found no association with a high fat diet consumed as adolescents and a slight association with a high fat diet consumed by cases as adults.

Thus, one correlational study found a positive, energy-independent association of total fat intake with the risk of prostate cancer but not with the risk of cervical or lung cancer. One case-control study found a positive, energy-independent association of total fat intake with the risk of pancreatic cancer, but three other case-control studies of pancreatic cancer found no association with fat intake. The results of two case-control studies of lung cancer were not consistent for males and females, thus raising questions of interpretation. Various types of fat did not show any specific effects on risk of the various cancers examined. In conclusion, there is some evidence that total fat intake may increase the risk of prostate cancer but not the risk of pancreatic, cervical, pancreatic or lung cancer. The effect of fat seems to be independent of the effect of energy.

iv. *Studies testing fat-containing foods.* A few studies tested the association of lipids as constituents of food with the risk of breast cancer (Refs. 41, 44, 46, 48, 49, 62 and 65 through 68). The results of these studies were contradictory. Meat consumption was positively associated with risk of colon cancer or rectal cancer (Refs. 62, 66 and 67) and with stomach cancer (Ref. 76), but not with risk of breast cancer (Refs. 41, 44, 46 and 49), lymphoma (Ref. 68), urothelial cancer (Ref. 65), or oral cavity or pharyngeal cancer (Ref. 69). An additional case-control study of stomach cancer found a decreased cancer risk with increasing consumption of vegetable fat (Ref. 74). Consumption of whole milk (Ref. 48) or milk (Ref. 68) was significantly associated with the risk of cancer of the breast, colon, rectal, lung, bladder, prostate, oral cavity, and of lymphoma, but not with ovarian cancer (Ref. 84). Consumption of dairy products was significantly associated with the risk of cancer of the breast (Ref. 46), rectum (Ref. 67), and lymphoma (Ref. 68) but not with the risk of colon cancer (Ref. 67). Consumption of margarine was not associated with the risk of colon cancer (Ref. 66).

Methodological limitations inherent in case-control studies using food frequency questionnaires may have contributed to the difficulty of interpreting these results. These limitations include recall bias, interviewer bias, inconsistency in estimation of food consumption, and homogeneity of the population tested. Interactions among nutrients or other food components beyond fat might also have weakened the results.

4. Other Relevant Information

a. *Breast cancer and colon cancer: public health aspects.* Breast cancer is the second leading cause of cancer death among women. In 1990, approximately 44,000 women died of breast cancer in the U.S., while 150,000 new female cases were diagnosed. Approximately 1 woman in every 10 will develop breast cancer in her life (Ref. 1, pp. 415–6). The prevalence of breast cancer in the United States was estimated to be 1,517,882 cases in 1990. Thus breast cancer represented 24 percent of all cancers in 1990 and 39 percent of all cancers in females (Ref. 73).

Breast cancer risk increases with age, but the slope of the age-specific incidence is different before and after menopause. Risk rises rapidly up to about the age of 50 to 55, at which time the rate of increase slows or even reverses in some populations. After menopause, another rise occurs in high-risk populations.

Breast cancer has tended to be more common among higher socioeconomic groups and among Caucasians. Recently, however, rates have been rising among blacks, Hispanics, and people of Asian origin. The health care costs for breast cancer for 1990 are estimated at $8.5 billion, with an additional $16.5 billion, if lost wages due to disability and early mortality are considered (Ref. 73).

Colon cancer is a common disease in developed countries. It is the third leading cause of cancer death in the western world, exceeded only by lung and breast cancer. In the United States, colon cancer is a major cause of illness and death, accounting for 14 percent of all cancers diagnosed. The current U.S. age-adjusted incidence rate for colon cancer is 34.7 new cases per 100,000 population (Ref. 70). In 1990 the prevalence was 338,980 cases in men and 432,435 cases in women in the United States (Ref. 73). Both incidence and mortality from colon cancer have been relatively stable for the past 30 to 40 years. Recently, however, there has been an indication that mortality is decreasing among women in North America and possibly among men in the United States (Ref. 3, p. 118). Health care costs for colon cancer (1990) were estimated at $4.3 billion, with an additional $8.4 billion in lost wages due to disability and early mortality (Ref. 73).

b. *Potential safety concerns of dietary fat intake restriction.* Restriction in the intake of dietary fat may reduce the consumption of essential fatty acids. The requirement of linoleic acid to avoid essential fatty acid deficiency is 1 to 2 percent of total caloric intake. Currently, the average linoleic acid consumption in the U.S. ranges between 5 and 10 percent of total calorie intake, and deficiencies of essential fatty acids are rare in the U.S. Thus, a reduction of total fat consumption from the current 36 to 37 percent of total calorie intake to about 30 percent is not likely to cause essential fatty acid deficiencies in the general population.

5. Conclusions

Although the results of animal studies are not entirely consistent, taken as a whole, the results show that high fat diets enhance carcinogen-induced tumor development of the mammary gland, colon, pancreas, and lung, independent of the effect of energy intake. There seems to be an optimal intake of linoleic acid to yield maximum mammary and pancreatic carcinogenesis in rats. The amount of dietary linoleic acid (3 to 5 percent by weight) for maximum mammary tumorigenesis in rodents is higher than the linoleic acid requirement for the rodent, exclusive of the tumor cells (1 to 2 percent by energy), and approximates the current, average consumption of linoleic acid in the U. S. Once the linoleic acid requirement is met, the total amount of fat in the diet, rather than types of fat, seems to be responsible for tumor development (Refs. 20 and 71).

The effects of different types of fat on tumorigenesis have not been studied extensively, and the results are as yet inconclusive. Generally, both a high saturated fat diet and a high polyunsaturated fat diet show tumor-enhancing effects. Most studies that examined the effects of omega-3 fatty acid-rich fish oils on tumorigenesis consistently concluded there was a suppression of tumorigenesis. However, most of these studies were flawed in biological plausibility, and the results are not easily extrapolated to humans. The mechanism by which fat affects tumorigenesis has not been definitively established.

International correlational studies of human populations reported that dietary

lipid intake, independent of energy intake, is associated with tumorigenesis particularly of the breast, colon, and prostate but not with the incidence of cervical or lung cancer. These results suggest that the effect of fat intake on cancer incidence may be site-specific.

Four cohort studies were reviewed. In a 20-year followup study in Finland, energy-adjusted total fat intake was not associated with the risk of breast cancer. In a large, 5 year followup study in Canada, the energy-adjusted intake of total fat was weakly but significantly associated with the risk of breast cancer. All three fat types (saturated, monounsaturated, and polyunsaturated) showed a general pattern of increasing risk with increasing fat intake. In a large cohort study of 88,752 nurses, Willett et al. (Ref. 62) found a significant association of dietary total fat, animal fat, saturated fat, and monounsaturated fat with the incidence of colon cancer. However, a Japanese cohort study demonstrated that fat intake did not increase the risk of colon or rectal cancer (Ref. 85).

The total fat intake was associated with the risk of breast cancer in most, but not all, case-control studies: Six studies found a significant relationship, one study found a borderline association, and two studies found no relationship. As in the animal studies, no specific effects of different types of fat were found in these studies. In some studies, all types of fatty acids were associated with carcinogenesis; in some other studies, only saturated or monounsaturated fatty acids were associated.

Because energy intake and lipid intake are highly correlated, it is possible that the association between dietary fats and cancer is confounded by energy intake. It also has been demonstrated in animal and human studies that energy intake in excess of an essential requirement is of primary importance in determining the incidence of induced and spontaneous tumors. However, FDA s evaluation of recent research reports, both in animal and human studies, provides convincing evidence that the effect of dietary lipids on tumorigenesis is independent of the effect of energy.

Few studies evaluated fats in the context of overall food consumption. The results of studies of the association between the risk of cancer and consumption of meat, milk, or dairy products are inconsistent. Methodological limitations may have obscured any association that exists.

There have been no clinical trials or dietary intervention studies examining the quantitative relationship between reduction in fat intake and altered cancer risk in populations. Therefore it is not possible to conclude how much reduction in fat intake is necessary, or how soon in life it must commence, to reduce the risk of cancer in the U.S. population. Intervention studies of cancer are difficult to perform because the rarity of outcome for specific types of cancer requires enormous sample sizes. In addition, the long latency, 20 to 30 years for most types of cancer, makes such studies difficult and costly. For this reason, observational epidemiology studies are generally accepted as sufficient, as was the case for the first Surgeon General s Report on smoking. Nevertheless, the weight of evidence shows that a diet that is low in total fat is consistent with a low risk of some types of cancer.

The 17-year followup study of the National Center for Health Statistics' First National Health and Nutrition Examination Survey (Ref. 72) examined the relationships between dietary fat and the risk of cancer of the breast, prostate, and colon in 5,454 men and 7,876 women. No evidence of increased risk of cancer in the group with the highest fat intake was found. The difference in fat intake between the groups with the highest and the lowest fat intakes, 37 percent energy versus 32 percent energy, was not as great as the differences in fat intakes between countries. These results suggest that a reduction in fat intake to less than 30 percent of total calories may be needed to observe any reduction in cancer risk in the United States.

Thus, the conclusions of the authoritative reviews that dietary fats have an important influence on cancer incidence and mortality, particularly at sites such as the breast, colon, and prostate, are supported by the results of recent animal and ecological studies. Results of human prospective and case-control studies are less supportive, in part because of limitations in the experimental design. However, the majority of case-control studies are consistent with the conclusion that fat intake is associated with the risk of breast and colon cancer.

Although cancer at many sites was affected by fat intake in animal studies, epidemiologic studies failed to show convincing evidence for the fat and cancer relationship at various sites. Furthermore, an international ecologic study found an association between fat intake and cancer of the breast, colon, and prostate but not of the cervix or lung. These results suggest that the effect of fat on cancer may be site-specific.

From the review of other authoritative documents and recent research reports, the agency concludes that dietary fat intake may affect the risk of breast, colon, and prostate cancer. More studies are needed to examine the relationship between fat intakes and cancer at other sites.

No scientific evidence is available that demonstrates that any specific fat type is more causative of cancer than another. All types of fat (saturated, monounsaturated, and polyunsaturated) may be associated. Therefore, total fat content, rather than any specific type, may be responsible for the tumor enhancing activity of fat in the current diet of the U.S. population.

III. Tentative Decision to Authorize a Health Claim Relating Ingestion of Dietary Fat to Reduced Risk of Cancer

FDA has reviewed the Federal government and other review documents as well as recent research and review articles relevant to dietary fat and cancer risk. In addition, the agency considered all comments received in response to the Federal Register notice of March 28, 1991, requesting scientific data and information on fat and cancer. The agency has tentatively concluded that all the publicly available evidence supports an association between dietary fat and cancer risk. FDA tentatively finds, based on this evidence and the authoritative reports, that there is significant scientific agreement among qualified experts. The agency is proposing to authorize a health claim for fat and cancer on the label and labeling of foods provided that such statements comply with the requirements of proposed § 101.73. Under this proposal, the claim will convey the message that diets low in fat may reduce the risk of some types of cancer, particularly breast, colon, and prostate. FDA also tentatively concludes that the message must be restricted to these three types of cancer because of the limitations of scientific data about other types of cancer.

IV. Description of and Rationale for Regulations

A. Relationship Between Dietary Fats and Cancer

Based on all of the evidence, FDA has tentatively determined that there is significant scientific agreement among experts qualified by training and experience to evaluate such claims, that all of publicly available evidence supports the conclusion that diets high in fat increase the risk of cancer, and,

more importantly, that diets low in fat is associated with the reduced risk of cancer. FDA recites this fact in proposed § 101.73(b)(1) and states that the research to date shows that it is total fat, and not any particular type of fat that is associated with cancer risk.

The specific health claim topic, as described in section (3)(b)(1)(A)(vi) of the 1990 amendments was dietary lipids and cancer. FDA has tentatively found that the intake of dietary lipids is associated with cancers of the breast, colon, and prostate. This tentative finding is based on the conclusions of a number of comprehensive reports by the Federal Government and the NRC which identified cancers at these particular sites as having a relationship to dietary fats. It is also supported by research published since the authoritative reports to determine if more recent research would necessitate modification of previous conclusions.

B. Significance of the Relationship

To reflect, in part, proposed § 101.14(d)(2)(v), FDA is including in proposed § 101.73(b)(2) dietary guidelines to recommend that total fat intake be at or below 30 percent of calories. Currently, adults in the United States consume, on average, a total fat intake of 37 percent of calories. The proposed regulation states that significant public health benefits can be derived from decreased consumption of foods high in fat, including the reduced risk of breast, colon, and prostate cancer.

C. General Requirements

1. Conformity With Proposed § 101.14

Proposed § 101.14 sets forth the general provisions applicable to health claims. In proposed § 101.73(b)(3)(i), FDA is proposing that health claims relating to an association between dietary lipids and cancer must meet all requirements for health claims proposed in § 101.14, as set forth elsewhere in this issue of the **Federal Register**.

2. Qualifying Nutrients: Total Fat

In proposed § 101.73(b)(3)(ii), FDA is proposing that a health claim relating diets low in fats to reduce the risk of cancer must meet requirements for "low fat" or "fat free."

The evidence for the association between intake of dietary lipids and risk of cancer pertains to total dietary fats. In the companion document on general requirements for health claims for food (published elsewhere in this issue of the **Federal Register**), FDA is proposing that for a substance such as dietary fats for which a low level of intake is needed to achieve dietary goals, the substance be present in a food at a low enough level to justify a claim. FDA is proposing that that level be the level that is necessary to make a "low fat" or "no fat" claim. As proposed in the companion document on "Definitions of Nutrient Content Claims for the Fat, Fatty Acid, and Cholesterol Content of Foods," these levels are, for a "low fat" claim, less than 3 g of fat per reference amount customarily consumed, per labeling serving size, and per 100 g. For a "no fat" claim, FDA is proposing that the food contain less than 0.5 g of fat per reference amount customarily consumed and per label serving size.

As explained in the companion document on general requirements for health claims, FDA is proposing that the food contain "low" or "no" fat to ensure that it contains a level of fat that is appropriate for inclusion in a diet that is low in fat. FDA seeks comments on whether a food that qualifies for a "reduced fat" or comparative claim should also qualify to bear this health claim.

D. Specific Requirements

In proposed § 101.73(b)(4)(i), FDA is proposing to require that any health claim made relating to dietary lipids and cancer specifically state that it is diets that are low in fats that may reduce the risk of some types of cancer.

In proposed § 101.73(b)(4)(ii), to reflect the strength of the scientific evidence regarding the relationship of dietary lipids to risk of cancer, FDA is proposing that any health claim make clear that ingestion of diets low in fats "may" reduce the risk of cancer. This requirement is based on this relationship and is supported by evidence documented and summarized in Federal government reports, in other authoritative documents, and in the science review incorporated previously in this document. However, given the fact that the etiology of cancer is multifactorial the claim cannot state that a low fat diet will definitely reduce the risk of this disease.

In respect to the multifactorial nature of the disease in proposed § 101.73(b)(4)(iii), the agency is proposing to require that health claims acknowledge the existence of other risk factors for cancer in addition to the dietary risk factor of fat intake. The agency believes that this additional information provides a context that is essential for an understanding of the nutrient to disease relationship.

As for terminology, in proposed § 101.73(b)(4)(iv), FDA is proposing that health claims refer to the nutrient disease relationship using the term "total fat." This terminology is consistent with colloquial usage. Thus, the claim will be clear and not misleading to the public. It also reflects the available evidence. In proposed § 101.73(b)(4)(iv), FDA provides that a combined fat and cancer and fat and cardiovascular claim may be used if a food qualifies for both claims. In proposed § 101.73(a), FDA is summarizing the scientific evidence that establishes a relationship that exists between saturated fat, cholesterol, and total fat and cardiovascular disease. FDA is proposing to authorize health claims on qualifying foods that meet the criteria for "low" saturated fat, cholesterol, and total fat or no cholesterol and total fat.

For the estimation of attributable risk, in proposed § 101.73(b)(4)(v), FDA proposes that no statement may be made on the precise level of reduction of risk of cancer that may be expected as a result of consuming a diet low in total fat. This requirement is proposed in conformity with proposed § 101.14(d)(2)(iii) which requires that the claim not be misleading. The review of Federal government documents and other authoritative reports and more recent scientific evidence revealed no scientific agreement on a precise level of risk reduction for the relationship of dietary fat to cancers.

In § 101.73(b)(4)(vi), FDA is proposing that the claim may not specify the particular types of fats and fatty acids that may be related to the risk of cancer. FDA tentatively finds that the evidence is not sufficient to characterize the relationship more specifically than between cancer and total fat.

E. Optional Information

For total dietary context, in proposed § 101.73(b)(5)(i), FDA proposes to permit claims to refer to the latest U.S. Dietary Guidelines for Americans (Ref. 6). The agency is proposing to permit such references to help ensure that the claim is presented in a way that will help consumers to understand it in the context of a total daily diet. The agency recognizes that a statement about the importance of good nutrition that does not make a connection between any substance and a particular disease, as is the case with many of the Dietary Guidelines, is not a health claim. H. Rept. 101-538, 101st Cong., 2d sess. 20 (1990). However, as is stated in the document on the general principles for health claims, FDA believes that it is appropriate for it to provide for the use of governmental dietary information in conjunction with a health claim to

ensure that that information is used in a consistent and nonmisleading manner.

Providing additional health claim information, in proposed § 101.73(b)(5)(ii), the agency is proposing to allow manufacturers to provide more detailed information to consumers. This information may provide a more accurate and complete description of the relationships among both dietary fats and risk of cancer and heart disease. A statement on how to obtain this additional information may be provided in or near the health claim. Such additional information, however, is not a substitute for that required in a health claim.

F. Sample Health Claims

FDA is also providing in proposed § 101.73(b)(6) two sample health claims. These model claims have been prepared by the agency to reflect all the requirements of proposed § 101.73. They are only samples, however, if these sample health claims are adopted by the agency, manufacturers will be free to use them. They will also be free to devise their own message provided that it complies with the regulation.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

VII. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the $100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the **Federal Register**. The agency requests comments on the RIA.

IX. Appendix to the Preamble—Consumer Summary on Dietary Lipids and Cancer and Dietary Lipids and Coronary Heart Disease

As described in the companion document (published elsewhere in this issue of the **Federal Register**) on general requirements for health claims, the agency is requesting comment on the need for consumer health claims summaries. The focus of the consumer summary would be to provide factual information to aid the consumer in understanding the diet-disease relationship. The following appendix is a proposed consumer summary on dietary lipids and cancer. The role or relationship of dietary fats to cancer risk is discussed, along with the relationship of dietary fats to coronary heart disease. FDA solicits comment on this document as explained in the proposal on general health claims published elsewhere in this issue of the **Federal Register**.

Appendix—Dietary Lipids and Cancer and Dietary Lipids and Coronary Heart Disease

Under the provisions of the Nutrition Labeling and Education Act of 1990, manufacturers may put clear information on the food label about the relationship between a nutrient, such as fat or cholesterol, and a disease or health-related condition. To prevent consumers from being misled, the Food and Drug Administration (FDA) allows only truthful label statements about diet and health relationships that are firmly supported by the current scientific evidence. There is agreement that the scientific evidence is strong enough to allow health claims about the association between total fat in the diet and the risk of some types of cancer and the association between saturated fat and cholesterol in the diet and the risk of coronary heart disease.

Many consumers have said that health claims on food labels could be useful to them in making improvements in their diets. However, label space is often limited. Therefore, this pamphlet provides information about diet and health claims that supplements what you may see on food labels.

In addition to the association between fat and cancer and between saturated fat and cholesterol and heart disease, FDA is allowing health claims about calcium and osteoporosis and sodium and hypertension. For information about these other diet and health relationships, write to: [TO BE INSERTED]

What is Coronary Heart Disease?

Coronary heart disease is a broad term that includes a number of diseases for which various medical names are used, including heart disease and atherosclerosis. Narrowing of blood vessels (medically called atherosclerosis) occurs in these diseases, which results in decreased flow of blood to some part of the body. The diseases include coronary heart disease that affects the heart and its supporting blood vessels, and other diseases that affect the blood vessels in other areas of the body. Atherosclerosis can result in angina pectoris, heart attack, sudden death, stroke or other serious problems.

Atherosclerosis occurs because of raised fatty or fibrous deposits (plaque) that develop in the walls of blood vessels in the affected area. The process of plaque development is gradual, and often begins in childhood.

What is Cancer?

Cancer is not one disease, but more than 100 different diseases. In each of these diseases, cells begin to grow out of control at one site in the body, and these abnormal cells spread to other parts of the body.

Why Are Heart Disease and Cancer Major Public Health Concerns?

Coronary heart disease and cancer are public health concerns because they are the two leading causes of death in this country. Illness and death from these diseases cost billions of dollars in health care costs and in lost work. Moreover, early deaths from these two diseases cheat many victims of valuable years of life.

Despite the recent sharp decline in the death rate from this condition, coronary heart disease still accounts for the largest number of deaths in the United States. Cancer is the second leading cause of death in this country. The leading causes of cancer death are lung cancer, colorectal cancer, breast cancer, and prostate cancer.

What Causes Cancer and Coronary Heart Disease?

Both of these diseases are caused by a combination and interaction of multiple environmental, behavioral, social, and hereditary factors. It is clear that diet, one of the environmental factors, play

an important role in the development of these diseases.

Heredity and other factors, including elevated blood serum cholesterol, cigarette smoking, high blood pressure, obesity, and an inactive life style, are known to increase a person's risk of developing coronary heart disease. Elevated blood cholesterol, one of the major risk factors for coronary heart disease, is associated with excess fat, especially saturated fat, and cholesterol in the diet.

Many studies have established a strong association between a diet high in saturated fat and cholesterol and increased risk of coronary heart disease. High saturated fat and cholesterol diets are estimated to be associated with one-third of the cases of coronary heart disease reported in this country.

The way diet affects blood cholesterol varies among individuals. However, blood cholesterol does increase in most people when they eat foods high in saturated fat and cholesterol and excessive in calories. Of these, saturated fat has the greatest effect; dietary cholesterol has less.

Cancer has many causes and several stages in its development. The risk factors for developing cancer include a family history of a specific type of cancer (such as breast, prostate or colon cancer), cigarette smoking, alcohol consumption, radiation, and dietary factors.

Currently, the strongest scientific evidence relating diet to cancer is that the amount of total fat in the diet may have a relationship with cancer. In particular, many experts agree that a high fat diet may influence the risk for developing breast, colon, and prostate cancers.

Not enough is known currently for scientists to decide whether different kinds of fats (animal or vegetable; saturated or unsaturated) may be responsible for an increased risk of developing cancer.

Because of scientific agreement that reducing total fat and saturated fat is likely to lower the rates of these two major chronic diseases, it is recommended that Americans 2 years of age and older choose a diet low in total fat and saturated fat. Animal products are the source of all dietary cholesterol. Eating less fat from animal sources will help to lower the cholesterol as well as the saturated fat in your diet.

Do Most People Get Too Much Fat, Saturated Fat and Cholesterol in What They Eat?

The average U.S. diet, it's estimated, contains about 37 percent of calories from total fat, 13 percent of calories from saturated fat, and 360 milligrams (mg) of cholesterol per day. Health experts recommend diets that contain 30 percent or less of calories from total fat, 10 percent or less of calories from saturated fat, and 300 mg or less of cholesterol a day. The U.S. Public Health Service has set a national health goal that all persons who are 2 years of age and older consume these levels of fat and cholesterol by the end of this decade.

How Do You Learn How Much Fat and Cholesterol Foods Contain?

You may or may not be able to tell that there's fat in a food by looking at it. Butter, margarines, shortenings, and oils are the more obvious sources of fat. In other foods, such as cheese, baked goods, nuts, and salad dressings, the fat is not as easily detected. Cholesterol content is not obvious at all in foods.

A good way to learn about fat and cholesterol content is to read nutrition labels. Most foods now have nutrition information on their labels.

The amounts of total fat and saturated fat in a serving of food are listed in grams (g) on the nutrition label. Cholesterol is listed in mg.

"Daily values" for fat, saturated fat, and cholesterol also appear on food labels. These numbers have been established by FDA for several nutrients that are important in diet and health relationships. The daily values are to help you learn how the amount of a nutrient in a serving of food relates to a reasonable amount for the day.

The daily value for total fat is 75 g, and for saturated fat is 25 g. That means total fat for a day of 75 g, of which no more than 25 g should be from saturated fat. These numbers are based on a 2,350-calorie diet that has 30 percent of calories from fat and 10 percent from saturated fat. A 2,350-calorie diet is about the calories recommended for an adult woman.

If you consume a different number of calories a day, it's not hard to figure out your own daily values for total fat and saturated fat. First, multiply the number of calories you consume by 30 percent (for example, $2000 \times .30 = 600$). Then divide that number by nine, which is the number of calories each g of fat provides (600 divided by 9 = 67 g of fat a day). Repeat for saturated fat ($2000 \times .10 = 200$; 200 divided by 9 = 22 g of saturated fat a day).

The daily value for cholesterol is 300 mg, which is an upper limit that is generally recommended for healthy people. A food that contains 150 mg of cholesterol per serving, therefore, would provide about half of the daily value for cholesterol.

What Do Label Claims About Fat and Cholesterol Mean?

In addition to the amount of fat and cholesterol listed on the nutrition label, you may see other claims about fat and cholesterol content on some food packages. There are two types of these claims—nutrient content claims and health claims.

Nutrient content claims describe the amount of fat, saturated fat, or cholesterol a food contains. These types of claims can be used on a label only if a food meets several definitions established by FDA.

Cholesterol Claims

A "cholesterol free" food has less than 2 mg of cholesterol and 2 g or less of saturated fat in a serving.

A "low cholesterol" food has 20 mg or less of cholesterol in a serving and in 100 g of food and 2 g or less of saturated fat in a serving.

A "reduced cholesterol" food has its cholesterol content reduced by 50 percent or more compared to the regular food product and contains 2 g or less of saturated fat in a serving.

Cholesterol claims may be made only on foods that contain a limited amount of fat (no more than 11.5 g per serving and per 100 g) unless the claim also tells the total amount of fat, for example, "cholesterol free, contains 12 g of fat per serving."

Fat Claims

A "fat free" food has less than a ½ g of fat in a serving and no added fat or oil.

A "low fat" food has 3 g or less of fat in a serving.

A "reduced fat" food has a 50 percent or more reduction in fat with at least a 3 g reduction in fat content.

A "low saturated fat" food has 1 g or less of saturated fat in a serving and no more than 15 percent of its calories from saturated fat.

A "reduced saturated fat" food has its saturated fat content reduced by 50 percent or more compared to the regular food product with at least a 1 g reduction in fat.

Also, the labels of some foods in which fat or cholesterol has been significantly reduced, but not enough to meet the definitions above, may have a statement that tells how much less fat or cholesterol the product contains than a comparable product; for example, "This pound cake contains 40 percent less fat than our regular pound cake."

Foods such as fruits and vegetables that meet the definitions for fat or cholesterol without special processing may have claims on them. However the

label must say that fat or cholesterol is not usually present in the food, for example, "broccoli, a fat-free food," "frozen perch, a low fat food," or "raspberries, a low saturated fat food."

Health claims are those made about the relationship between the amount of a nutrient you eat and the risk of a disease, for example, between total fat and cancer or between saturated fat and cholesterol and heart disease.

Health claims about the relationship between fat and cholesterol and heart disease can only be made on products that are low in saturated fat and cholesterol, and have 15 percent or less of their calories from fat. To make a health claim, the product also cannot contain another nutrient that increases the risk of a diet-related disease other than atherosclerosis, for example, a high amount of sodium which has a relationship to high blood pressure.

Health claims about the relationship between fat and cancer can be made only on foods that are low in fat and do not contain another nutrient that increases the risk of a diet-related disease other than cancer.

These are some of the kinds of foods on which you may see health claims about nutrients related to cancer and heart disease: fruits, fruit juices, vegetables, breakfast cereals, dried peas and beans, skim milk, pasta products, and diet salad dressings.

Other Risk Factors for Cancer and Heart Disease

Coronary heart diseases and cancer are complex diseases with multiple causes, and they (usually) develop over a long period of life. Hereditary as well as environmental factors contribute to the risk for developing these diseases. In addition to practicing good nutrition, several other controllable factors are part of a healthy lifestyle and may help to decrease your chances of cardiovascular disease and cancer. These include maintaining a healthy body weight and good physical fitness, not smoking cigarettes, drinking only in moderation if at all, and not abusing drugs.

Facts To Keep in Mind

It's the total combination of foods that you eat regularly—both the kinds and the amounts—that is important in terms of good nutrition. Eating a particular food or a specific food is not a magic key that will assure you have a more healthful diet.

Eating a healthy diet, in itself, does not guarantee good health. A healthy diet, however, is an important part of a healthy lifestyle.

In addition to what you eat, many factors may be related to your own chance of developing a particular disease, for example, your heredity, your environment, and the health care that you get. Our knowledge about most diet-health relationships is incomplete, and will improve as scientific knowledge increases. However, enough is known today about some of these relationships to encourage specific dietary practices that are believed to be beneficial.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6, of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371).

2. Section 101.73 is amended by adding paragraph (b) to read as follows:

§ 101.73 Health claims: lipids and cardiovascular disease and lipids and cancer.

* * * * *

(b) *Cancer*—(1) *Relationship between lipids (fat) and cancer.* (i) Cancer is not one disease, but a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells. Cancer has many causes and stages in its development. Both environmental and genetic risk factors may be involved in affecting the risk of cancer occurrence. Risk factors include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, ultraviolet or ionizing radiation, and dietary factors.

(ii) The strongest positive association between fat intake and cancer risk has been found between total fat intake and some types of cancer. Based on the totality of the evidence available at this time, and despite some inconsistencies found in results of human studies, there is significant scientific agreement among experts, qualified by training and experience to evaluate such evidence, that diets high in total fat are associated with an increased cancer incidence. Research to date, although not conclusive, demonstrates that the total amount of fats, rather than any specific type of fat, is positively associated with cancer risk. The mechanism by which total fat affects cancer has not yet been established.

(iii) A question that has been the subject of considerable research is whether the effect of fat on cancer is site-specific. Studies which compared fat intake and cancer mortality in different countries or population groups found an association between total fat intake and cancer of the breast, colon, and prostate, but not at other sites. Although both human and animal studies are consistent in the association of fat intake with specific sites, the studies relying on animal data are more compelling. FDA concludes that the claim must be restricted to cancer of the colon, breast, and prostate due to the lack of adequate evidence for other types of cancer.

(iv) The question of whether the association of total fat intake to cancer risk is independently associated with fat intakes, or whether the association of fat with cancer risk is the result of the higher energy (caloric) intake normally associated with high fat intake, has been raised. After reviewing the evidence, FDA has concluded that there is adequate evidence from both animal and human studies to find that total fat intake alone, independent of energy intake, is associated with cancer risk.

(2) *Significance of fat intakes and risk of cancer.* Currently the average U.S. diet is estimated to contain 36 percent to 37 percent of calories from total fat. Current dietary guidelines and nutrition goals for the nation recommend that dietary fat intake be reduced to a level of 30 percent or less of energy (calories) from total fat. The scientific evidence supports the conclusion that this

lowered level is associated with a potential reduction in the risk of breast, colon and prostate cancer. Although there is evidence that reductions in total fat intake below the level of 30 percent of calories from total fat may confer even greater health benefits, the recommended levels for total fat were set at 30 percent of calories because they can be achieved without drastic changes in usual dietary patterns and without undue risk of nutrient deficiency.

(3) *General requirements.* A food label or labeling may contain a health claim stating that diets low in total fat may reduce the risk of some types of cancer, particularly colon, breast, and prostate cancer, in the general population provided that the following conditions are met by the product:

(i) The food meets all general requirements of § 101.14 for health claims.

(ii) The food meets requirements of § 101.62 for a "low fat" or "fat free" food.

(4) Health claims may be used on the label and labeling provided such statements comply with the following specific requirements:

(i) The claim states that diets low in fat (i.e., total fat) may reduce the risk of some types of cancer;

(ii) The claim is stated using words such as "may" or "might" in accordance with the strength of the evidence for the relationship;

(iii) The claim states that cancer has many causes, and that high total fat diets are only one of several factors associated with the risk of cancer;

(iv) In specifying the nutrient, the claim shall use the term "total fat", unless the food also meets the qualifications for a label statement on the cardiovascular disease-fat relationship in which case a combined statement may be used;

(v) The claim shall not quantitate the degree to which the risk of cancer may be reduced by diets low in total fat content; and

(vi) The claim shall not specify types of fats or fatty acids that may be related to the risk of cancer.

(5) Health claims describing the relationship between dietary lipids and cancer may include the following as optional information:

(i) The claim may indicate that low fat intake as part of a total dietary pattern is consistent with the latest U.S. Dietary Guidelines for Americans published jointly by the U.S. Department of Agriculture and the Department of Health and Human Services. Concepts or quotes from this publication may be used on the label provided that they are truthful and not misleading; and

(ii) The claim may include a reference that would direct interested consumers to more complete consumer information on the relationship of low total fat diets and cancer risk.

(6) The following sample health claims may be used on the label or labeling of a food to convey the relationship between dietary lipids (i.e., total fat or fat) and cancer:

Sample Health Claims

Developing cancer is associated with many factors, such as a family history of the disease, cigarette smoking, and what you eat. Eating a healthful, low fat diet may help reduce the risk for some cancers, including breast, colon, and prostate cancer.

Cancer is associated with many dietary and other risk factors. A diet low in total fat may reduce the risk of some types of cancers, including breast, colon, and prostate cancer.

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services

Note: The following tables will not appear in the annual Code of Federal Regulations.

BILLING CODE 4160-01-M

Table 1

Dietary Lipids and Cancer: Animal Studies 1989-April 1991

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Shao et al., 1990 (Ref. 10)	The effects of energy source and energy restriction on tumor development and survival rate	Female, 4 to 5 month-old, C3H/Bi mice, 15 per group	40 weeks	Ad lib and 40% energy restriction High fat: 68.2% energy lard, free carbohydrate Low fat: 4.5% energy lard, 63% energy carbohydrate	Murine mammary tumor virus (MuMTV)	Mammary: No significant difference in incidence or survival rates between high fat and low fat groups Significantly increased incidence and survival rates with energy restriction Combined mortality from all causes (tumor-related and nontumor-related) were higher in the order of: low fat, ad lib > high fat, ad lib > high fat, restriction > low fat restriction (statistics not tested)	Energy consumption, not fat intake, may play a greater role in MuMTV-induced mammary tumorigenesis; however, the nontumor-death rate was very high (26 of 60 total) which greatly reduces the significance of the findings
Welsch et al., 1990 (Ref. 11)	The effect of caloric consumption and fat level on mammary cancer	Female, 55-day old, Sprague-Dawley rats, 41 to 42 per group	16 weeks	Ad lib. and 12% energy restriction High corn oil: 20 weight % Low corn oil: 5 weight %	7,12-Dimethylbenz(a) anthracene (DMBA)	Mammary: High fat diet significantly (2 times) increased the yield (number and weight) of mammary carcinoma A 12% energy restriction significantly reduced the yield (number) of mammary carcinogenesis in high corn oil group, but not in low corn oil group The 12% energy restriction abolished the effect of fat level	When energy intake was sufficient, high fat corn oil significantly enhanced DMBA-induced mammary tumorigenesis in rats Because caloric intakes among groups were the same, the fat effect was independent of the energy effect Fat and energy might have separate functions in mammary tumorigenesis

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Sinkeldam et al., 1990 (Ref. 13)	Interaction of dietary fat (lard) and fiber on colon cancer	Male, 4-week-old, wistar rats, 30 per group	37 weeks	Ad lib 15 energy % lard 0.7 g fiber 2.2 per 3.8 100 Kilocalories (kcal) 27.5 energy % lard 0.7 g fiber 2.2 per 3.8 100 kcal 40 energy % lard 0.7 g fiber 2.2 per 3.8 100 kcal	N-methyl N-Nitro-N-nitrosoguanidine (MNNG)	Colon: High fat diet significantly enhanced incidence and multiplicity (see below, data pooled) % incidence fat / total energy% / polyps / carcinoma / tumor 15 / 44 / 9 / 48* 27.5 / 51 / 23* / 60 40 / 61 / 11 / 62 fat / Multiplicity energy % (#/tumor-bearing rats) Polyps / Carcinoma / Total Tumor 15 / 1.6 / 1.1 / 1.7 27.5 / 1.5 / 1.1 / 1.7 40 / 2.4* / 1.5 / 2.6 High fiber significantly decreased body weights and abolished the effects of fat level on colon tumorigenesis *Means significantly different from other fat energy % within tumor type	High fat enhanced MNNG-induced colon tumorigenesis in rats; however, the response was neither dose-dependent nor consistently significant The results might have been confounded by inadequate provision of linoleic acid in 15% and 27.5% lard diet groups Energy intakes were similar among different fat groups; therefore, the fat effect was independent of energy effect

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Neuberne et al., 1990 (Ref. 14)	Interaction of fat and vitamin A in colon tumorigenesis	Male, weanling, Spargue-Dawley rats, 25 to 30 per group	24 weeks	5 or 24 weight % corn oil Vitamin A 3 mg per kg 10 mg per kg 30 mg per kg	Dimethylhydrazine dihydrochloride (DMH)	Colon: High fat versus low fat: no significant difference in the incidence or malignancy Vitamin A significantly lowered the incidence in low fat group, but not in high fat group	Diets were not isocaloric; food consumption, body weights were not reported The differences in energy intakes and body weight changes might have confounded the effects of fat The high peroxidation level of high corn oil diet, which was not controlled to approximate human dietary conditions, might also have confounded the results
Birt et al., 1989 (Ref. 17)	To determine the energy effect in pancreatic tumorigenesis	Male, 6-week-old, Syrian hamster, 30 per group	91 weeks	Corn oil: 4.3 weight % 20.5 weight %	Tumor initiator: N-nitrosobis-(2-oxopropyl) amine (BOP)	Pancreatic ductular carcinoma: Both incidence (%) and yield (# carcinoma per effective animal) were significantly (3 to 4 times) enhanced in the high fat group compared to the low fat group; no differences in survival rates	Ad lib or pair feeding Caloric intakes were similar between groups; therefore the fat effect was independent of energy effect

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Appel et al., 1990 (Ref. 18)	Whether the linoleic acid level or the total fat level is the main determinant of pancreatic carcinogenesis	Male, weanling, SPF albino Wistar rats, 40 (lard group) or 23 (chow group) per group	15 month	High fat: 20 weight % lard 1.2 weight % linoleic acid Low fat: 4.5 weight % lard 0.5 weight % safflower oil 0.6 weight % linoleic acid Low fat supplemented: 1.4 weight % lard 3.6 weight % corn oil 2 weight % linoleic acid Chow: 6 weight % fat (3% linoleic acid)	Tumor inducer: azaserine	Pancreatic neoplasm: Linoleic acid supplementation did not significantly affect pancreatic neoplasm Fat level also did not significantly affect pancreatic neoplasm	The amount of dietary fat did not significantly affect azaserine-induced pancreatic carcinogenesis in rats; however, levels of linoleic acid in the test diets might not be adequate for optimal tumorigenesis The level of linoleic acid supplementation was too narrow to test the effect of linoleic acid Energy intakes were similar among groups

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Birt et al., 1990 (Ref. 19)	The effect of type or level of fat on pancreatic carcinogenesis	Male, 4 to 8-weeks-old, Syrian hamsters, 30 per group	84 weeks after BOP treatment	Control: 4.3% corn oil High corn oil: 20.5% corn oil Low beef tallow: 0.5% corn oil and 3.8% beef tallow High beef tallow: 0.6% corn oil and 19.9% beef tallow High mix: 5.1% corn oil and 15.4% beef tallow (as weight %)	Tumor inducer: BOP	Pancreatic ductular tumor and gall bladder and common duct tumor Pancreatic ductular tumor: Incidence and multiplicity of adenoma and adenocarcinoma, but not carcinoma in situ, was significantly higher (~2 times) in beef tallow than corn oil groups High fat (both corn oil and beef tallow) significantly increased carcinoma multiplicity in situ compared to low fat groups; however, fat level did not affect adenoma or adenocarcinoma multiplicity	The effect of the level and type of dietary fat differed with each of lesions of BOP-induced tumors examined The comparison of fat types might have been hampered by the fact that high or low beef tallow diets did not provide adequate linoleic acid for tumor development Caloric intakes were similar among groups The results in gallbladder or common duct tumor might have been weakened by the low

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Imaida et al., 1989 (Ref. 21)	The effect of high fat on lung tumorigenesis	Male, 6-week-old, ICR mice, 30 per group	25 weeks	Control: CRF-1 diet (3.5 kcal per g) High fat: 20% Corn oil supplementation to CRF-1 (4.7 kcal per g) Main fatty acid composition(%) Control / High fat oleic 22.4 / 32.8 linoleic 50.2 / 51.9 linoleic 4.6 / 1.8	Lung carcinogen: 4-nitro-quinoline 1-oxide (NQO)	Lung: Corn oil supplemented high fat diet significantly enhanced incidence (80% versus 58%, high fat versus control) and yield (# tumor per mouse, 2.5 versus 1.2) compared to the control group	High fat (or high corn oil) in the diet significantly enhanced lung tumorigenesis in mice; however, diet composition, except main fatty acid was not reported. There are apparent mistakes in the reported main fatty acid composition and we do not know the adequacy of linoleic acid in test diets. Furthermore, nonisocaloric diets used and body weight gains were significantly different between groups which might have confounded the effect of fat level

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Katz and Boylan, 1989 (Ref. 22)	The effect of polyunsaturated fatty acid (PUFA) level on metastasis of transplanted mammary tumor	Female, aged virgin (14 to 16-month-old) or retired breeders (10 to 12-month-old), Fischer 344 rats, 12 per group	4 weeks before and 6 weeks after tumor transplant	High fat: 23% corn oil (4.59 kcal per g) Low fat: 5% corn oil (3.68 kcal per g) purina chow (6% fat)	13,762 rat mammary adenocarcinoma transplanted subcutaneously into just posterior to the 4th nipple	Pulmonary: High fat, fed either before or after the tumor implant, significantly enhanced pulmonary metastasis in rats (495 versus 135 mm^3, high fat versus low fat) This tumorigenic effect of high fat was abolished by previous feeding with chow diet; metastasis was comparable between chow and low fat groups	High fat (or high corn oil) in the diet significantly enhance pulmonary metastasis implanted from the 13,762 mammary tumor in rats; however, nonisocaloric diets were used Because energy intakes and body weight changes were not reported, energy-independent fat effect is not clear in the report

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Birt et al., 1989 (Ref. 23)	The effect of corn oil level on initiation and promotion of skin tumor	Female, 4-week-old, SENCAR mice, 30 to 40 per group	43 weeks	Corn oil 24.6 weight % 5.0 weight %	Tumor initiator: 12-0-tetradecanoylphorbol-13-acetate (DMBA) Tumor promoter: 12-0-tetradecanoylphorbol-13-acetate (TPA)	Skin papillomas: Incidence was not affected by fat level during DMBA period but promotion was significantly enhanced by high corn oil compared to low corn oil during TPA treatment period; final carcinoma yield (# per effective animal) was not affected by fat level	High fat (or high corn oil) diet significantly accelerated DMBA- and TPA-induced skin tumorigenesis in SENCAR mice The effect was evident during the promotion period, but not during the initiation period because mice consumed similar energy by training, the effect of fat level was independent of the effect of energy or body weight changes
Borgeson et al., 1989 (Ref. 24)	The effect of fish oil on transplanted mammary tumor	Female, heterozygous BALB/cnu/+mice, 11 to 12 per group	32 days	Corn oil 10 weight % MaxEPA 10 weight %	Human mammary carcinoma MX-1, transplanted subcutaneously on the left side of each nude mouse	Mammary: fish oil significantly depressed the growth (mj tumor yield) compared to corn oil	Fish oil depressed transplanted mammary tumorigenesis; however, the total fat level was very low and the fish oil diet did not provide adequate linoleic acid for growth of the host and tumor

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Fritsche and Johnston, 1990 (Ref. 25)	Whether n-3 fatty acid would affect transplanted mammary tumor growth and metastasis	Female, weanling, BALB/C mice, 10 to 15 per group	3 weeks prior to and 45 days to 13 weeks after the transplant	Corn oil 10 weight % Fish oil (menhaden oil and corn oil) at 10 weight % Linseed oil 10 weight % Corn oil 2% n-3 Fatty acid 53% n-6 Fatty acid Fish oil 24% n-3 Fatty acid 14% n-6 Fatty acid Linseed oil 56% n-3 Fatty Acid 18% n-6 Fatty Acid	BALB/cfc 3H mouse mammary tumor cell lines 410 and 410.4 (derived from spontaneously arising mammary adenocarcinoma) transplanted subcutaneously into the inguinal area of each mouse	Transplanted mammary tumor cells at inguinal area Different fat types did not significantly affect incidence of tumor; linseed oil, but not fish oil, significantly reduced the yield of tumor (weight) compared to corn oil Linseed and fish oil significantly reduced prostaglandin-E synthesis; fish oil reduced 410.4 tumor prostaglandin-E synthesis more than linseed oil, yet tumor growth was significantly inhibited only by linseed oil	The effects of n-3 fatty acid rich fish oil and linseed oil on transplanted mammary tumor growth were not consistent; however, fish oil and linseed oil might not have provided adequate linoleic acid for optimal tumor growth

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Adams et al., 1990 (Ref. 12)	The effect of fish oil on metastasis of transplanted mammary and lung tumor	Female, weanling, Fischer 344 rats, 15 per gr	8 weeks before and 3 to 5 weeks after tumor transplant	Low fat: 5% corn oil High fat: 23.5% corn oil 8% corn oil and 15.5% fish oil 3% corn oil and 20.5% fish oil Fish Oil=Max EPA	13,762 MF mammary adenocarcinoma sublime (spontaneous model) was injected into thigh: 13,762 MAT:B ascites tumor cell sublime (experimental model) was injected into tail vein and grown in lung	Transplanted mammary and lung tumor 13,762 MF mammary tumor Levels or types of fat did not significantly affect incidence or growth 13,762 MAT:B lung tumor Low fat significantly inhibited the growth of the metastatic foci compared to high fat, high corn oil group 15.5% fish oil, but not 20.5% fish oil, significantly inhibited the growth of metastatic fish oil compared to high corn oil 20.5% fish oil significantly inhibit the growth of the metastatic foci compared to high corn oil, in one experiment, but not in another	The effects of corn oil level or fish oil level on metastasis of transplanted mammary or lung tumor were not consistent Diets might have provided adequate linoleic acid for growth of tumor; however, the fish oil level used were unrealistically high

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Sakaguchi et al., 1990 (Ref. 26)	The effect of n-3 fatty acid on human colon cancer cell lines inoculated into nude mice	6 to 8-week-old, BALB/c nude mice, 12 to 13 per group	4 weeks	Control: Low fat: 4.6 weight % lipids (chow diet) High saturated fatty acid (SFA): High fat: 19.2 weight % coconut oil and 0.8 weight % lipids High n-3 fatty acid: 19.2 weight % Max EPA and 0.8 weight % lipids % of n-6 Fatty acid Control 12.7 High SFA 4.0 High n-3 fatty acid 2.5	Human colon cancer cell lines, COLO-320 or HT-29 were injected subcutaneously into dorsum of the chest wall	Transplanted colon tumor: Fish oil significantly reduced (~50% reduction) volume and weight of tumor compared to the control and high SFA groups; there was no difference in tumorigenesis between the control and high SFA groups	High level of fish oil in the diet significantly suppressed the development of transplanted human colon cancer cells in mice; however, the test diets used might not have provided adequate linoleic acid for growth of tumor and the level of fish oil was unrealistically high Isocaloric diets were used and there was no differences in body weight changes among groups

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Deschner et al., 1990 (Ref. 15)	Combination of Max EPA with various levels of corn oil on colon tumor	Female, 5-week-old, CFI mice, 10 per group	2 weeks before and 48 weeks after azoxy-methanol treatment	16% corn oil and 4.4% Max EPA 10.2% corn oil and 10.2% Max EPA 4.4% corn oil and 16% Max EPA 20.4% corn oil 4.4% corn oil 4.4% corn oil was fed ad lib; the remaining diets were provided in controlled amounts as 40 g per cage per 2 days or 50 g per cage per 3 days to maintain body weights and reduce wastage	Azoxy-methanol	Colon: 4.4% fish oil diet group showed significantly higher incidence compared to 10.2% fish oil, 16% fish oil and 4.4% corn oil diet; there was no difference in incidence among 10.2% fish oil, 16% fish oil, and 4.4% corn oil groups 10.2% fish oil diet significantly reduced tumorigenesis compared to 4.4% fish oil diet (incidence: 30% versus 87.5%, # tumor per tumor bearing mouse: 1.3 versus 2.9) 16% fish oil diet did not affect incidence but significantly elevated tumor yield compared to 10.2% fish oil diet Compared to high corn oil diet, low corn oil diet significantly reduced the incidence (40% versus 63.3%): Effect of fat level on tumor yield was not significant	Biphasic response has been observed; 4.4% fish oil elevated, 10.2% fish oil suppressed, and 16% fish oil again elevated the tumorigenesis Corn oil level did not consistently affect the tumorigenesis Antioxidants were used

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Reddy et al., 1991 (Ref. 16)	The effect of n-3 rich fish oil and n-6 rich corn oil fed either during the initiation or/and during the postinitiation period on colon carcinogenesis	Male, 5-week-old, F344 rats, 39 per group	2 weeks before and 42 weeks after the treatment	Low corn oil: 5% corn oil High corn oil: 23.5% corn oil High fish oil: 18.5% menhaden oil and 5% corn oil	Azoxymethane	Colon: High corn oil diet, fed during the postinitiation period but not during the initiation period, significantly increased azoxymethane-induced tumorigenesis (incidence and multiplicity of colon adenoma and adenocarcinoma) compared to low corn oil diet High fish oil fed either during the initiation or the postinitiation period, significantly reduced azoxymethane-induced incidence and multiplicity of colon adenoma and adenocarcinoma compared to high corn oil; there was no difference in tumorigenesis between low corn oil and high fish oil diet groups	Azoxymethane-induced colon tumorigenesis in rats were significantly enhanced by high fat (high corn oil) diet and significantly suppressed by high fish oil diet; however, the fish oil level, tested, was unrealistically high Caloric intakes were similar among groups and there was no difference in body weight gains; therefore, the effect of corn oil level (total fat) was independent of energy effect

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
O'Connor et al., 1989 (Ref. 27)	The effect of n-3 fatty acid:n-6 fatty acid ratio on the development of pancreatic preneoplastic lesions	Male, 14-day-old, Wistar rats, 15 per group	4 months	Corn oil varied from 0 to 20 weight % menhaden oil varied from 20 to 0 weight % n3:n6 = 0.01 to 7.0 total fat = 20 weight %	Azaserine	Pancreatic tumor: Increased ratio of n-3:n-6 in the diet resulted in significantly decreased atypical acinar cell nodules (AACN) in the number and volume Type Oil: #AACN per cm^3: % vol of pancreas 20% corn oil: 632: 6.01 20% menhaden oil: 318*: 2.37* *Significantly different from the corn oil group There was significant, but unstable, regression between increased n3:n6 ratio and decreased AACN diameter More than 15 weight % menhaden oil (less than 5 weight % corn oil) in the diet did not further suppress the AACN development High menhaden oil significantly decreased serum prostaglandin-thromboxaneB_2, prostaglandin-E_2 and 6-Keto-prostaglandin-$F_{1\alpha}$	Preneoplastic lesion, not tumor, was tested Because less than 5 weight % corn oil (more than 15 weight % menhaden oil) in the diet did not affect the tumorigenesis, 5 weight % of n-6 fatty acid rich corn oil may be required for optimal tumorigenesis The results suggest that high n-3 fatty acid in the diet may suppress the development of azaserine-induced preneoplastic lesion of the pancreas in rats Isocaloric diets were used, and there were no differences in body weight changes among groups

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Orengo et al., 1989 (Ref. 28)	The effect of menhaden oil on photocarcinogenesis in hairless mouse	4 to 5 1/2 month-old, 40 SKH-Hr-1 mice, 40 per group	2 weeks before and 20 weeks after ultraviolet radiation	Corn oil 0.75 weight % 4 weight % Menhaden oil 4 weight % 12 weight % total fat = 0.75 ~ 12 weight %	Ultraviolet radiation	Skin: 12% menhaden oil significantly prolonged latency period compared to 4% menhaden oil, 4% corn oil, or 0.75% corn oil 4% menhaden oil significantly prolonged latency period compared to 4% corn oil, but not 0.75% corn oil 12% menhaden oil significantly suppressed multiplicity compared to 4% corn oil, but not 4% menhaden oil or 0.75% corn oil 4% menhaden oil significantly suppressed multiplicity compared to 4% corn oil, but not 0.75% corn oil Latency (med. tumor time, week) / Multiplicity (# tumor per animal at 20 week) Corn oil 4% 19.6[a] 1.43[b] 0.75% 21.9[a] 0.47[c] Menhaden Oil 4% 25.2[a] 0.41[c] 12% 26.1[a] 0.23[c] Different letter as a superscription shows a statistically significant difference	n-3 fatty acid-rich fish oil in the diet significantly suppressed the development of ultraviolet radiation-induced skin tumorigenesis in mice; however, the test diets, except 4% corn oil, might not have provided adequate linoleic acid for growth of tumor and the host animal Total fat level was very low Iso caloric diets used

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Locniskar et al., 1990 (Ref. 29)	The effect of fish oil on skin tumorigenesis	Female, weanling SENCAR mice, 30 per group	4 weeks initiation period and 42 weeks promotion period	(wt%) Menhaden oil / Corn oil / Coconut Oil 0 / 1.5 / 8.5 [illegible] / [illegible] / 7.5 4 / 1.5 / 4.5 8.5 / 1.5 / 0 0 / 10 / 0 Total fat 10 weight %	Initiator: 7,12-dimethyl benz(a) anthracene (DMBA) Promoter: 12-O-tetradecanoyl phorbol-13-acetate (TP.	Skin: No differences in the incidence of papilloma or carcinoma, and in the multiplicity among groups	Fish oil was not protective in the DMBA- and TPA-initiated skin tumorigenesis in mice; however, test diets, except 10% corn oil, might not have provided adequate linoleic acid for tumor growth The total fat [illegible] was very low Caloric intake, food consumption, and body weight changes were similar among groups
Yam et al., 1990 (Ref. 30)	The effect of n-6 fatty acid:n-3 fatty acid ratio on transplanted tumors	Male, 26 to 30-weeks-old, C57BL/65 mice, 30 per group	12 to 16 days	Soybean oil 4 weight % Linseed oil 4 weight % Fish oil 4 weight %	Transplant of EL4-lymphoma cells (insulin producing cells) or thymoma cells (insulin-dependent cells) into right flank muscle	Transplanted lymphoma and thymoma cells In EL4 mice, linseed oil, but not fish oil, significantly suppressed the growth of tumor (weight) compared to the soybean oil group In thymoma mice, fish oil, but not linseed oil, significantly suppressed the growth of tumor compared to the soybean oil group	Test diets contained unrealistically low total fat and the findings cannot be extrapolated to normal human physiology Furthermore, linseed oil and fish oil diets might not have provided adequate linoleic acid for tumor growth

Table 1--continued

Reference (author, date)	Objective	Test animals	Duration of Study	Diet	Additional Treatment	Results	Assessment
Ling et al., 1991 (Ref. 31)	The effects of fish oil and medium-chain triglyceride in parenteral nutrition regimen on transplanted tumor	Male, Sprague-Dawley rats (age not reported), 90 to 100 g, 10 per group	11 days	Control: Intralipid containing 2.4 weight % lipids Test: 2.6 weight % fish oil with medium-chain triglyceride of 40% fish oil: 60% medium-chain triglyceride	Transplant of Yoshida Sarcoma cells by subcutaneous injection Intravenous tumor necrosis factor (TNF)	Transplanted Sarcoma cells The replacement of long-chain fatty acid with fish oil of medium-chain triglycerides in the TPN solution significantly inhibited tumor growth as volume, but not as w	Fish oil with medium-chain triglyceride TPN regimen did not provide adequate linoleic acid for growth of the host animal and tumor

Table 2

Dietary Lipids and Cancer: Human Studies 1988-April 1991

Reference (author, date)	Study design and Population	Objective	Method of Dietary Measure	Type of Cancer	Results	Assessment
Prentice et al., 1988 (Ref. 37)	Ecologic; 21 Countries; 45 to 69 year old women	To offer explanations for international variations in breast cancer rates	Food disappearance data rather than actual food intakes are used to estimate per capita consumption	Breast cancer	Breast cancer incidence was strongly correlated with national estimates of per capita intake of dietary fat, but not with other calorie sources (protein and carbohydrate). There was a weak correlation for total calories ($p = 0.09$). Total calories alone explained only 14% of the variation in breast cancer incidence compared with 58% for fat calories alone. When fat and other sources of calories are entered simultaneously into regression analysis, fat calories remained highly significant ($p = 0.0004$) with unchanged regression coefficient. Nonfat calories were not significant ($p = 0.88$).	Ecological studies all suffer from exclusion failure. Comprehensive controlling of confounding factors is not possible. In this study, adjustment for other dietary factors + total calories was done by regression. Because food disappearance data was used, more affluent countries would incorrectly show higher consumption, reflective of higher waste.

Table 7--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Hursting et al., 1990 (Ref. 38)	Ecologic: Registry data in 20 countries for 35 to 64 year olds	To test the hypothesis that different kinds of fatty acids have different tumor-promoting capabilities	Per capita dietary intakes were obtained form food balance sheets for 1975 to 1977 and assessed by a multiple regression analysis	Breast, cervix, lung, colon, and prostate	The incidence of breast cancer was significantly associated with intakes of total fat (r=0.72), Saturated fat (r=0.57), n-6 polyunsaturated fat (n=0.5), but not with monounsaturated fat or n-3 polyunsaturated fat The incidence of female colon cancer was significantly associated with intakes of total fat (r=0.62) and saturated fat (r=0.47), but not with polyunsaturated fat, monounsaturated fat, n-6 polyunsaturated fat, or n-3 polyunsaturated fat The incidence of prostate cancer was significantly associated with intakes of total fat (r=0.69), saturated fat (r=0.55), and polyunsaturated fat r=0.46), but not with n-3 polyunsaturated fat; n-6 polyunsaturated fat intake showed a borderline association (r=0.46, p=0.074) The incidence of both cervical and lung cancer was not significantly associated with any type of fat intake or total fat intake Total calorie intake was not associated with cancer at any site when controlled for total fat intake	Dietary assessment: Dietary fat consumption disappearance increases with social and economic development and may simply be a marker for affluence, which would affect the incidence figures for cancers, such as improved cancer detection N-3 polyunsaturated fat intake among the populations was relatively small and invariable Confounding: All regression analyses were adjusted for age and intakes of all other component fats as well as for total calories As is the case with all ecologic studies, because populations, rather than individuals are measured, associations may be spurious Comprehensive controlling of confounding factors is not possible Correlations were reported only for female cancers and male prostate cancer; results reported to be similar for males were not shown

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Kneckt et al., 1990 (Ref. 39)	Prospective; 20 year followup; 3,988 initial cancer-free Finnish women aged 20 to 69 years From 30 different regions of Finland: 54 cases were identified	To examine the relationship between dietary fat and breast cancer	Examined role of total fat, saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), cholesterol intakes, and energy intake through dietary history	Breast Cancer	The overall relative risk (RR) for the association between relative fat intake and occurrence of breast cancer is: Overall RR 1.7 (0.6-4.8)* SFA intake 1.4 (0.5-3.7)* MUFA intake 2.7 (1.0-7.4)** PUFA intake 1.2 (0.6-2.8)* Cholesterol intake 2.2 (1.0-5.0)** * = Nonsignificant ** = borderline significant Breast cancer is inversely associated with energy intake, but not significantly related to fat intake	Method of dietary assessment: Dietary history was collected 20 years prior up to diagnosis, so recall bias is eliminated However, changes in diet over the 20 year followup interval were not evaluated Dietary confounders: Adjustment was made for total energy intake Confounders: Adjustments were made for age, body-mass index, stature, smoking, parity, menopausal status, and rural versus urban geography

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Howe et al., 1991 (Ref. 40)	Prospective study; 5 year followup period (1982-1987); 56,837 women, 40 to 59 years enrolled in the Canadian National Breast Screening study; 519 breast cancer cases were identified during the followup	To examine the relationship between energy sources and breast cancer risk	The self-administered diet-history questionnaire on 86 food items; and an interview-administered dietary history; subjects had completed the dietary questionnaire before diagnosis	Breast cancer	Except for the lowest quartile, there was a significant association between increasing fat intake and the incidence of breast cancer (RR for the highest quartile=1.3 : 95% HIGHEST =1.00-1.82) All three fat types (SFA, MUFA, and PUFA) showed a general pattern of increasing risk of breast cancer with increasing intake The exceptions were the first quartiles for SFA and MUFA (The mean % of calories from fat was 31% and 47% for the lowest and highest quartiles, respectively) Menopausal status did not affect the results	Dietary measure: Comparison of the results from the interview-administrated dietary history and the self-administered dietary history showed good validity and reliability Subjects had completed the dietary questionnaire before diagnosis, eliminating recall bias Confounders in diet: The association between fat intake and risk was assessed after adjusting for other sources of calories Total calorie intake was not associated with increased risk Adjusted for education, age at menarche, age at first pregnancy, nuliparity, surgical menopause, age at menopause, history of benign breast disease, and breast cancer in first degree relatives

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Mills et al., 1988 (Ref. 41)	Nested case-control; 142 fatal breast cancer and 852 age-matched controls among CA Seventh-day Adventist women from 1960 to 1980; 30 to 85 years; whites	To test the hypothesis that breast cancer mortality is related to the usual frequency of use of specific foods of animal origin, including meat, cheese, milk and eggs	A 21-item food frequency questionnaire	Breast	No significant relationship between the consumption of animal products (meat, milk, cheese, eggs) and breast cancer risk Among women with relatively early age at menopause (≤ 48 years), a suggestive but nonsignificant, positive association between meat consumption and the risk of breast cancer was noted	Although there was significant variation in the frequency of meat consumption between cases and controls, both groups were low meat consumers by American standards: 47% of the total population never or only occasionally consumed meat Dietary measure: The 21-item food frequency questionnaire was not sufficiently detailed to allow analysis of specific nutrients; therefore, the consumption of fat specifically was not tested for its relationship with the risk of breast cancer

Table 2--continued

Reference (author date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Rohan et al., 1988 (Ref. 42)	Case-control: 451 female Australian case-control pairs; 20 to 74 years old; Cases were with first diagnosis with breast cancer 1982 to 1984 Controls were without a history of breast cancer; randomly selected from the electoral roll; age matched with the case 113 premenopausal pairs and 262 postmenopausal pairs The remainders were either premenopausal or discordant on menopausal status	To test the hypothesis that the risk of breast cancer increases with increasing intake of total fat, protein, and energy; and decreases with increasing intake of vitamin A	A 179 food item, self-administered food frequency questionnaire; cases were instructed to disregard any dietary changes that had occurred subsequent to their diagnosis of breast cancer	Breast	No significant association between dietary intake of fat, energy, protein, or carbohydrate and breast cancer risk	Dietary measure: Instructing the cases to disregard dietary changes subsequent to their diagnosis of breast cancer may have helped eliminate some of the recall bias The range of total fat intake among the total population was 35% versus 46% in the lowest versus highest quintile of fat intake Dietary fat intake in this population may not be sufficiently heterogeneous to detect variation in disease risk Dietary confounders: The difference in fat intakes between the cases and the controls was not reported Energy intake was not adjusted in the risk analysis for lipid intake

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Gerber et al., 1989 (Ref. 43)	Case-control: Hospital-based population of French women 25 to 65 years; Cases: 120 with a first diagnosis of breast cancer Controls: 109 with admission for neurologic syndromes of other than cardiovascular or tumoral origin, or for lumbalgias or disc pathologies	To address the question of the specific role of fatty acids in relation to breast cancer	Nutritional data from a questionnaire on the dietary history: Weekly or monthly frequency of consumption for 55 key food items in lipid and vitamin consumption	Breast	Pre-menopausal and postmenopausal groups considered separately Intakes of total lipids, SFA, MUFA, PUFA, and olive oil were greater in cases than in controls (borderline-significance: p=0.07) Intakes of sunflower oil was greater in cases Fatty acid serum distribution is comparable in both samples, except arachidonic acid, which is significantly lower in premenopausal patients than in premenopausal controls Plasma lipid peroxidation is significantly lower in patients than controls	Major confounding factor: The association between calcium and decreased peroxidation can be fortuitous or reflect the decreased rate of lipid peroxidation association with an increased rate of cell division The authors admit that the fat intake result is controversial and have undertaken a larger case-control study

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Toniolo et al., 1989 (Ref. 46)	Case-control: Cases: 250 women with breast cancer, but no metastases; Controls: 499 women from a randomized, stratified sample of the general population All < 75 year old and from the Vercelli province in Italy	To investigate the role of diet in breast cancer	An interviewer-administered dietary history questionnaire	Breast	Cases consumed more calories (2,419 vs 2,294 kcal per day) and total fat (94.4 vs 88.2 g per day) compared to the control Age and calorie-adjusted relative risk showed a significant association for SFA intake (p=0.001) and total fat intake (p=0.056) The intake of dairy products was significantly associated with the risk of breast cancer Neither meat consumption nor poultry consumption significantly increased the risk	Well-done study; Dietary assessment: Questionnaire had been tested previously, validated, and used in a study with, which produced comparable results Variation of fat intake in diet is 26% to 46% in this study, as opposed to only 32 to 44% in Willet's Confounding for nondietary risk factors: Adjusted for age at menarche, age at menopause, age at first birth, height, weight, Quetelet index (weight divided by height squared), socioeconomic status, and martial status
Ewertz and Gill et al., 1990 (Ref. 47)	Case-control: 1,486, breast cancer cases diagnosed over a 1 year period in Denmark; <70 year 1,336 age-stratified random sample from the general population as the control	To elucidate the influence of dietary factors and hormones on breast-cancer risk	Self-administered questionnaire, given 1 year after the diagnosis: the semi-quantitative food-frequency questionnaire collected food intake data for the year prior to diagnosis for 21 food items	Breast	Total fatty acid intake was significantly and linearly associated with breast cancer risk (RR for the highest quartile=1.45; p<0.001 for the test of a trend)	Dietary measure: The 21 food item included in the questionnaire covers about 80% of fat consumption The questionnaire was designed with two global questions to monitor the frequency of consumption of meat and vegetables The sum of the frequencies of consumption was compared with the global frequency and weights were assigned to adjust overestimations Confounders: Effect of energy intake was not controlled

Table 2--continued

Reference (autho date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Mettlin et al., 1990 (Ref. 48)	Case-control Cases: 3 334 men and women (5C of each); ages 19 to 9/ years Controls: 1,300 mer and women, hospital-based	To test the hypothesized positive association between fat and cancer, and hypothesized inverse association between cancer and vitamin A, D, riboflavin, and calcium	Dietary questionnaire for milk-drinking habits	oral, stomach, colon, rectum, lung, Breast, uterus, cervix, prostate, bladder	Controls were more likely to never drink whole milk than cases, after adjusting for sex, age, smoking, education and county of residence Findings were significant only when comparing whole milk to no milk (reference group) and for the oral cavity, stomach, colon, rectum, lung, bladder, prostate and breast	This study is of little value because it does not address the correlation of milk intake with dietary fat intake Many other factors which may be associated with milk drinking habits were not controlled Biases inherent in hospital based sample
Boyd et al., 1988 (Ref. 54)	Randomized clinical trial; 295 women with ≥ 50% of the breast volume occupied by mammographic dysplasia; ≥ 30 year (mean age 44), (147 control and 48 intervention): 5% of the control group and 20% of the treatment group lost during followup; 76% of subjects premenopausal	To determine (1) if long-term compliance with a low fat diet can be achieved and (2) if mammographic dysplasia increases one's risk of breast cancer	Dietary advice: Control group to maintain healthy diet without changing dietary fat intake Intervention group to reduce fat intake to 15% of the calories A 3-day food record and a 1-day dietary recall	Breast cancer	(1) Combined control and intervention groups experience higher cancer than expected in the general population (2) Dietary compliance was maintained over the 1-year intervention period	This study is important as an precursor for future intervention trials; it tells us that compliance is possible for at least 1 year, and it supports the hypothesis that mammographic dysplasia is a high risk factor in breast cancer development However, the time is too short and the numbers too small to draw any conclusions about dietary fat and the incidence of breast cancer

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Verreault et al., 1988 (Ref. 55)	Survey of 666 women with a newly diagnosed infiltrating breast carcinoma 1982 to 1984; Quebec City area, Canada	To study the possible effect of diet on the progression of breast cancer, once it has occurred	An interviewer administered food frequency questionnaire covering 114 food items for the year preceding diagnosis	Breast	After the adjustment for energy intake, total fatty acid intake showed no association with the frequency of nodal development after diagnosis After adjusting for energy intake, age, body weight, and tumor size, the intake of SFA was not significantly associated with the frequency of axillary node development at diagnosis among post-menopausal patients PUFA intake was negatively and significantly associated with nodal development	Dietary measures: The type of PUFA is not identified The study assessed a growth of nodes (proxy for progression of the disease), but not directly the risk of cancer
Boyd et al., 1989 (Ref. 56)	Case-control; 30 women with extensive mammographic dysplasia (≥ 75% of the breast involved) and 16 women without dysplasia (≤ 25% dysplasia); 30 to 50 years; Breast center at Women's College Hospital and National Breast Screening Center at the Mt. Sinai Hospital	To determine biochemical associations with mammographic dysplasia	A 7-day recall plus a 4-day food record	Breast	No significant difference in consumption of total fat, different types of fat, cholesterol, total calories, carbohydrate, or protein for those with and without dysplasia	Dietary concerns: There may be an insufficient difference in nutrient intake between the two groups to detect an effect Confounders: Because the study's objective was to determine plasma lipid levels, dietary fat was examined as a confounder for lipid plasma levels - the study did not examine for confounders of dietary fat intake

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary Measure	Type of cancer	Results	Assessment
Eid and Berry et al., 1988 (Ref. 52)	Case-control; 85 Israeli women (ages not given) who were undergoing biopsies for breast masses 37 had carcinoma, 27 had fibroadenoma, 21 had other types of masses	To study the effects of the quality of fat (i.e., saturated versus polyunsaturated) and carcinogenesis	Dietary measures not necessary; fatty acid composition measured directly through biopsy Breast tissue from each individual was analyzed for fatty acid composition (16 also had adipose tissue biopsied from buttocks to compare breast tissue fat as an indicator for overall subcutaneous body fat: 98% correlation)	Breast	The quality of dietary fat does not appear to be associated with the development of neoplasia of the breast: PUFA:SFA Ratio: Fibroadenoma 0.99; Other Cancer 0.98; 1.03 The PUFA:SFA ratio was no different between the group with cancer, fibroadenoma, or other tumors	Age is a possible confounder However, an analysis of 400 biopsies revealed insignificant correlation between age and polyunsaturated to saturated ratio All subjects are patients with breast lesions Data was reported only as a ratio for tissue fatty acids; the actual amount is important as well
Brisson et al., 1989 (Ref. 57)	Case-control; 290 newly diagnosed breast cancer patients and 645 women who participated in the Canadian National Breast Screening Study as the control; 40 to 62 year; in Quebec	To evaluate the association of the morphology of breast tissue seen on mammograms with breast cancer risk and to assess the relation of diet, especially intake of fat and vitamin A, to the high-risk mammographic images	An interviewer-administered food frequency questionnaire of intake of 114 food items during the previous year	Breast Cancer	Among controls, energy adjusted intakes of saturated fat, but not polyunsaturated fat or cholesterol was significantly associated with an increase in extent of high-risk mammographic features The risk of breast cancer incidence increases regularly with the extent of nodular and homogeneous densities on the mammogram	Dietary measure: acceptable; suffers recall bias Confounding: adjusted for age, weight, parity, and education Fiber intake was measured and considered separately in analysis

Table 7--Continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary Measure	Type of Cancer	Results	Assessment
Pryor et al., 1987 (Ref. 45)	Case-Control; White females between the ages of 20 and 54; 172 cases are women who were diagnosed with histologically confirmed first primary breast cancer 190 matched controls	To assess how intake of dietary fat and fiber during adolescent years is related to the incidence of breast cancer	Used National Cancer Institute food frequency questionnaire to assess past intake during adolescent years	Breast Cancer	Stratified on groups High fat intake consistently lowered the odds ratio (OR) below 1.0 in premenopausal women, but not significantly (OR = 0.7, confidence interval (CI) = 0.3-2.1 for highest versus lowest quartile) The relationship was inconsistent and not significant in postmenopausal women (OR = 0.7, CI = 0.2-2.7 for highest versus lowest quartile) The relation of breast cancer to dietary intake during adolescence is not clear	Dietary measure: very long recall period, producing bias Controlling: Done for age, education, age at first pregnancy through multiple logistic regression Fiber intake adjusted in analysis Fat from dairy products considered separately from other sources

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Hoim et al., 1989 (Ref. 53)	Case-control; 240 women 50 to 65 years who had surgery for breast cancer (1983-1986); mainly post- menopausal	To examine the relationship between dietary habits and prognostic factors for breast cancer	A dietary history interview within 4 months after resection of the primary tumor for prediagnostic food consumption	Breast cancer	Patients with tumors ≥ 20 millimeter (mm) in diameter had significantly higher mean percent energy from total fat and monounsaturated fat, and significantly lower mean energy from carbohydrates compared to patients with tumors < 20 mm; there was no significant difference in the total energy intake mm Tumor size < 20 ≥ 20 p Total energy, energy % 36.3 38.1 0.02 Monounsaturated fatty acid energy % 12.4 13.2 0.003 Carbohydrate energy % 46.3 44.6 0.06 Total energy in millijoules 8.2 7.8 Nonsignificant	Poor study due to lead-time bias: Timing not corrected for the women who have surgery earlier (more routine care, self-exam, better diets, etc.) Adjustment was made for fiber, carbohydrates, and total energy

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary Measure	Type of Cancer	Results	Assessment
Iscovich et al., 1989 (Ref. 46)	Case-control; 150 women with breast cancer, diagnosed 1984 to 1985, 0 to 75 year mean 56 year; controls: for each case, one hospital control, matched by age and hospital, and one neighborhood control, matched by residential area and age	To uncover associations between diet and breast cancer	An interviewer-administered semiquantitative food frequency questionnaire on 147 food items during the 5 year period up to 6 months prior to interview	Breast cancer	Intake of energy total fat, protein, and carbohydrates were significantly associated with the risk of breast cancer Intakes of processed meat, fried meat, animal fat, eggs, grains, and pulses were significantly associated with the risk of breast cancer Intakes of fruit and vegetables were negatively associated Intakes of red meat, poultry, and vegetable oil were not significantly associated	Confounders: Adjustment for [illegible], age, age at [illegible] pregnancy, and parity Adjustment for total calorie intake was [illegible] done No significant difference was found between the effects of fat, protein, and carbohydrate
Boyd and McGuire 1990 (Ref. 58)	Case-control; 30 women with extensive mammographic densities (≥ 75% dysplasia) and 16 controls without radiological changes (<25% dysplasia); 30 to 50 years	To determine if mutagenic products generated by lipid peroxidation may influence breast cancer rate	4 day food record	Breast cancer	The group with extensive mammographic dysplasia excreted twice the amount of malonaldehyde int the urine compared to the control group ($p<0.02$) The quantity of malonaldehyde in the urine is an indicator of lipid peroxidation in diet or tissue No difference in nutrient intakes including total fat between the two groups	Because the main objective of this study was to examine malonaldehyde, [illegible] the selected variables considered for confounding Confounding for fat was not considered

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Simard et al., 1990 (Ref. 49)	Case-control: 68 women with breast cancer age-matched and 343 women as the control; 40 to 49 year; in Montreal	To compare fibrocystic patients with age-matched controls selected within the same cohort population of women attending the Canadian National Breast Screening Study (NBSS)	A semiquantitative food-frequency questionnaire for the breast cancer patients A 24 hour dietary recall for the control subjects	Breast	The breast cancer patients consumed significantly more poultry, fish, pastry, and margarine; and, less milk and butter	Dietary Assessment: The method for collecting food consumption was different between the control and the cases The risk was assessed with current food consumption while it was noted that 16% of cancer patients had been on a reducing diet
Vaint Veer et al., 1990 (Ref. 50)	Case-control: 133 newly diagnosed breast cancer cases; 25 to 44 year (98% premenopausal) or 55 to 64 year (97% postmenopausal); 289 age-stratified healthy controls from general population; Netherlands	To design and carry out a study which examines the role of dietary fat in breast cancer, but overcomes problems of many other studies; specifically, methodological problems in dietary assessment and confounding by energy intake is corrected through the use of a standardized and reproducible dietary history technique	A 236 food item diet history interview was conducted to cover the dietary pattern in the 12-month period prior to diagnoses or the interview date	Breast	Age-adjusted dietary fat intake in breast cancer cases was significantly higher than that in healthy controls (120 vs 92 g) The age-adjusted OR showed a significant positive trend with increasing fat intake The multivariate adjusted OR was 3.5 for subjects in the highest quintile of fat intake compared to those in the lowest quintile The OR, adjusted for energy intake and age, was 1.54 per 24 g fat or 10% fat energy Intake of each type of fat (SFA, MUFA, PUFA) was positively associated with the risk as well	Dietary Measure: Reproducibility of the questionnaire was verified by a repeated measurement one year after in 39 control subjects Confounding by Nondietary factors: Adjustment was made for familial history, history of benign breast disease, education, employment, age at menarche, age at first full-term pregnancy, parity usage of oral contraceptives, smoking, body mass index, and alcohol intake

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Van't Veer et al., 1991 (Ref. 51)	Case-control: Newly diagnosed 133 women breast cancer cases and 289 population controls in the Netherlands; 25 to 44 and 55 to 64 year	To examine several combinations of dietary factors - total fat, fermented milk products and fiber on breast cancer occurrence because these dietary factors are hypothesized to alter estrogen metabolism by the intestinal microflora	A 236 food item, interviewer-administered diet history questionnaire; Dietary pattern in the 12-month period prior diagnosis	Breast	Dietary fat intake was positively associated with the risk of breast cancer after adjustment for age (OR=0.57; CI=0.36-0.90) When total fat is included as a main effect, fiber, fermented milk and total fat produce an interactive effect which is positively associated with the risk (OR=0.33; 0.15-0.73)	Dietary method: Most cases were interviewed within 6 months after diagnosis Energy intake was not adjusted Nondietary confounders considered: Age, alcohol intake, history of benign breast disease, familial history, smoking, educational level, oral contraceptive use, age at menarche, parity, body mass index and geographical area

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Willett et al., 1990 (Ref. 62)	Prospective; 88,751 registered nurses; 34 to 59 year; no history of cancer, inflammatory bowel disease, or familial polyposis; 150 colon cancer cases were documented during the 6-year followup (1980-86)	This is part of the Nurses' Health Study Cohort Its objective is to determine risk factors for cancer and coronary heart disease	A 61 food-item, interviewer-administered, semi-quantitative food frequency questionnaire focusing on fat and fiber foods was used The dietary interview was done in 1980	Colon	Total energy intake or body-mass index was not associated with the incidence of colon cancer Age and energy-adjusted intakes of total fat, animal fat, SFA, and MUFA were significantly associated with the incidence of colon cancer; intakes of vegetable fat, linoleic acid, and cholesterol were not RR C.I. Total fat 2.0 1.1-3.6 Animal fat 1.9 1.1-3.2 SFA 1.4 0.8-2.3 MUFA 1.7 1.0-2.9 Strongest associations with beef, pork, or lamb eaten as a main dish; daily eaters had 2 1/2 times the risk of those less than once a month eaters (P for trend = 0.01) Consumption of whole milk, cheese, and ice cream was not significantly related to the risk	Dietary assessment: The dietary method was validated by comparing its results with results of one-week weighed food record method in a random cohort Since the interview was done in 1980, prior to disease development, there is no recall bias Controlling dietary factors: Controlling for physical activity did not alter the association of the intake of animal fat or meat with the risk Energy adjustment was done

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
La Vecchia et al., 1988 (Ref. 66)	Case-control: 339 cases of colon cancer and 236 cases of rectal cancer; both sexes; 1985 to 1987; median ages, colon cancer = 61 year, rectal cancer = 62 year; northern Italy 776 controls; both sexes; median age = 58 years The controls were also patients admitted to hospital for acute, nonneoplastic or digestive disorders	To examine the relationship between diet and colorectal cancer in a population in which there is good heterogeneity in dietary consumption	A 29 food item interviewer-administered food frequency questionnaire on food consumption prior to diagnosis	Colon and rectal	Age and sex adjusted consumptions of beef or veal and pasta or rice were significantly associated with the risk of colon and rectal cancer Age and sex adjusted consumption of butter and olive oil, but not margarine, was significantly associated with the risk of colon cancer but not the risk of rectal cancer	Dietary method: Energy consumption was not adjusted in the data analysis Frequencies, but not quantities of food consumption were analyzed Confounding of nondietary factors: Adjustment was made through multiple logistic regression for age, sex, social class, and area of residence
Neoptolemos et al., 1988 (Ref. 59)	Case-control: Cases: 30 men and 19 women, between the ages of 49 and 92, with colorectal cancer Controls matched for age and sex	To assess the erythrocytic fatty acid profile in a relatively homogenous group of patients with cancer of the colon and rectum, using closely- matched controls	Fatty acids were determined in erythrocytes and adipose tissue An interviewer-administered 7-day dietary recall during hospitalization on the day before surgery	Colorectal	Marginally increased levels of stearic acid ($p<0.06$) and oleic acid ($p<0.06$) and decreased arachidonic acid ($p<0.04$) in cancer patients Marginally increased levels of stearic acid ($p=0.06$) and oleic acid ($p=0.06$) and decreased arachidonic acid ($p=0.04$ occurred in cancer patients These findings indicate a disturbed fat metabolism in cancer patients	The study did not address the association of diet intake and the risk of cancer

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
West et al., 1989 (Ref. 61)	Case-control: 231 colon cancer patients and 391 population controls Both sexes; 40 to 79 year; whites; 1979 to 1983 in Utah	To evaluate the role of fiber and fat ingestion on colon cancer development, as well as to study the associations between intake of energy, types of fat, protein, vitamins A and C, and cruciferous vegetables and the disease	A 99 food item interviewer-administered, food frequency questionnaire for 2 to 3 years prior to the interview; over 90% of foods eaten by Utah residents	Colon	Both in females and in males, total fat intake was significantly associated with the risk (OR=1.9 in females and 2.0 in males. in the highest quartile) Intakes of different types of fats (MUFA, SFA, PUFA) were not consistently associated with the risk	Dietary analysis: recall bias; omitted data due to physician's refusal (23 of 324 cases), patient's refusal (70 of 324), death before the interview (53 of 324) Dietary confounders: Adjustment of data by multiple logistic regression for fiber and body mass index; energy intake was not controlled in the data analysis
Benito et al., 1990 (Ref. 67)	Case-control: 286 colorectal cancer cases, 295 population controls, and 203 hospital controls; Majorcan residence; mean age and was 64 year both sexes	To investigate the role of dietary factors in the etiology of colon and rectum cancer	A 99 food item interviewer-administered food frequency questionnaire for average consumption for the previous year	Colorectal	A significantly increased risk of colon cancer was found for consumption of fresh meats (RR=2.87) while consumption of cruciferous vegetables afforded protection (RR=0.48) Consumption of dairy products significantly increased the risk of rectal cancer but not the risk of colon cancer Consumption of oil was not associated with the risk of colon or rectal cancer	Dietary survey: The average interval between diagnosis and interview was relatively short, 3 months Adequacy of controls: The results were reported by comparisons with the population controls only Adjustment of confounders: Age and sex, but not energy intake were adjusted in the data analysis

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Ghadirian et al., 1991 (Ref. 63)	Case-control: 179 pancreatic cancer patients in Greater Montreal from 1984 to 1988; 35 to 79 year; both sexes 239 population-based, age, sex, and place of residence matched controls	This study was a subset of the SEARCH collaborative Study Group for the case-control study of cancers of the pancreas, bile ducts and gallbladder of the International Agency for Research on Cancer	A more than 200 food-item and beverage, interviewer-administered food frequency questionnaire was used	Pancreatic	After adjustment for age, sex, energy intake, response status, and cigarette consumption, total fat intake (OR=2.24) and SFA intake (OR=4.32) were significantly associated with the risk of pancreatic cancer	Dietary intake measurement: 25% of the cases and 83% of the control were interviewed directly; 75% of the cases and 17% of the control were interviewed by proxy Confounders: Adjustments made for age, sex, energy intake, response status, and cigarette consumption
Goodman et al., 1988 (Ref. 64)	Case-control: 226 men and 100 women with lung cancer; 597 men and 268 women population-based controls, sex and age matched to the cases; five ethnic groups in Hawaii; 30 to 84 years	The specific objective of this study was to test the effects of dietary fat and cholesterol on lung cancer	An interviewer-administered diet history questionnaire on food consumption for a usual month prior to diagnosis; the food items would provide ≥ 85% of the intakes of cholesterol and fat	Lung	Intakes of total fat SFA and MUFA were significantly higher in the cases compared to the controls in men, but not in women; in women, only the same tendencies were found (nonsignificant) Cholesterol intake was significantly associated with the risk in smoking men (OR=2.2), but not in women or past smokers; the association was consistent for three of four ethnic groups analyzed separately	Dietary measurement: Among cases, 28% of men and 32% of women were interviewed by proxy Among controls, 6% of men and 7% of women were interviewed by proxy Dietary confounders: Fat intake was not adjusted in the assessment of cholesterol and the risk association; cholesterol was not adjusted in the assessment of fat intake and the risk association Adjustment for other confounders: Adjustments for age, ethnicity and cigarette smoking

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Franceschi et al., 1989 (Ref. 68)	Case-control: 208 nonHodgkins lymphoma cases and 401 control subjects who were in the hospital for acute, nonimmunologic or neoplastic conditions; men and women; 18 to 80 year; northeastern part of Italy	The role of various lifestyle factors, including dietary habits, was investigated in the etiology of nonHodgkins lymphoma	Food frequency questionnaire including 14 food items or groups of foods and 7 beverages	Lymphoma: NonHodgkins lymphoma is a heterogeneous group of disorders resulting from malignant transformation of lymphoid cells	The consumption of butter and oil was positively related with NonHodgkin's lymphoma risk The consumption of milk also was positively related with the risk The consumption of meat or fish was not related with the risk	Dietary survey: The questionnaire method was verified by a repeated telephone survey on a subpopulation Selection of controls: The controls were also hospitalized patients Confounders: The data was presented after adjustment for age and sex, but not for total fat or energy intakes
Steineck et al., 1990 (Ref. 65)	Case-control: 323 urothelial cancer cases in Stockholm, Sweden during 1985 to 1987 and 392 population-based controls selected by gender and age stratified random sampling	To investigate the association between urothelial cancer and dietary factors, with special reference to vitamin supplements, dietary vitamins, and fried foods	A 56 food item food frequency questionnaire; recall dietary habits 3 years prior to interview	Urothelial	A dose-response relationship was seen with an increasing intake of fat (RR=1.7 in the highest quintile) and the risk Adjustment for fried foods, in addition to gender, age, and smoking decreased the relative risk (RR=1.3 in the highest quintile) No association was noted for meat other than fried meat	Dietary measure: long recall period, inadequacy of the questionnaire to analyze fat intake Dietary confounders: failure to adjust energy intakes Other confounders: Adjustment made for gender, age and smoking

Table 2--continued

Reference (Author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Franceschi et al., 1991 (Ref. 69)	Case-control: 302 oral cavity and pharynx cancer cases and 899 controls admitted to hospital for acute, nonneoplastic, and non-digestive disorders; in Pordenone province, northeast Italy	To examine the relationship between dietary indicators and the risk of cancer of the oral cavity and pharynx	A 40 food item food frequency questionnaire	Oral cavity, pharynx	Intakes of beef, poultry, fish were not associated with the risk	Control group selection: The controls were hospitalized patients Method of Dietary Measure: Food items questioned were limited and hardly allowed any inference concerning total energy and micro nutrient intake Dietary confounders: Total calorie intake was not adjusted for data analysis Other confounders: Adjustment made for age and sex, occupation, smoking, drinking
Howe, 1990 (Ref. 73)	Meta-Analysis of 12 Case Control Studies	To evaluate the consistency of 12 studies of diet and breast cancer	varied	breast	Consistent, statistically significantly positive association between breast cancer risk and saturated fat intake in post menopausal women (RR = 1.5 p = .0001)	Not controlled for: total caloric intake. Problem of multiple comparisons
Buiatti 1990 (Ref. 74)	case-control study in Italy: 1016 cases 1159 population-based controls	To evaluate dietary factors and their contribution to gastric cancer mortality	Dietary questionnaire: frequency of intake and portion size in 12 month period 2 years before interview (146 food items)	stomach	Decreased cancer risk with increased vegetable fat (statistically significant) No association with animal fat	Did not adjust for total calories
Baghurst, 1991 (Ref. 75)	Case-control 104 cases, 253 population-based controls	Assess relationship of diet to pancreatic cancer	Quantitative food frequency questionnaire 179 food items (usual intake)	pancreas	Increased risk with increased cholesterol intake (significant); increased risk with decreased PUFA (significant) Others not significant when controlled for total energy	Controlled for total energy Difficult to interpret results

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Demirer, 1990 (Ref. 76)	Case-control (Turkey) 100 cases 100 control population-based and hospital (39+61)	Assesses role of diet in stomach cancer	Dietary questionnaire assessed for past 15 years	stomach	Increased risk with decreased meat consumption (statistically significant)	Poorly controlled study Fat consumption is not measured directly
de Verdieu, 1990 (Ref. 77)	Case-control (Sweden) 720 cases (268 rectal, 452 colon) 624 controls population based	Assess association between colorectal cancer and intake of total energy, protein, fat, fiber and body mass	Quantitative food frequency questionnaire (55 food items) for previous 5 years	colorectal	The following are significant for trends only, not for individual levels: Increased risk with increased energy Increased risk with increased total fat (for both colon and rectal cancers) Also increased risk with increased saturated fat increased risk with increased monounsaturated fat increased risk with increased PUFAS rectum only	Adjusted for fiber intake only, not total energy. High non response rate among cases (21%)
Farrow and Davis, 1990 (Ref. 78)	Case-control (148 male cases, 188 population-based controls)	Assess relationship between diet and pancreatic cancer	Telephone interview and self administered food frequency questionnaire (135 food items assessed 3 years prior to diagnosis	pancreatic	Increased risk with increased protein only (statistically significant); no risk associated with total fat, saturated fat, cholesterol, or omega-3 fatty acids	Wives used as surrogates when necessary for cases and for controls Controlled for total caloric intake Adjusted for major risk factors of pancreatic cancer such as smoking Study is well done

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Jain, 1990 (Toronto) (Ref. 79)	Case control 839 cases 772 controls (pop-based)	Dietary factors and lung cancer risk	In-person interview diet consisted of 81 food items (usual intake)	lung	Borderline increased risk with highest cholesterol consumption level No association with fats	Dietary questionnaire focused on usual intake which could be influenced by disease, rather than 2-3 years previously Controlled for smoking but not total energy
Kato, 1990 (Japan) (Ref. 80)	Case-control 427 cases 3014 controls(all underwent gastroscopic examination)	Assess stomach cancer risk factors for purposes of prevention	Dietary questionnaire self administered; limited number of food items-usual intake	stomach	No association with meat consumption or "Western-style breakfast (actual fat intake not measured)	No adjustment for confounding factors (smoking, total energy) Fat consumption not assessed directly Controls underwent gastroscopic exam so potentially could be diseased (i.e. misclassification bias)
La Vecchia, 1990 (Italy) (Ref. 81)	Case-control (110 women cases and 843 hospital controls for acute conditions non-neoplastic, non-respiratory	Laryngeal cancer risk and dietary factors	In person questionnaire 10 indicator foods assessed prior to onset of symptoms	laryngeal	No relationship with indicators of dietary fat	Controlled for smoking and some other confounders but not total energy Limited dietary assessment
La Vecchia (1990) (Ref. 82)	Case-control 247 cases 1089 controls hospitalized for acute nonneoplastic or digestive conditions	Diet and pancreatic cancer	In-person questionnaire on 14 indicator foods assessed at least 1 year prior to onset of symptoms	pancreas	No relationship with indicators of dietary fat	Controlled for smoking and some other confounders but not total energy Limited dietary assessment

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Maclure, 1990 (Ref. 83)	Case-control 410 cases 605 controls (population based)	Assess dietary factors in risk of renal adeno-carcinoma	Questionnaire in person at home on average food consumption in early 1970's	Renal	Animal fat and saturated fat weakly associated with risk, with and without adjustment for energy Total energy not associated	Recall bias 20-year period for recall Well controlled Low participation rate (69% for cases and 59% for controls)
Mettlin, 1990 (Ref. 84)	Case-control (303 cases and 606 controls hospitalized for non-malignant diseases	Assess ovarian cancer risk in relationship to milk drinking (lactose)	Self-administered questionnaire with 66 food items assessed prior to onset of symptoms	ovarian	Total milk consumption not associated with increased risk Drinking whole milk regularly associated with increased risk compared with drinkers of skim and 2%	Can not use results of this study to assess risk of fat consumption Authors assume that whole milk is a major source of dietary fat among adults (but didn't assess cooking milk, etc)
Stemmermann, 1990 (Ref. 85)	Prospective 8006 Hawaii Japanese men ages 46-68 at the beginning of the study 22 years duration	To assess the impact of fat and calcium intake on the risk of developing cancer in each large-bowel subsite	24 hours diet recall interview	colon/rectal	Age-adjusted mean intake of fat in patients with colon cancer is lower than that of non-cases (P=.05) no difference between rectal cases and non-cases. No interaction between fat and calcium intake No difference in mean calcium intake between colon or rectal cancer cases versus non-cases	Not adjusted for total energy intake

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Slatery, 1990 (Ref. 86)	Case-control white males from Utah aged 45-74; 362 cases, 685 population-based controls	To evaluate prostate cancer risk associated with fat consumed during adolescent years	Food frequency questionnaire-compared reported results with national food consumption trends to assess the accuracy of the dietary instrument	prostate	Men who consumed a high fat dies as adults were at a slightly increased risk of developing aggressive prostate cancer after adjustment for adolescent diet (OR=1.8, P=.05) whereas men who consumed a high saturated fat diet as adolescents were not at increased risk of developing these tumors after controlling for adult diet.	Recall bias large factor Multiple confounders not adjusted for (only age and high saturated fat diet in adolescent) Total energy intake not adjusted Borderline significance
Zhang, 1990 (Ref. 87)	Case-control of Chinese women in Shanghai: 186 cases, 186 hospital controls, 186 neighborhood controls	To assess the relationship between diet and breast cancer	Diet Histories	Breast	Cases have a significantly greater daily caloric intake than controls. After adjusting for the total energy intake, increased consumption of total fat is significantly associated with breast cancer (RR is 1.7, p =.05) for the highest vs lowest quintile of fat intake.	Well-done analysis. Major confounders adjusted for. Both hospital and neighborhood control used.
Slattery, 1988 (Ref. 88)	Case-control - Cases: 119 females, 110 males Controls: 204 females, 180 males	To assess the relationships of physical activity and diet to the development of colon cancer in Utah.	quantitative food-frequency questionnaire	colon	Total fat intake shows borderline increase in the risk for colon cancer in males (OR = 2.1, P=.09) and females (OR = 2.0, P=.09) between highest and lowest range of intake. Adjusted for age, BMI and fiber intake	Total energy intake not adjusted for.

Table 2--continued

Reference (author, date)	Study Design and Population	Objective	Method of Dietary measure	Type of cancer	Results	Assessment
Hislop, 1990 (Ref. 89)	Case-control of Canadian women; Cases: 801 histologically confirmed benign breast disease Controls: 865 age-matched	to investigate the relation between diet and histologic types of benign breast disease	self-administered questionnaire consisting of usual frequency of consumption during the past year of 39 specific food items	breast	Severe atypias and borderline carcinoma in situ were directly associated with frequent meat fats consumption (result not statistically significant: OR = 3.2 ; 95% CI 0.75-13.21)	Small subgroups; findings not statistically significant
Morales Suarez-Varela, 1990 (Ref. 90)	cross-sectional	to evaluate the relation of Spanish diet to rectal cancer morbidity and mortality	consumption by province was determined from National Statistics Institute publications for total lipids, total animal fats, total vegetable fats (in g/person/day)	rectal and colon	a positive correlation between morbidity and mortality and total lipid consumption was found. All morbidity and mortality rate (males, females and total) showed correlation in excess of .4 (p<.001)	Total energy not adjusted Lifestyle confounders not adjusted (smoking, etc)

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