Breast Cancer: Weighing the Evidence for a Promoting Role of Dietary Fat

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It has been hypothesized that a high-fat diet promotes the development of postmenopausal breast cancer. This contention is supported by data showing high international correlations between fat intake and breast cancer rates, modest positive associations with a high-fat diet in case-control studies, and animal model studies that have consistently demonstrated that dietary fat influences mammary cancer development at several stages in the carcinogenic process. A number of plausible biologic mechanisms have been suggested that may explain such promotional effects. In contrast, dietary fat intake is unrelated to the risk of breast cancer in cohort studies. The conflicting findings from cohort studies have created uncertainty regarding nutritional recommendations and breast cancer prevention. After reviewing key scientific findings that are relevant to this issue, the following conclusion is drawn: In the absence of data from dietary intervention trials, the weight of available evidence suggests that the type and amount of fat in the diet is related to postmenopausal breast cancer and that the inability to detect associations within populations (cohort studies) is because of measurement error and the relative homogeneity of diets measured. It is expected that the results from intervention trials will clarify this issue. [J Natl Cancer Inst 1997;89:766-75]

Animal model studies and international correlations of fat and breast cancer incidence and mortality rates indicate a promotional role of dietary fat in postmenopausal breast cancer. Case-control studies also support this conclusion. In contrast, there is little variation in the rates of postmenopausal breast cancer among women according to their reported fat intake in large-scale cohort studies. These conflicting findings, noted elsewhere (1-5), have created a controversy in public policy regarding nutritional recommendations. Although much attention has been focused on the null findings in cohort studies, there are important qualitative differences between the animal and human data that need to be considered when setting research priorities and establishing nutritional recommendations. In the absence of more definitive evidence from carefully controlled intervention trials, this review summarizes key points on why the weight of evidence suggests that the amount and type of fat in the diet is a determinant of breast cancer, and that the lack of association in cohort studies likely results from the difficulty of measuring fat intake, particularly within populations that have similar eating patterns.

Animal Models

Animal studies have not only contributed to knowledge of carcinogenesis but also have provided the basis for regulatory public health decisions (e.g., the Delaney Clause). In terms of dietary fat and breast cancer prevention, it seems surprising therefore that animal model studies have received little attention compared with cohort studies. The need to develop strong supporting data in animal models before conducting intervention trials has recently been stressed by De Luca and Ross (6) in a commentary on the failure of the recent α-Tocopherol, β-Carotene (ATBC) Lung Cancer Prevention Study. The ATBC trial was conceived on the basis of epidemiologic and mechanistic evidence, despite the fact that there was no published evidence that β-carotene prevented lung cancer in animal models. In marked contrast, there is a wealth of information from laboratory animal studies dating back a century supporting a role for dietary fat in breast cancer and a variety of biologically plausible mechanisms by which the promoting action of fat could occur.

In the early 1950s, Tannenbaum and Silverstone (7) demonstrated that a high-fat diet stimulated mammary tumor development in mice when compared with a low-fat diet (12% versus 3% hydrogenated cottonseed oil). In further studies, the effect was demonstrated to be independent of caloric intake, and the response to fat was nonlinear, with a plateau occurring around 16% fat (wt/wt).

Later, studies by Carroll and Khor (8) and others (9) showed that the tumor-enhancing effect of fat was exerted during the postinitiation (promotion) phase of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary carcinogenesis in rats and in mice. Similar findings in transplanted mammary tumor models (10) support the idea that fat acts after the initiating event, since...
transplantable tumors have progressed through all but the meta-
static stage of carcinogenesis.

These studies have been extended to include the last and most lethal stage in carcinogenesis, i.e., the metastatic stage. Katz and Boylan (11), using a metastatic rat mammary tumor model, and Rose et al. (12,13), using human breast cancer cells inoculated into nude mice, demonstrated that high fat intake significantly increased the size and number of pulmonary metastases compared with mice fed low-fat diets.

Studies on the quantitative aspects of the fat effect are important because it is necessary to determine whether there is a dose–response effect or a threshold effect in tumor promotion. Such information can be useful in formulating dietary recommendations. In the first case, the dose–response effect for fat may be linear or nonlinear in nature. In the second possibility, the promoting effect of fat may be dependent on the amount of fat intake, reaching a threshold level beyond which tumor promotion occurs, regardless of how much fat is consumed. Reports by Cohen et al. (14) in the rat model and Zevenbergen et al. (15) in the mouse model support the second hypothesis, suggesting a point between 20% and 30% fat as a percentage of food intake in calories. Recently, Tang et al. (16) published a rat model study consistent with the threshold hypothesis. No difference in mammary tumor incidence was reported in animals fed diets containing 5%-25% of energy from fat or in animals fed diets containing 30%-40% energy from fat. However, analysis of combined group incidence clearly showed that mammary tumor incidence was significantly higher in the 30%-40% group compared with the 5%-25% group. These results suggest that one reason for the null effect reported in cohort studies may be that the lowest percent fat intake among individuals or groups in the population lies above the hypothetical threshold for promotion.

The type and amount of fat appears to be an important determinate of its promoting effect (7). In animal model studies, specific types of fat exert different effects under high-fat conditions, arguing against the possibility that the tumor-promoting effects of fat are due simply to its high caloric content, as some have contended (17). Several examples follow.

The essential polyunsaturated fatty acid, linoleic acid, commonly found in vegetable oils, such as sunflower, safflower, and corn oil, and the precursor of prostaglandins plays a key role in the fat effect. Carroll and Khor (8) and Ip (18) showed that a minimum amount of linoleic acid up to 4% of energy is necessary, but not sufficient, for fat to exert its tumor-promoting effects. In the N-methyl-nitrosourea (NMU) mammary tumor model, Cohen et al. (19) found that safflower and corn oil rich in linoleic acid exerted significantly increased tumor incidence compared with olive oil (rich in oleic acid) and coconut oils (rich in medium-chain saturated fatty acids). Olive-oil fed rats exhibited high levels of oleic acid in serum and mammary gland and decreased levels of prostaglandins in normal mammary gland and mammary tumors, suggesting an effect at the level of linoleic acid prostaglandin pathway (20). Hopkins et al. (21) reported that the addition of 3% oleic acid to a diet high in saturated fat did not increase mammary tumor incidence in the DMBA model; however, when 3% linoleic acid was added, tumor incidence was significantly increased. A similar nonpromoting effect of olive oil was reported by Lasekan et al. (22).

The results of animal model studies with olive oil are of particular interest, since incidence rates of breast cancer in Mediterranean countries where olive oil is a staple are relatively low compared with most Western countries [reviewed in (23)]. The incidence of breast cancer in Spain is about 40% lower than that of North America or Northern Europe (23), and Greek women who consume 42% of energy as fat [mainly from olive oil (24,25)] have significantly lower rates of breast cancer than U.S. women whose energy intake from fat is approximately 35% (26).

Diet containing high levels of very long chain n-6 polyun-saturated fatty acids (PUFA), such as eicosapentanoic acid, which is present in fish oil, lack tumor-promoting effects in breast cancer models (27,28). The failure to promote development appears to be dependent on the ratio of n-6 to n-3 fatty acids in the diet. Eicosapentanoic acid has attracted attention because it is an inhibitor of eicosanoid production from the n-3 family by competition with linoleic acid for desaturates and influences a number of physiologic processes, including immune rejection reactions, blood clotting, and n-6 eicosanoid synthesis (29). The high content of marine mammals and fish in the Eskimo and Japanese diets, respectively, and the associated high blood levels of eicosapentanoic acid may be associated with low breast cancer rates in these populations (30).

In summary, a significant body of evidence compiled over a period of 50 years from animal model bioassays supports the concept that high fat intake promotes mammary tumorigenesis and that dietary fat also influences the metastatic dissemination of breast tumor cells to remote sites. This is supported by a meta-analysis conducted by Freedman et al. (31) of 100 animal experiments showing a specific independent tumor-promoting effect of dietary fat. In addition, because high-fat diets containing different types of fatty acids exert different effects on tumor development, it is clear that the effect of fat cannot be due solely to its high caloric density. Last, intake of high levels of certain fats, such as olive oil and fish oil, does not promote tumor development in animal models—a finding that may be related to the low breast cancer rates characteristic of Mediterranean and Eskimo populations, despite their overall high fat consumption.

Mechanisms

Dietary fat affects a variety of processes that may be involved in the progression of breast cancer, adding further weight for a causal effect (32). These mechanisms can have either direct or indirect effects. Direct effects include 1) conversion of essential fatty acid to eicosanoids, short-lived hormone-like lipids that derive primarily from dietary linoleic acid; 2) reaction between oxygen and the conjugated double bonds in PUFA leading to reactive oxygen species which, in turn, induce DNA damage; and 3) interaction between fatty acids and genomic DNA leading to alterations in gene expression. Indirect effects include 1) effects of hypothalamus–pituitary axis-influencing hormone levels, 2) effects at the level of membrane (lipid)-bound enzymes such as mixed function oxidases that regulate estrogen catabo-

lism, 3) structural and functional changes in cell membranes resulting in alteration of hormone and growth factor receptors, and 4) effects on immune functions.

Eicosanoids, which include prostaglandins, leukotrienes, and thromboxanes, are known to mediate a variety of physiologic
functions, including cell motility, immune function, and inflammation, and to be deregulated in neoplastic cells (33,34). Tumor cells produce large amounts of eicosanoids compared with their normal cell counterparts (20,35), and eicosanoids that are ultimately derived from linoleic acid (n-6 eicosanoids) have been linked to increased tumor development, growth, and metastasis (34,36). Both oleic acid and eicosapentaenoic acid block the de-saturase reaction, the first step leading from linoleic acid to eicosanoids, which may explain, in part, their inhibitory effects on tumorigenesis (33,34). High-fat diets enhance the metastatic dissemination of human breast cancer (MCF-7) to the lung in the nude mouse model (12,13,36). This effect has been shown to be linoleic acid dependent and to be mediated by specific products of the related lipoxygenase pathway that signals the transcription of messenger RNA for type IV collagenase, a key enzyme in the metastatic process leading to invasion of the extracellular matrix (37,38).

Free radical-mediated lipid peroxidation has been implicated in a variety of pathologic processes including carcinogenesis (39,40). Free radical reactions have been shown by Troll and Weisner (41) to be mediators of tumor promotion by phorbol esters in the two-stage mouse skin model. With regard to breast cancer, the role of lipid peroxidation is controversial. Horvath and Ip (42) reported that, although supplementation of the diet with two antioxidants, vitamin E and selenium, inhibited DMBA tumor development, indices of lipid peroxidation did not decrease in parallel with tumor incidence. With the use of the DMBA model, Lane et al. (43) also found no association between high fat intake, lipid peroxidation, and mammary tumor development. Gonzalez et al. (44) reported that the growth of human breast cancer cells in nude mice was stimulated by high-PUFA diets and inhibited by high-fish-oil diets and found that thioarbituric acid-reactive species (products of lipid peroxidation) were increased in the animals fed fish oil. These results suggest that increased peroxidation was protective, a viewpoint that has also been championed by Horrobin (45). This conclusion was supported by the fact that the addition of antioxidants to the fish-oil diet abrogated its inhibitory effect on tumor growth.

Recently, a direct mechanism for DNA-adduct formation associated with high-PUFA diets has been proposed. Peroxidation of PUFA is known to release several bifunctional α and β unsaturated aldehydes (enals) as end products, including malondialdehyde, acrolein, and trans-4-hydroxy-2-nonenal (46). The latter compound readily forms exocyclic adducts with deoxyguanosine and has since been shown to be mutagenic (47). The role of exocyclic adducts in breast cancer remains to be determined. Djuric et al. (48,49) have demonstrated that free radical damage to thymine bases in peripheral white blood cell DNA was greater in individuals consuming high-fat compared with low-fat diets, and Malins et al. (50) have presented evidence that free radical-mediated ring opening reactions in DNA bases are associated with the progression of human breast cancer.

Recent studies (51-57) indicate that high fat intake alters the expression of genes involved in mammary tumorigenesis. Linoleic acid was shown to modulate gene expression in MCF-7 cells transfected with the coding sequence for the Harvey Ras oncogene 4-H-ras (52). Moreover, in cultured rat mammary tumor cells, linoleic acid has been shown to decrease the amount of p53 protein (product of tumor suppressor gene p53) and simultaneously stimulate tumor cell growth, indicating that linoleic acid can influence the activity of specific gene products at the post-translational level (54). The mechanism by which specific fatty acids enter the nucleus and influence gene expression remains to be clarified. At present, the most plausible mechanism involves binding to a cytoplasmic fatty acid-binding protein, followed by translocation to the nucleus where the fatty acid interacts with nuclear receptors of the steroid hormone receptor superfamily (58,59).

The risk of developing breast cancer is closely linked to events of reproductive life, suggesting a role for endogenous estrogens in breast cancer development (60). It has been hypothesized that high fat intake may act indirectly via the hypothalamus–pituitary axis, specifically by raising circulating sex hormone concentrations such as estrogen (61). Higher levels of serum estrogens have been found in high-risk Western populations compared with low-risk Asian populations (62-64) and vegetarians (65-67). Key et al. (64) found that plasma estradiol levels in women living in rural Britain were 171% higher than in women living in rural China. Two prospective studies (68,69) reported that high estrogen levels in women preceded breast cancer occurrence in postmenopausal women. Intervention studies (70-75), although without concurrent controls, in menopausal and postmenopausal women consuming high-fat diets show reduced serum concentrations of estrogens when placed on low-fat diets. However, these reports must be viewed with caution. As Potischman et al. (76), Toniole et al. (77), and Hankinson et al. (78) have pointed out, the inter- and intra-laboratory reproducibility and validity of hormone measurements is poor, particularly when they are present at low levels in postmenopausal women. Other problems plague these studies, including small sample sizes, single samples, and failure to use standardized methods. Therefore, at present, there is no consensus on the role of increased circulating estrogens (free or bound) as antecedents of breast cancer (79).

Sex hormone-binding globulin (SHBG) is an important regulator of plasma sex steroids. Decreased levels of SHBG in high-risk groups resulting in increased unbound “free” estrogen have been reported (80). Similarly, high fat intake may impact estrogen bioavailability (bound versus free) by increasing free fatty acid levels in serum, which, in turn, displace estrogen from serum albumin, rendering it free for uptake by estrogen receptors (81).

The relative ease by which dietary fat can alter cellular lipid profiles has important implications for cell functions, particularly membrane-bound enzyme systems. It is well established that mixed-function oxidases play a key role in biotransformation involved in chemical carcinogens, drugs, and steroids. Evidence indicates that dietary fat can influence the activity of mixed-function oxidases (82-84). For example, liver microsomes obtained from rats fed a high proportion of corn oil exhibit elevated levels of cytochrome P450 compared with animals fed low-corn oil or high-coconut oil diets (78).

Breast cancer risk has been associated with altered estrogen catabolism. According to Bradlow et al. (85), conversion of estrone (E) to the catechol estrogen 2-OH-estrone decreases breast cancer risk, whereas conversion to 16α-OH-estrone in-
creases risk. High fat intake was demonstrated to redirect metabolism from the 2-OH to the 16α-OH pathway (86). In contrast, Adlercreutz et al. (87) found that elevated 2-OHE\textsubscript{2} levels are characteristic of high-risk (Finnish) populations and 16α-OH of low-risk populations (Japanese). These discrepancies are likely due to differences in the analytic methods but support the idea that diet can alter estrogen metabolism by influencing the hepatic microsomal mixed-function oxidases.

High fat intake alters membrane fluidity, thereby influencing membrane permeability and membrane bound receptors for hormones and growth factors involved in breast cancer growth and development (31).

Dietary lipids have been shown to modulate immune functions in humans and rodents (88-91). In a clinical intervention study (92), high fat intake suppressed cellular immune functions believed to be related to cancer such as natural killer (NK) cell activity (92). The effect on the immune system has been proposed to occur at the level of the cell membrane. Immune cells (i.e., T and B lymphocytes and NK cells) are dependent on membrane recognition sites for 1) secretion of antibodies, 2) synthesis of antigen receptors, and 3) activation of lipid mediators of the signal transduction cascade (inositol triphosphates, tyrosine kinases, and eicosanoids) (88,91). Hence, alterations in immune cell membrane structure due to incorporation of specific amounts and kinds of fatty acids have a profound influence on immune functions (88).

**Ecologic Data**

Large international differences in cancer rates have provided a basis for formulating hypotheses on diet and cancer etiology. The age-adjusted incidence of breast cancer varies from 22 per 100,000 in Japan to 68 per 100,000 in The Netherlands (93). The ratio of breast cancer mortality between the United States and Japan is 3:1 for premenopausal women and 8:1 for postmenopausal women (94,95). Similarly, survival rates of postmenopausal breast cancer are greater in Japan than in Western countries and cannot be explained by known prognostic factors, except possibly a low-fat diet (96) or leanness (97). Prognostic studies (98-100) of women with postmenopausal breast cancer show increased recurrence with increasing intake of fat.

The international correlation coefficients between per capita fat intake and age-adjusted incidence and mortality from breast cancer are approximately 0.8 (101-103). Although food disappearance data only indirectly reflect dietary patterns, the large international differences in fat intake have been confirmed by dietary surveys within national populations. For example, the percentage of calories from fat consumption between 1950 and 1975 was approximately 40%-45% in the United States (104) and 10%-25% in Japan (105,106). The current rate of postmenopausal breast cancer in Japan is associated with a current national dietary fat intake of 25% of total calories (107).

Prentice and Sheppard (108) showed that international correlations between fat intake and breast cancer persist over time. By the use of data for 10 countries, regression analysis was employed to model the changes in disease incidence rates between the early 1960s and 1975-1977 in relation to per capita fat consumption as measured by food disappearance data. With the use of a log-incidence ratio for the two time periods, the proportion of the variation in breast cancer incidence explained by fat disappearance was 0.79. Although food disappearance data do not reflect actual food-consumption habits because of differences in reporting and food wastage (109-112), it is generally accepted that these correlations are not artifacts (110-112).

Most other breast cancer risk factors, including family history, age at menarche, age at menopause, excess body weight, parity, lactation, and radiation, either alone or in combination, do not explain all of the global variations in postmenopausal breast cancer rates (113-115).

An ecologic study (116) also indicates a correlation between age at menarche and adult height with breast cancer rates. It has been suggested that the higher age at menarche in Japan may account for as much as 40% of the difference between the rates in the United States and Japan, although an analysis of breast cancer incidence rates in 10 countries for women aged 45-69 years by Prentice et al. (102) showed no significant association of age at menarche after controlling for per capita fat disappearance. In studies of determinants of menarche in Canadian and American girls, energy-rich diets were moderately related to an earlier age at menarche (117) or with body fatness (118), respectively. An association with dietary fat, at least within the limited range of 80-95 g per day, was not demonstrated. If dietary factors at young ages are related to age at menarche and such factors persist over a life span, part of the association between age at menarche and breast cancer rates may be due to even recent dietary factors. The association between height and breast cancer risk in epidemiologic studies has not been consistent. For example, height was not associated with breast cancer risk in premenopausal women and only weakly associated in postmenopausal women in the Nurses Health Cohort Study (119).

In rural China, Chen et al. (120) found that the mortality rate of breast cancer is exceedingly low and that the diets consisted of 15% calories from fat. Even the variation in breast cancer rates in rural China is attributed to a high-fat diet. In a survey of 65 rural counties in China, animal food intake was positively correlated with breast cancer mortality (121). In a separate analysis of these data, the coefficient of the correlation of total lipid intake with breast cancer mortality was only 0.12 (122). Reasons for the low correlation may include imprecise nutrient estimates, nonrandom sampling of age, and selection of counties in geographic proximity that had similar rates. Nevertheless, the standardized regression coefficient for lipids was larger than for any other breast cancer risk factor.

Genetic differences do not account for ethnic variation in breast cancer mortality rates. Asian migrants to the United States have intermediate breast cancer rates between U.S. Caucasian women and Asian women who live in Japan, China, and the Philippines (123). In Asian migrants living in the United States (124), exposure to “Western lifestyles” is an important determinant of breast cancer. In another study (125), the age-standardized incidence ratio of breast cancer in Chinese-American women is 2.3 relative to native Chinese women but 0.55 relative to the white American population (125). These differences are not due to menstrual and reproductive factors (126), but are believed to reflect the adoption of Western diets among Chinese migrants (127). The rates of breast cancer in second-generation Chinese migrants to the United States remain
lower than those of the general U.S. population (128), possibly in part because of continued adherence to the traditional Asian diet (129).

**Dietary Intake Measurements**

There are high international correlations between dietary fat intake and rates of colon and prostate cancers as well as breast cancer. Cohort studies of breast cancer have generally been unable to detect an association with levels of fat intake. However, cohort studies of fat intake and colon and prostate cancers have also been inconsistent. For example, Giovannucci et al. (130) found an increased risk of colon cancer in the Health Professionals Follow-up Study (HPFUS) with high meat intake. In contrast, using a similar questionnaire, Bostick et al. (131) observed no association between meat intake and colon cancer in Iowa. Other studies (132,133) of meat and colon cancer have also shown no associations. In the HPFUS, Giovannucci et al. (134) observed an increased risk of prostate cancer for men only in the upper quintile of red meat intake. Other prospective studies of meat and prostate cancer have found both positive (135) and null findings (136). For coronary heart disease, Ascherio et al. (137) found an unadjusted linear trend in saturated fat intake in the HPFUS but no association after adjusting for fiber intake. These examples show that inconsistencies in cohort studies of dietary fat and disease may result from differences in study population characteristics, differences in the mechanistic pathways for specific diseases, the presence or lack of threshold levels, bias, and chance. However, the discrepancy between the international correlations and cohort studies for all three cancers is likely due to measurement error in the cohort studies and the inability to detect associations within populations that have a relatively narrow range of fat intake.

The most common food-intake measurements include dietary records and self-administered food-frequency questionnaires. In some cohort studies, fat intake as determined by a single food-frequency questionnaire was unrelated to breast cancer incidence. The reason may be that in Western populations with homogeneous dietary habits, virtually everyone is “overexposed” in terms of calories and especially fat (138), and therefore there is insufficient variation in the diet to relate it to disease risk.

In the Framingham (139) and Tecumseh studies (140), there was no relationship between diets rich in saturated fat and cholesterol, as measured by dietary recall, and serum cholesterol levels. The Western Electric Study (141), which employed extensive interviewing of subjects and wives by nutritionists using food models, failed to link serum cholesterol levels and myocardial infarction to dietary intake after 4 years of follow-up. After 20 years of follow-up, the coefficient of correlation between changes in dietary variables using a dietary score and changes in serum cholesterol concentration was 0.12 (142). These results reflect the inadequate characterization of dietary intake by quantitative measurements (143,144) and variability in individual dietary intake of some foods from one day to the next. Even 7-day food records (the so-called “gold standard”) do not provide an accurate characterization of diet (145). A recent statistical model developed by Prentice (5) has shown that measurement error in dietary assessment can reduce or eliminate positive associations between total fat intake and breast cancer risk in epidemiologic studies.

The so-called “validation” of the food-frequency questionnaire in the recent meta-analysis of cohort studies by Hunter et al. (145) is a misrepresentation of the accuracy of dietary data. True “validity” would require nonintrusive observation of the respondent’s total diet over a long time (146). No such study has ever been or likely will be done. What has been done in the meta-analysis were studies that examined the concordance of food-frequency questionnaire responses with multiple food records or recalls. This is not a true “validation” method because recalls and records themselves do not represent the time period of interest, contain error, and inaccurately represent intake (147). The average correlation coefficient between the two measures of fat intake was approximately 0.5—which is not “reasonably accurate” as Hunter et al. (148) suggest but leaves much of the data unexplained, regardless of statistical significance.

The reported intake of specific foods may be influenced by socially acceptable norms (149,150), media attention (151), professional recommendations, and distorted memories of dietary intake (152,153). Food-frequency questionnaires may be filled out with the assistance of spouses, and participants may not acknowledge their true eating habits or make guesses. The National Health and Nutrition Examination Surveys (conducted from 1981 through 1991) found a decrease in the reported mean percentage of total food energy intake derived from dietary fat since the 1970s (154) yet an increase in the prevalence of obesity from 1976 to 1991 (155). In contrast, Framingham data from 1966-1969 to 1984-1988 find an apparent increase in saturated fat intake, but only after adjustments for missing nutrient information on the fatty acid content of foods (156).

Studies of reported energy intake in dietary surveys have conclusively established widespread underreporting. In a review of 37 dietary surveys, Black (157) showed that 68% of the groups of men and women in these surveys had reported intakes that were incompatible with normal energy expenditures. Using the National Health and Nutrition Survey II data on self-reported dietary intake, Klesges et al. (158) calculated that up to 31% of adults underreport dietary intake as measured by estimated basal metabolic rate. The highest degree of underreporting was in women, less educated, and overweight individuals. In another approach, Mertz (159) summarized three studies that collectively showed an underreporting of 20% of total calories when self-reported food intake was compared with actual food intake. Such underreporting is likely to be especially evident among obese individuals.

Studies (160-162) using doubly labeled water, a technique for measuring energy expenditure based on differences between the isotopic elimination rates of the stable isotopes of hydrogen and of oxygen, have shown that most dietary records are systemically biased toward underestimation. The bias is greatest among subjects who report low intake of energy. In a sample of 29 women at high risk for breast cancer, Martin et al. (161) calculated that reported energy intake as determined by food records was 22% lower than energy intake (P<0.05) as measured by doubly labeled water. Single 24-hour food recalls and food-frequency questionnaires also do not provide accurate measures of energy expenditure as measured by this technique (162). Using 24-hour urine nitrogen excretion as a biomarker for protein...
intake. Bingham and Cummings (163) found underreporting among all study subjects who reported a fat intake of 60 g or less. It needs to be stressed that energy intake is not a direct measure of fat intake, although fat provides the greatest percentage of energy.

The results from these metabolic findings are especially relevant to the interpretation of the above-mentioned pooled cohort analysis by Hunter et al. (145). In that study, only 84 (1.7%) of the 4980 breast cancer cases reportedly consumed less than 20% energy intake from fat as measured by the food-frequency questionnaires. These women did not have a decreased rate of breast cancer.

Food-frequency questionnaires usually focus on dietary intake over the past year, which may not be similar to foods consumed at younger or older ages. It has been hypothesized that a high-fat diet during childhood may be an important determinant of breast cancer (2). This cannot be measured by food-frequency questionnaires. In adults, food habits may change with the onset of certain illnesses as people age, with smoking cessation, or during attempts to reduce weight, as a large percentage of adult women do. Similarly, nutrient values in the food tables used in food frequency questionnaires are based on a single point in time. Nutrient values for foods containing fat may change greatly over time, especially for foods with hidden sources of fat, such as ice cream and commercially baked cakes and cookies.

Biases in reporting past eating habits include not only recall of which foods were eaten but also the lack of detail about the ways in which food was prepared, especially outside the home. It is especially difficult to estimate fat intake compared with other types of foods. The amount of fat consumed from meat varies considerably according to the cut of the meat, whether the meat is trimmed, the degree and method of cooking, and whether the fat surrounding the meat is actually consumed. Fat intake also varies by the amount of fat consumed in gravy made from meat drippings. Many food-frequency questionnaires do not measure these aspects of cooking.

Slattery et al. (164) have hypothesized that the identification of nutritional risk factors in breast cancer case-control and cohort studies has been hampered by the inability to relate environmental and nutritional factors to unique disease pathways because of genetic heterogeneity. This can be interpreted to mean that within populations consuming homogeneous diets, an association of diet with disease would be difficult to detect (165).

Summary

Although a meta-analysis of 12 case-control studies of breast cancer showed a modest positive association with dietary fat intake (odds ratio for highest versus lowest quintile of saturated fat, 1.46) (166), the findings from the pooled cohort studies by Hunter et al. (145) showed no role of dietary fat in breast cancer. In U.S. women, the lifetime risk of being diagnosed with breast cancer is 12.3% (167). Common diseases, it may be argued, have common causes. Clearly, breast cancer and diet meets this premise. In general, animal model evidence indicates that fat exerts its effect on the promotion and progression stages of tumorigenesis, that the effect is independent of caloric intake, that the dose-response effect is nonlinear, and that the type of fat is important in this effect. What remains unclear is the absolute levels at which the promotional effects occur. There are a variety of plausible mechanisms by which this action occurs, although none have been proven definitively. The food disappearance data likely overstate fat intake, but the remarkably strong and consistent international correlations with breast cancer mortality have not been demonstrated to be invalid or due to other factors.

Migrant studies show that the rates of breast cancer increase among immigrants who acquire “Western” lifestyles. There is an overall modest association in case-control studies but a null association in cohort studies, but there are also inconsistencies between individual case-control studies and individual cohort studies. Inconsistencies in epidemiologic data are not surprising given the narrow range of fat intake among study subjects within populations, the very small numbers of women who reportedly consumed low-fat diets in these studies, different definitions of fat intake (total fat versus saturated fat), measurement error as described by Prentice (5), the underreporting of energy intake as demonstrated by several and varied methods, and the inability to define possible high-risk subgroups. As pointed out by Hegsted (165), “dietary hypothesis can never be disproved by epidemiologic studies within communities” but that “when significant correlations are observed, they are likely to be meaningful, simply because practically everything is weighed against finding such relationships.”

With regard to research priorities, it can be concluded that, while further mechanistic studies are called for, additional case-control or cohort analyses will not add any additional useful information in determining the role of fat in breast cancer promotion. The most rigorous assessment is the conduct and completion of carefully controlled trials to prevent the occurrence of breast cancer in high-risk women and to reduce recurrence in women with breast cancer after primary treatment. Some intriguing data are awaiting confirmation in longer observational periods. Boyd et al. (168) found a reduction in the area of mammographic density, a risk factor for breast cancer, in women enrolled in a low-fat, high-carbohydrate diet (mean, 21% of fat calories) after 2 years of follow-up. In evaluating the outcome of intervention studies, it is necessary to consider the duration of intervention and the degree of sustained compliance, objectives that have their own methodologic difficulties (169).

As we await the results from randomized clinical trials, in terms of current public health recommendations the American Health Foundation has recommended an optimal diet of 25% calories from fat for adult women (170). This diet is in line with general recommendations from the American Cancer Society, the National Cancer Institute’s Five-a-Day program (171), Dietary Guidelines for Americans (172), and the Food Pyramid Guide (173). In this case, there is little downside to reducing fat in the diet in regard to the development of breast cancer as well as other diseases.

Adjuvant dietary recommendations of 15% of calories from fat for women with postmenopausal breast cancer are currently being evaluated in the Women’s Intervention Nutrition Study (174). It has been proposed that second-generation trials consist of a low-fat diet in combination with a high-fiber diet and regular physical exercise to prevent breast cancer recurrence (175). In premenopausal women, recent data from randomized trials
support statistics showing improved long-term survival with ovarian ablation \(^{176}\). An additional recommendation, initially presented at the Society of Surgical Oncology in 1989 \(^{177}\), is adherence to an adjuvant 15% fat diet in these women.

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Note

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