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DIETARY FAT AND BREAST CANCER

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■ **Abstract** One of the most often studied associations in epidemiology is dietary fat and breast cancer risk. That migrants from low-risk countries increase their risk on immigrating to higher-risk countries suggests that some modifiable lifestyle or environmental factor is responsible for the development of breast cancer. Although early international correlational studies and experimental animals studies support dietary fat as a risk factor for breast cancer, more recent data from case-control studies and cohort studies have been equivocal, thus the analytical data do not support a strong positive association. The conflicting results from analytic studies may be due to methodologic issues associated with study design, dietary assessment tools, measurement error, improper statistical analyses, and a lack of heterogeneity in fat intake among the study population. Moreover, current dietary questionnaires may be inadequate in capturing true dietary intakes or capturing the risk with exposure during earlier periods of a woman's life. Although two large clinical trials investigating the fat/breast cancer relationships issue are underway, researchers are generally skeptical at their ability to detect an independent association between fat and breast cancer risk. Further epidemiologic studies using current methodology may not prove to be fruitful in generating definitive answers to shed light on this controversial issue. In addition, rather than concentrating on dietary fat, researchers should focus on diets that are not only low in saturated fat, but also high in fruit and vegetable consumption. Researchers should take advantage of advances in molecular and genetic technology for a different perspective in examining the issue. For example, markers of susceptibility to breast cancer that can detect women at higher risk for breast cancer may be helpful in clarifying the role of dietary fat. More comprehensive and multiple approaches to studying dietary factors and breast cancer are recommended.

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INTRODUCTION

Dietary factors including specific food, food groups, or nutrients have been shown to play important roles in preventing several cancers (1, 11, 12). Some foods and macronutrients have also been suspected of increasing the risk of certain cancers. However, the link between dietary fat and risk for breast cancer has been controversial for many years, and studies of laboratory animals and human populations have only raised more unanswered questions. It is important to bear in mind that dietary fat is intricately connected to other lifestyle factors, such as caloric intake, weight gain, obesity, and physical activity. To separate the independent effects of dietary fat to breast cancer risk may be unrealistic. In addition, individual genetic susceptibility may further hinder this relationship. Nevertheless, for this review, we focus on the magnitude of the problem, breast cancer incidence and mortality statistics, the proposed mechanism of action via estrogens and its effects on tumor promotion, and progression, and we provide evidence from epidemiological data by critically assessing their weaknesses and strengths. We selected for our review the English language literature of meta-analyses based on studies performed in the 1980s–1990s and individual studies done since 1990. In the final section of this review, we propose some future directions, with the perspective that this issue deserves further research from multiple approaches.

Breast Cancer Incidence and Mortality Statistics

Breast cancer is the most common cancer among women worldwide, and among women in the United States, it accounts for almost 30% of newly diagnosed cancers and 17% of cancer-related deaths (1, 73, 74). Incidence rates are highest in North America and northern Europe and lowest in Asia and Africa, although rates have been increasing markedly in several Asian and developing countries (74). It was postulated that if these increases persist, the annual worldwide incidence counts will be over one million by the year 2000.

Among white women in the United States, age-adjusted breast cancer mortality rates have remained fairly constant since 1930, whereas age-adjusted incidence rates have increased slowly for many decades (54, 55, 73). Most of the increase in incidence rates has been attributed to an increased use of screening by mammography among premenopausal women; the incidence of estrogen receptor–positive tumors has also increased over time (24). The increased incidence with no apparent increase in mortality could be partially explained by several factors: early detection of early stage tumors by mammography; better prognosis associated with estrogen receptor–positive compared with estrogen receptor–negative tumors; and advances in medicine, such as new treatments (e.g. gene therapy) developed for advanced-stage breast cancer.

The differential incidence rates of breast cancer between women from Asia (20–30 cases per 100,000 persons per year), Asian-Americans in the United States (50–60), and US Caucasians (90–120) suggest that lifestyle and environmental factors may be associated with the development of breast cancer (35, 79). As a result of comparing incidence rates in migrant populations, much attention has been paid to changes in dietary practices, particularly fat consumption, to explain the increases in breast cancer rates with migration. Although the migrant observations support the role for dietary fat in the etiology of breast cancer, results from analytic epidemiology are still equivocal.

Estrogen and Breast Cancer Risk/Effect of Fat on Tumor Carcinogenesis

Before evaluating any causal risk or protective factor, there must be a biologically plausible association between the putative factor and disease. Indeed, several possible mechanisms have been proposed to explain the effect of fat on tumor carcinogenesis. In general, the association is thought possibly to be indirect, with dietary fat influencing breast cancer risk by hormonal pathways, with 16-alpha-hydroxylation (versus 2-hydroxylation) associated with elevated risk (18). It is likely that sex hormones, especially estrogen, play a promotional role in breast carcinogenesis, stimulating mitotic division of initiated cells and proliferation (1). However, the manner in which hormonal factors affect breast carcinogenesis is still unclear. With recent advances in genetics and molecular biology, several oncogenes and tumor suppressor genes involved with the progression of breast cancer have been identified; there may very likely be an interactive effect between these genetic alterations and dietary fat on breast cancer development.

REVIEW OF STUDIES

Animal Experiments

The first evidence in support of a relationship between dietary fat and the development of breast cancer comes from animal experimental studies in the early 1940s (93). Since then, more than 100 studies have been conducted to investigate the

hypothesis that dietary fat could modulate breast cancer risk. Most of the animal studies have focused on the amount, type, and source of dietary fat, as well as the effect of dietary fat independent of caloric intake and body weight (19, 103). Animal studies have also been used to examine the timing of the effect of fat, i.e. whether its effect is most relevant during the initiation or the promotion stage.

It has been shown that an increased amount of both vegetable and animal fat accelerates mammary tumor growth; therefore, increased fat intake generally does not affect the initiation of tumorigenesis, only its promotion (103). Different types of fat also have different effects on mammary tumorigenesis. For example, olive oil, which is 79% oleic acid and 7% linoleic acid, has no effect, not even an inhibitory one, whereas palm oil (43% oleic acid and 11% linoleic acid) produced fewer tumors in rats than did corn oil (37% oleic). In addition, supplementation of olive oil diets with linoleic acid can block the inhibitory activities of an olive oil diet in rats treated with chemical carcinogens. It has been proposed that the inhibitory activities of olive oil may be a function not of monoenoic fatty acid levels but of low levels of linoleic acid (103).

Fay et al (17) conducted a meta-analysis of 97 reports that studied the effects of different types of dietary fatty acids on mammary tumor incidence. The findings were as follows: n-6 polyunsaturated fatty acids have a strong tumor-enhancing effect; saturated fats have weaker tumor-enhancing effects; n-3 polyunsaturated fatty acids have a small, nonsignificant protective effect; the effects of n-6 polyunsaturated fats are stronger than that of saturated fats even at low levels; and there is no effect of monounsaturated fats on mammary tumorigenesis.

Several studies have also focused on other potentially beneficial oils, such as primrose and fish oils (which are rich in omega-3-fatty acids). However, a dose dependency on the suppression of mammary tumors has not been demonstrated with these oils.

Welsch (103) reviewed the effect of fat on the metastasis of mammary tumor cells. Although some studies have shown that certain types of fat, such as that from beef tallow and corn oil, and diets high in *cis*-fatty acids can increase rates of metastasis, these results are neither consistent nor conclusive. A review by Rose et al (87) found that a high-fat diet rich in omega-6 polyunsaturated fatty acid in animal models could enhance metastasis of human breast cancer cells.

Recent work in this field has focused on fat intake during pregnancy and its effects on breast cancer risk in the offspring. Hilakivi-Clarke & Clarke (37) showed that rats fed a high-fat diet in utero were more likely to have undifferentiated mammary glands than rats fed a low-fat diet. In addition, these glands were more likely to contain lower levels of estrogen receptors, which suggests that a high-fat diet may be a relevant factor in increasing estrogenic activity during pregnancy. This area needs further exploration in human studies.

Epidemiologic Studies

The most compelling evidence for an association between dietary fat and risk of breast cancer in human populations comes from international correlation studies.

However, these studies rank lowest on the scale of epidemiologic studies on establishing causality and are generally used for hypothesis-generating purposes only (36, 56, 89). The more compelling observational studies, including case-control and cohort studies, have generated conflicting results, and the scientific community still awaits results from randomized clinical trials (5, 108a).

Several meta-analyses have been performed that pooled the results from case-control and cohort studies in an attempt to summarize the findings. Given different interpretations of the same data, the issues regarding dietary fat as a risk factor for breast cancer have generated many debates among the scientific community (4, 30, 43, 48, 50, 51, 67, 76, 82, 100, 106, 109, 110). We intend first to summarize the findings from descriptive epidemiologic studies (i.e. correlational studies) and the major meta-analyses of case-control and cohort studies on fat and breast cancer relationship performed over the past 10 years. We then present the findings from recent individual studies examining dietary fat and breast cancer risk.

Correlational Studies

Correlational, also known as ecological, studies use data from whole populations to compare disease frequencies and risk factor levels between different groups (36, 56). International correlational studies conducted with incidence and mortality data from several countries support an association between dietary fat and breast cancer, with correlation coefficients between 0.7 and 0.9 (2, 15, 29, 33, 90, 92). Correlational studies done within the same geographic location also support a link between dietary fat and breast cancer (22, 61, 72). In addition, data from international cancer registries indicate that Asian migrants to the United States have a higher incidence of breast cancer than do their counterparts living in Asia (79); these data coincide with data that suggest the migrants also have higher dietary fat patterns (60, 66). However, the migrant populations may also modify other dietary and reproductive risk factors as they begin to adopt the American culture.

Despite the magnitude of these associations, ecological studies, by nature of their design, cannot be used to establish causality of exposure and disease; any founded associations are generally further tested with analytic studies (i.e. case-control and cohort studies), and clinical trials, if possible. In addition, published correlational studies generally do not consider the possibility of confounding of the association by third variables. Even with adjustment for confounders at the aggregate level, e.g. age at menarche and weight, the inability to infer the findings based on the ecological level to the individual level still hold (55, 56). Finally, most of the correlational studies on dietary fat and breast cancer are based on national food disappearance or food-consumption data (2, 15, 29, 33, 72, 90, 92); therefore, caution should be taken when interpreting such data. It has been suggested that actual intake of fat is quite different from fat-disappearance calculations (91).

Analytic Studies

The first analytic observations linking dietary fat intake and breast cancer risk in humans was published in 1975 in studies among Seventh-Day Adventists (75).

The results from these studies suggest that fried food, fat used in frying, and dairy products (except milk) increased the risk of breast cancer.

By nature of the study designs, analytic studies establish causal inference better than correlational studies do and, next to randomized clinical trials, are the best designs for relating a risk factor to an outcome in free-living human populations. However, thus far, the results from case-control studies on dietary fat and breast cancer risk have been equivocal, and taken together, the results from cohort studies do not support a strong association. Several meta-analyses have been performed for case-control and cohort studies to account for the inconsistent results arising from differences in methods, presence of methodological issues, and inadequate statistical power that may affect the ability to detect a true association between dietary fat and increased breast cancer risk, if one truly exists.

Case-Control Studies

Table 1 summarizes three published meta-analyses on case-controls studies and selected individual studies published between 1990–1999. Most studies utilized some type of food-frequency questionnaire to assess fat intake levels. The multivariate odds ratio (OR), if available, comparing the highest to the lowest level of intake, and the associated confidence interval are also presented. Some of the individual studies summarized are included in the meta-analyses, and these are noted. Despite whether the meta-analysis utilized individual-level data or summarized risk estimates, the three meta-analyses generally support a positive association between total fat and breast cancer risk (OR between 1.2–1.5) (6, 32, 45). However, stratification by menopausal status showed that the effect was highest among postmenopausal women (OR = 1.5) and lowest among premenopausal women (OR = 1.1) (45). The meta-analysis by Boyd et al (6) showed a significant effect for total fat (OR = 1.2), saturated fat (OR = 1.4), and monounsaturated fat (OR = 1.4) but not for polyunsaturated fat (OR = 0.9).

Harrison & Waterbor (32) combined the case-control studies included in the two previous meta-analyses and computed OR estimates using both individual-level patient data and summary data from the literature. They found in a random-effects model that adjusts for heterogeneity between studies that geographic location was a significant effect modifier of the association between total fat and breast cancer. Case-control studies conducted in Europe had the highest OR estimate (OR = 1.5), followed by studies conducted in North America (OR = 1.3), and studies conducted in other areas (OR = 1.2) (32). Despite the elevated risk associated with increasing total fat, none of these estimates was statistically significant in this particular analysis. It is worth noting, however, that none of these three meta-analyses adjusted for other factors, including total energy intake and other potential breast cancer confounders, in their analyses.

Among the 21 case-control studies published between 1990–1999 and described in Table 1, nine (studies 1–3, 5, 10–11, 16–17, 21) showed a significantly positive association with total fat, saturated fat, monounsaturated fat, and/or food

TABLE 1 Summary of three meta-analyses and (selected) published case-control epidemiologic studies on dietary fat and breast cancer, 1990–1999

Study no.,[a] first author (Ref., year publ.)	Year(s) of study	Study location	Cases/ Controls	Dietary assessment method	OR (95% CI or *P* value)[b]	Comments
Howe (45, 1990) meta-analysis of 12 case-control studies	Studies completed by the end of 1986	NR	4427/6095	Food frequency	OR for highest versus lowest quintile (all subjects): total fat, 0.4 (*P* value < 0.0001); saturated fat, 1.6 (not reported) OR for highest versus lowest quintile (premenopausal): total fat, 1.1 (*P* value, 0.21) OR for highest versus lowest quintile (post-menopausal): total fat, 1.5 (*P* value < 0.0001)	Original study data used in meta-analysis; univariate summary ORs computed by conditional logistic regression, with 240 strata defined by the 12 studies and 20 age groups; significant trend (*P* value < 0.05) with increasing quintiles for total fat and saturated fat
Boyd (6, 1993), meta-analysis of 16 case-control studies published between 1978–1991 (included studies 3–6, 9)	NR	NR	6831/7105	Food frequency, diet history, 24-h recall	OR for highest versus lowest level of intake: total fat, 1.2 (1.1–1.3); saturated fat, 1.4 (1.2–1.6); monounsaturated fat, 1.4 (1.2–1.7); polyunsaturated fat, 0.9 (0.8–1.1)	Summary natural log relative risk estimates and variance from each study used in meta-analysis; univariate summary ORs computed by random effects model to account for variability across studies; summary ORs reflect comparison between lowest and highest level of intake described in each study (e.g. tertile, quartile, etc, different from study to study)
Harrison (32, 1999), meta-analysis of 23 case-control studies included in meta-analyses performed by Howe and Boyd (included studies 2–8)	NR	NR	NR	Food frequency, diet history, 24-h recall	OR for highest versus lowest level of intake (studies in Europe): total fat, 1.5 (not significant) OR for highest versus lowest level of intake (studies in North America): total fat, 1.3 (not significant) OR for highest versus lowest level of intake (studies in other areas): total fat, 1.2 (not significant)	Summary natural log relative risk estimates and variance from each study used in meta-analysis; univariate summary ORs computed by random effects conditional model to account for variability across studies; summary ORs reflect comparison between lowest and highest level of intake described in each study (e.g. tertile, quartile, etc, different from study to study)

(*Continued*)

TABLE 1 (*Continued*)

Study no.,[a] first author (Ref., year publ.)	Year(s) of study	Study location	Cases/ Controls	Dietary assessment method	OR (95% CI or *P* value)[b]	Comments
1. Van't Veer (98, 1990)	1985–1987	Netherlands	133/289	Food frequency (pattern in past 12 months)	OR for highest versus lowest quintile: total fat, 3.5 (1.6–7.6)	Subjects age 25–64; multivariate ORs computed by unconditional logistic regression adjusted for first- and second-degree familial history, history of benign breast disease, education, employment status, age at menarche, age at first full-term pregnancy, parity, ever use of oral contraceptives, smoking habits, body mass index, current alcohol intake, and energy intake; significant trend (P value < 0.05) with increasing quintiles for total fat; significant differences (based on 95% CI) in mean intake between cases and controls for total fat, saturated fat, and monounsaturated fat
2. Yu (111, 1990)	1982–1984	Shanghai, China	186/372 (186 population & 186 hospital controls)	Food frequency	OR for highest versus lowest quintile: total fat, 1.7 (1.0–2.1); saturated fat, 0.9 (0.5–1.4); monounsaturated fat, 1.9 (1.1–3.2); polyunsaturated fat, 1.2 (0.8–2.1)	Mean age of subjects = 52 years; multivariate ORs computed by conditional logistic regression adjusted for other sources of calories, education, and body mass index
3. Ewertz (16, 1990)	1983–1984	Denmark	1486/1336	Food frequency	OR for highest versus lowest quartile: total fat, 1.5 (1.2–1.8)	Subjects,<,age 70; multivariate OR computed by unconditional logistic regression adjusted for age and place of residence; significant trend (P value < 0.05) with increasing quartiles for total fat
4. Ingram (52, 1991)	1985–1987	Western Australia	99/209	Food frequency	OR for highest versus lowest consumption (based on median): total fat, 1.4 (0.8–2.5); saturated fat, 1.0 (0.6–1.8); monounsaturated fat, 1.6 (0.9–2.9): polyunsaturated fat, 0.9 (0.4–1.7)	Subjects age 22–86; univariate ORs computed by conditional logistic regression

5. Richardson (85, 1991)	1983–1987 1987	Montpellier, France	409/515	Food frequency	OR for highest versus lowest tertile: total fat, 1.6 (1.1–2.2); animal fat, 1.6 (1.1–2.2); saturated fat, 1.9 (1.3–2.6); monoun-saturated fat, 1.7 (1.2–2.5); polyunsaturated fat, 1.2 (0.9–1.7)	Subjects age 28–66; multivariate ORs computed by unconditional logistic regression adjusted for age, family history of breast cancer, history of benign breast disease, age at menopause and menarche, parity, age at first full-term pregnancy, and education; significant trend (P value < 0.05) with increasing tertiles for total fat, animal fat, saturated fat, and monounsaturated fat
6. Lee (65, 1991)	1986–1988	Singapore	200/420	Food frequency	OR for highest versus lowest tertile: total fat, 0.8 (0.4–1.4); saturated fat, 0.9 (0.5–1.7); monounsaturated fat, 1.0 (0.5–1.8); poly-unsaturated fat, 0.4 (0.2–0.7)	Subjects age 24–88; multivariate ORs computed by unconditional logistic regression adjusted for age and age at first birth; significant trend (P value $<$ 0.05) with increasing tertiles for polyunsaturated fat
7. Zaridze (113, 1991)	1987–1989	Moscow, Russia	139/139	Food frequency	OR for highest versus lowest quartile (among post-menopausal women): total fat, 0.5 (0.04–7.0); saturated fat, 1.7 (0.2–11.8); monounsaturated fat, 1.8 (0.2–16.7); poly unsaturated fat, 0.1 (0.03–0.7)	Multivariate ORs computed by conditional logistic; regression adjusted for energy intake, age at menarche, and education; significant trend (P value $<$ .05) with increasing quartiles for polyunsaturated fat
8. Graham (27, 1991)	1986–1989	Western New York state	439/439	Food frequency	OR for highest versus lowest quartile: total fat, 0.9 (0.6–1.4); saturated fat, 1.0 (0.7–1.5)	Subjects were postmenopausal women age 41–85; multivariate OR computed by unconditional logistic regression adjusted for age, education, age at first pregnancy, age at menarche, relative with breast cancer, benign breast disease, number of pregnancies, nutritional traits, and body mass index
9. Kato (53, 1992)	1990–1991	Japan	908/908	Food frequency (for 8 foods)	OR for daily consumption vs $\leq$ 1–2/wk: meats, 0.9 (0.7–1.2); oily foods, 1.2 (0.9–1.5)	Subjects age 20+; univariate ORs computed by conditional logistic regression

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TABLE 1 (*Continued*)

Study no.,[a] first author (Ref., year publ.)	Year(s) of study	Study location	Cases/ Controls	Dietary assessment method	OR (95% CI or *P* value)[b]	Comments
10. Goodman (25, 1992)	1975–1980 1980	Oahu, Hawaii	272/296	Food frequency (dietary history)	OR for highest versus lowest quartile: total fat, 1.3 (0.8–2.1); saturated fat, 1.5 (1.0–2.5); animal protein, 1.6 (1.0–2.6)	Subjects were Japanese and Caucasian women between age 45–74; multivariate OR computed by unconditional logistic regression adjusted for age, ethnicity, age at first birth, age at menopause, and body mass index (Benn's index)
11. Qi (84, 1994)	1986–1987	Tianjin, China	244/244	Food frequency (dietary history)	OR for highest versus lowest quartile: total fat, 3.3 (1.3–8.2); saturated fat, 2.5 (1.3–5.1); monounsaturated fat, 3.1 (1.5–6.7); polyunsaturated fat, 2.4 (0.6–9.5)	Subjects age 18–75; multivariate ORs computed by conditional logistic regression adjusted for total calories
12. Martin-Moreno (71, 1994)	1990–1991	Spain	762/988	Food frequency	OR for highest versus lowest quartile (among all women): total fat, 1.0 (0.7–1.3); saturated fat, 1.0 (0.6–1.5); monounsaturated fat, 0.9 (0.6–1.3); polyunsaturated fat, 1.3 (1.0–1.8); oleic acid, 0.8 (0.5–1.1); linoleic acid, 1.2 (0.9–1.7)	Subjects age 18–75; multivariate ORs computed by unconditional logistic regression adjusted for age, geographical region, socioeconomic status, body mass index, and total energy intake; ORs reported separately by menopausal status; no significant associations for fat in either manopausal stratum
13. Yuan (112, 1995)	mid-1980s	Shanghai China & Tianjin,	834/834	Food frequency	OR for highest versus lowest quintile: total fat, 1.2 (0.7–2.0); saturated fat, 1.3 (0.6–2.6); monounsaturated fat, 1.2 (0.7–2.2); polyunsaturated fat, 1.3 (0.4–4.3)	Results from 2 studies combined; subjects age 20–69; multivariate ORs computed by conditional logistic regression adjusted for age and age at first birth

14. Trichopoulou (96, 1995)	1989–1991	Athens, Greece	820/1548	Food frequency	OR for more than once/day vs once/day: olive oil, 0.8 (0.6–1.0) OR for 4 times/month increment: butter, 1.0 (1.0–1.1); margarine, 1.1 (1.0–1.1); seed oils, 1.0 (1.0–1.1)	Multivariate ORs computed by unconditional logistic regression adjusted for age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, body mass index, total energy intake, and consumption of fruits and vegetables; no evidence of effect modification by menopausal status
15. La Vecchia (63, 64; 1995 & 1998)	1991–1994	Italy	2569/2588	Food frequency	OR for highest versus lowest quintile: olive oil, 0.9 (0.7–1.1) OR for 10 g/day increase: saturated fat, 1.1 (1.0–1.2); monounsaturated fat, 1.0 (0.9–1.0) OR for 5 g/day increase; polyunsaturated fat, 0.9 (0.9–1.0) OR for highest versus lowest quartile: saturated fat, 1.5(1.1–2.0); monounsaturated fat, 1.0 (0.8–1.2); polyunsaturated fat, 0.7 (0.6–0.9)	Subjects age 23–74; multivariate ORs computed by unconditional logistic regression adjusted for study center, age, education, parity, age at first birth, menopausal status, alcohol, total energy intake, and various types of oils and fats
16. Ronco (86, 1996)	1994–1995	Montevideo, Uruguay	169/253	Food frequency	OR for highest versus lowest quartile: total fat, 1.8 (1.0–3.2); saturated fat, 2.4 (1.3–4.3)	Subjects age 20–79; multivariate ORs computed by unconditional logistic regression adjusted for family history of breast cancer, body mass index, parity, age at menarche, menopausal status, and total energy intake; significant trend (P value < 0.05) with increasing quantities for saturated fat
17. De Stefani (13, 1998)	1994–1996	Montevideo, Uruguay	390/397	Food frequency	OR for highest versus lowest quartile: total fat, 1.5 (0.9–2.6); saturated fat, 2.5 (1.4–4.4); monounsaturated fat, 2.5 (1.5–4.1); polyunsaturated fat, 1.0 (0.6–1.6); linoleic acid, 0.7 (0.4–1.2); alpha-linoleic acid, 3.2 (1.9–5.6)	Subjects age 20–79; multivariate ORs computed by conditional logistic regression adjusted for age, residence, urban/rural status, family history of breast cancer, body mass index, age at menarche, parity, alcohol drinking, total energy intake, dietary fiber, and folate intake; significant trend (P value < 0.05) with increasing quartiles for total fat, saturated fat, monounsaturated fat, and alpha-linoleic acid

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TABLE 1 (*Continued*)

Study no.,[a] first author (Ref., year publ.)	Year(s) of study	Study location	Cases/ Controls	Dietary assessment method	OR (95% CI or *P* value)[b]	Comments
18. Witte (107, 1997)	1957–1989	LA County, Connecticut, Quebec	140/222 (sister controls	Food frequency	OR for highest versus lowest quartile: total fat, 0.4 (0.2–0.8); saturated fat, 0.5 (0.2–1.1); monounsaturated fat, 0.5 (0.2–1.0); polyunsaturated fat, 0.3 (0.1–0.7); oleic acid, 0.4 (0.2–0.9); linoleic acid, 0.3 (0.1–0.7); red meat, 0.6 (0.3–1.3)	Cases diagnosed with premenopausal bilateral breast cancer; multivariate ORs computed by unconditional logistic regression adjusted for age, age at menarche, parity, oral contraceptive use, alcohol intake, body mass index, and energy (using the residual approach): significant trend of protective effect (P value < 0.05) with increasing quartiles for total fat, monounsaturated fat, polyunsaturated fat, oleic acid, and linoleic acid
19. Potischman (77, 1997)	1990–1992	Atlanta, Seattle/ Puget Sound, central New Jersey	1588/1451	Block food frequency	OR for highest versus lowest quartile: total fat, 1.1 (0.8–1.4); saturated fat, 1.1(0.9–1.4)	Subjects age 20–44; multivariate ORs computed by unconditional logistic regression adjusted for age and age at first birth
20. Potischman (78, 1998)	1990–1992	Atlanta, Seattle/ Puget Sound, central New Jersey	1647/1501	Block food frequency	OR for highest versus lowest quartile (diet during adolescence): high-fat snacks and desserts, 1.1 (0.9–1.3); animal fat, 1.0 (0.8–1.2); high-fat foods, 0.9 (0.7–1.1)	Subjects age 20–44; multivariate ORs computed by unconditional logistic regression adjusted for age, study site, race, education, age at and number of full-term births, alcohol intake, oral contraceptive use, average lifetime exercise, exercise at ages 12–13; dietary recall during adolescence validated with mothers of subjects (unreliably recalled foods excluded)
21. Cade (8, 1998)	1990–1992	Southampton & Portsmouth, England	220/825	Food frequency	OR for highest versus lowest quartile: saturated fat, 2.4 (1.1–5.0); monounsaturated fat, 0.9 (0.4–1.8); polyunsaturated fat, 0.6 (0.3–1.3)	Subjects age 50–65; to attempt to reduce recall bias, interviews were performed at mammography screening, before women knew of the results; multivariate ORs computed by unconditional logistic regression adjusted for "demographic and reproductive factors determined by previous modeling"

[a]First three cases are meta-analyses and are not numbered.

[b]OR, Odds ratio; 95% CI, 95% confidence interval; *P*, probability; NR, not reported.

items associated with increased levels of these fats (e.g. meats, butter, margarine). The remaining 12 studies either showed a nonsignificant, slightly elevated effect (studies 4, 7, 13, 14) or a null or protective effect for these dietary fats (studies 6, 8–9, 12, 15, 18–20). In general, the majority of the studies showed no effect for polyunsaturated fats, oleic acid, and linoleic acid. One study that examined α-linoleic acid found a significant positive effect (OR = 3.2) (13). Of the 17 studies that tested for trend across categories of intake (where a positive trend indicates a positive dose–response relationship between increasing levels of fat consumption and increasing risk), eight studies detected a statistically significant trend (studies 1, 3, 5–7, 16–18). Of the two studies presented that examined olive oil, one (study 14) showed a slightly protective effect [OR = 0.75, 95% confidence interval = (0.57, 0.98)], and one demonstrated no effect [OR = 0.9, 95% confidence interval = (0.7, 1.1)] (study 15).

Cohort Studies

Table 2 summarizes the two published meta-analyses on cohort studies and the individual studies published between 1990–1999. The multivariate relative risk (RR) estimate, if available, comparing the highest with the lowest level of intake and the associated confidence intervals are also presented. Some of the individual studies summarized are included in the meta-analyses and these are noted. The meta-analysis by Hunter and colleagues (49) and that by Harrison & Waterbor (32) indicate that there is no association between dietary fat intake or any of its subcomponents (i.e. saturated fat, monounsaturated fat, polyunsaturated fat) and increased risk of breast cancer.

The meta-analysis by Hunter and colleagues (49) used individual-level data and adjusted for a multitude of breast cancer risk factors, whereas the analysis by Harrison & Waterbor (32) generated univariate summary RR estimates using a random-effects model to account for heterogeneity between studies. Harrison & Waterbor compared the risk estimates using both individual level data and summary data from the literature and found that both methods yielded similar summary estimates of RR (32).

Findings from 11 individual cohort studies published between 1990–1999 are also summarized in Table 2 (two sets of analyses were published for the Nurses' Health Study, one with 8 years of follow-up data, and one with 14 years of follow-up data). Overwhelmingly, the cohort studies do not support a positive association between total dietary fat intake and increased risk of breast cancer. However, 5 of the 11 studies showed nonsignificantly elevated risk for total fat, including the studies conducted in a Finland cohort (RR = 1.7) (59), the Canadian Breast Screening Study (RR = 1.3) (44), the Iowa Women's Health Study cohort (RR = 1.2) (62), the New York City cohort (RR = 1.5) (95), and the Norway cohort (RR = 1.3) (21). Only one study that followed-up a small cohort in Southern California reported a significantly increased risk for total fat (RR = 2.0) (3). Most notably, the largest assembled cohort with the largest number of incident breast

TABLE 2 Summary of two meta-analyses and (selected) published cohort epidemiologic studies on dietary fat and breast cancer, 1990–1999

Study no.,[a] first author (Ref., year published)	Year (s) of study	Study location	Cases/ cohort[b]	Dietary assessment method	RR (95% CI)[c]	Comments
Hunter (49, 1996) meta-analysis of 8 cohort studies (included studies 2–6, 10)	Combined years of follow-up between 1976–1993	California, Canada, Iowa, Netherlands, New York, US, Sweden	4980/337,819	Food frequency	RR for highest versus lowest quintile: total fat, 1.1 (0.9–1.2); saturated fat, 1.1 (1.0–1.2); monounsaturated fat, 1.0 (0.9–1.2); polyunsaturated fat, 1.1 (1.0–1.2); animal fat, 1.0 (0.9–1.1)	Original study data used in meta-analysis; multivariate summary RRs computed by Cox proportional hazards regression adjusted for age at menarche, menopausal status, parity, age at first birth, body mass index, height, education, history of benign breast disease, history of breast cancer in mother or sister, oral contraceptive use, fiber intake, alcohol intake, and energy intake
Harrison (32, 1999) meta-analysis of 9 cohort studies included in meta-analysis performed by Hunter (included studies 1–6, 10)	Not reported	Not reported	Not reported	Food frequency	RR for highest versus lowest level of intake in studies in Europe: total fat, 1.2 (not significant); OR for highest versus lowest level of intake In studies in North America: total fat, 1.0 (not significant); OR for highest versus lowest level of intake (studies in other areas): total fat, 1.0 (not significant)	Summary natural log relative risk estimates and variance from each study used in meta-analysis; univariate summary RRs computed by random-effects conditional model to account for variability across studies; summary RRs reflect comparison between lowest and highest level of intake described in each study (e.g. tertile, quartile, etc, different from study to study)
1. Knekt (59, 1990)	1966–1972 (20 years follow-up)	Finland	54/3,988	Dietary history method	RR for highest versus lowest quartile: total fat, 1.7 (0.6–4.8); saturated fat, 1.4 (0.5–3.7); monounsaturated fat, 2.7 (1.0–7.4); polyunsaturated fat, 1.2 (0.6–2.8)	Cohort consisted of women age 35–49 at start of study; multivriate RRs computed by Cox proportional hazards regression adjusted for age and total energy; significant trend (P value < 0.05) with increasing quartiles for monounsaturated fat
2. Howe (44, 1991)	1982–1987 (6 years follow-up)	Canada	519/56,837	Dietary history method	RR for highest versus lowest quartile: total fat, 1.3 (0.9–1.9); saturated fat, 1.1 (0.7–1.6); monounsaturated fat, 1.2 (0.8–1.9); polyunsaturated fat, 1.3 (0.9–1.8)	Cohort consisted of women age 40–59 at start of study (Canadian Breast Screening Study); multivariate RRs computed by unconditional logistic regression adjusted for other sources of calories; significant trend (P value < 0.05) with increasing quartiles for monounsaturated fat
3. Kushi (62, 1992)	1986 (4 years follow-up)	Iowa	459/34,388	Food frequency	RR for highest versus lowest quartile: total fat, 1.2 (0.9–1.5); saturated fat, 1.1 (0.8–1.4); monounsturated fat, 1.1 (0.9–1.3); polyunsaturated fat, 1.2 (0.9–1.5)	Cohort consisted of women age 55–69 at start of study (Iowa Women's Health Study cohort); multivariate RRs computed by Cox proportional hazards regression adjusted for total energy

4. Graham (28, 1992)	1980 (8 years follow-up)	New York state	359/18,586	Food frequency	RR for highest versus lowest quintile: total fat, 1.0 (0.7–1.4) animal fat, 1.1 (0.8–1.6); vegetable fat, 1.1 (0.8–1.5)	Cohort consisted of white women over age 50 (assumed to be postmenopausal); multivariate RRs computed by Cox proportional hazards regression adjusted for age and education
5. Willett (105, 1992)	1980 (8 years follow-up)	US	1,439/89,494	Food frequency	RR for highest versus lowest quintile (all women combined): total fat, 0.9 (0.8–1.1); saturated fat, 0.9 (0.7–1.0); monounsaturated fat, 0.9 (0.8–1.1); linoleic acid, 0.9 (0.8–1.1)	Cohort consisted of women age 30–55 at start of study (Nurses' Health Study); multivariate RRs computed by Cox proportional hazards regression adjusted for age, age at menarche, age at first full-term pregnancy, parity, history of breast cancer in mother or sister, history of benign breast disease, menopausal status, alcohol intake, body mass index, total vitamin A intake, total energy intake, and time period; RR similar in pre- and post-menopausal women
6. van den Brandt (97, 1993)	1986 (3.3 years follow-up)	Netherlands	437/1,598 (case-cohort design)	Food frequency	RR for highest versus lowest quintile: total fat, 1.1 (0.7–1.6) saturated fat, 1.4 (0.9–2.1); monounsaturated fat, 0.8 (0.5–1.1); polyunsaturated fat, 1.0 (0.6–1.4)	Cohort consisted of women age 55–69 at start of study; case-cohort study design; multivariate RRs computed by Mantel-Haenszel estimation methods adjusted for age, history of benign breast disease, family history of breast cancer, age at menarche and menopause, oral contraceptive use, parity, age at first birth, body mass index, education, alcohol use, and cigarette smoking; significant trend (P value $<$ 0.05) with increasing quintile for saturated fat
7. Barrett-Connor (3, 1993)	1972–1974 (15 years follow-up)	Rancho Bernardo, southern California	15/590	24-h dietary recall	RR for highest versus lowest quintile: total fat, 2.0 (1.2–3.4)	Cohort consisted of women age 40–79 at start of study; multivariate RRs computed by Cox proportional hazards regression adjusted for age, age at menopause, parity, body mass index, and alcohol; age-adjusted mean intakes of total fats, saturated fats, monounsaturated fats, polyunsaturated fats, oleic acids, linoleic acids, and linolenic acids were significantly higher in cases than noncases
8. Toniolo (95, 1994)	1985–1991 (median 22 months follow-up)	New York City	180/829 (case-control ratio in nested case-control design)	Block food frequency	RR for highest versus lowest quintile: total fat, 1.5 (0.9–2.5); saturated fat, 1.5 (0.9–2.5); oleic acid: 1.6 (0.9–2.7); linoleic acid, 1.1 (0.7–2.0); meat, 1.9 (1.1–3.2)	Cohort consisted of women age 35–65 at start of study; nested case-control study design; multivariate RRs computed by conditional logistic regression adjusted for height, body mass index, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, first-degree family history of breast cancer, history of benign breast disease, race, religion, and energy intake; significant trend (P value $<$ 0.05) with increasing quintile for meat intake

(*Continued*)

TABLE 2 (*Continued*)

Study no.,[a] first author (Ref., year published)	Year (s) of study	Study location	Cases/ cohort[b]	Dietary assessment method	RR (95% CI)[c]	Comments
9. Gaard (21, 1995)	1977–1983 (7–13 years follow-up; average 10.4 years)	Norway	248/25,892	Food frequency	RR for highest versus lowest quartile: total fat, 1.3 (0.9–1.8); saturated fat, 1.0 (0.8–1.6); monounsaturated fat, 1.7 (1.2–2.5)	Cohort consisted of women age 20–49 at start of study; multivariate RRs computed by Poisson regression adjusted for age, height, body mass index, menopausal status, smoking, and energy intake; significant trend (P value < 0.05) with increasing quartile for monounsaturated fat
10. Wolk (108, 1998)	1988–1990 (avg. 4.2 years follow-up)	Central Sweden	674/61,471	Food frequency	RR for highest versus lowest quartile: total fat, 1.0 (0.8–1.3); saturated fat, 1.1 (0.8–1.4); monounsaturated fat,1.0 (0.7–1.2); polyunsaturated fat, 1.0 (0.8–1.3)	Cohort consisted of women age 40–76 at start of study (Sweden Mammography Cohort); multivariate RRs computed by Cox proportional hazards regression adjusted for age, parity, age at first birth, family history of breast cancer, body mass index, education, cholesterol, fiber, alcohol, and total energy intake
11. Holmes (40, 1999)	1980 (14 years follow-up)	US	2,956/88,795	Food frequency	RR for given increment of fat intake per day: total fat (5% of energy), 1.0 (0.9–1.0); animal fat (5% of energy), 1.0 (1.0–1.0); vegetable fat (5% of energy), 1.0 (0.9–1.0); saturated fat (5% of energy), 0.9 (0.9–1.0); monounsaturated fat (5% of energy), 0.9 (0.9–1.0); polyunsaturated fat (5% of energy), 0.9 (0.8–1.0); *trans*-unsaturated fat (1% of energy), 0.9 (0.9–1.0); omega-3 fat from fish (0.1% of energy), 1.1 (0.9–1.1)	Cohort consisted of women over age 30–55 at start of study (Nurses' Health Study); multivariate RR computed by pooled logistic regression adjusted for energy, age, energy-adjusted vitamin A intake, alcohol, time period, height, parity, age at first birth, weight change since age 18, body mass index at age 18, age at menopause, menopausal status, use of hormone replacement therapy, family history, benign breast disease, and age at menarche; RR similar in pre- and post-menopausal women

[a]First two studies are meth-analysis and are not numbered.
[b]Cases/Cohort, number of incident cases in cohort study.
[c]RR, relative risk; 95% CI = 95% confidence interval; OR, odds ratio.

cancer cases, the Nurses' Health Study, did not report any appreciable increases in breast cancer risk with total fat or any other forms of dietary fat (40). Aside from the large numbers of subjects included in the Nurses' Health Study cohort, this analysis also derives its strength from having multiple, repeat assessments of diet over time. No significant associations were found using various permutations of these multiple assessments.

Randomized Controlled Trials

Currently, several randomized controlled trials to test the dietary fat–breast cancer hypothesis are underway, including (*a*) the Women's Health Initiative (108a), which recruited about 65,000 women and will test if a diet low in fat (20% kcal) and saturated fat (7% kcal) will reduce the incidence of breast cancer, and (*b*) the Canadian Diet and Breast Cancer Prevention Study Group (5), which enrolled about 4700 high-risk women randomized to a low-fat (15% kcal) versus "usual" diet (30%–35% kcal) and will test whether the low-fat diet reduces the risk of developing breast cancer. Additionally, a multicenter study called the Women's Healthy Eating and Living trial is investigating whether a healthy dietary pattern, including low fat (20% kcal), maintained for 6 years would reduce breast cancer recurrence in women recently diagnosed with breast cancer. The scientific community eagerly awaits the results from these studies, which are expected to be completed by 2007, although researchers are skeptical that these studies will be able to detect an independent association between dietary fat and breast cancer risk or the applicability of these results to the general population.

USING CAUSAL CRITERIA TO ASSESS THE ASSOCIATION

A critical appraisal (i.e. causal criteria) proposed by Hill (38) can be applied to the controversial association between dietary fat and risk of breast cancer. These criteria include the assessment of the literature for evidence of the consistency and strength of the association, the presence of a dose-response relationship, the temporal relationship, and biological plausibility or mechanism, and they provide a framework for evaluating evidence regarding a potential causal association with data from observational studies (26, 101).

International correlation and time trend studies consistently demonstrate a strong association between fat intake and breast cancer risk (83), but in case-control studies, the pooled OR was only ∼1.35 (between 1.2 and 1.5). When comparing the highest and lowest levels of fat intake, the pooled OR was ∼1.50 (Table 1). However, the strongest designed cohort study (40) failed to produce a consistent association; this may be due to difficulties in detecting small differences in fat consumption.

The dose-response relationship does not seem to be consistently demonstrated in the studies reviewed in Tables 1 and 2, with the exception of a few studies

that demonstrated significant trends in quartiles of fat distribution. The temporal relationship between dietary fat and breast cancer risk is consistent with a causal pathway, as supported by data showing that dietary fat consumed 12–15 years previously appears to be most predictive of subsequent development of breast cancer (26).

Although experimental animal studies provide preliminary evidence of an effect of dietary fat on the growth and proliferation of mammary cells, its metabolic pathway in humans remains to be investigated. Recent advances in molecular epidemiology make the evaluation of the biological mechanism or plausibility more readily available; it is increasingly important to consider this aspect in causal inference (101). Determination of polymophorisms or changes in the levels of hormones, lipids, and their receptors or DNA adducts in women under dietary fat intervention might provide insight into the biological mechanisms explaining the relationship of fat and breast cancer.

METHODOLOGICAL ISSUES

Study Design

Among the hierarchy of epidemiological studies, although analytic studies are superior to correlational studies for making causal inferences between a risk factor and an outcome, they also have their own issues inherent in their design that limit the interpretation of their results. The positive association seen among case-control studies may sometimes be attributed to recall bias, in which patients with breast cancer differentially recall higher levels of past fat consumption than do control subjects (20). Giovannucci and colleagues (23) showed that although an association was not detected among the cohort that completed the food-frequency questionnaire prior to the diagnosis of breast cancer (OR = 0.9), an OR of 1.4 was detected among a selected group of cases and controls who completed a dietary questionnaire after the diagnosis of cancer (23). This study indicates that there may be some factor responsible for the artifactually high estimates arising from case-control studies, or artifactually low estimates arising from cohort studies. It is most probable that recall bias in case-control studies is responsible for these differences in effect estimates between study designs.

Confounding

Although observational studies are ideal for relating an exposure to an outcome in a free-living human population, they are notorious for being affected by confounding (70). This implies that an observed association is partly or completely due to a third, unmeasured factor or the effects of a third factor that was not accounted for in the analysis. The problem of confounding is inherent in both case-control and cohort study designs. Although the randomization process in controlled clinical trials is designed to minimize confounding, intervention studies investigating the

link between dietary fat and development of breast cancer may be vulnerable to the effects of confounding factors as well (48). For example, in the Women's Health Initiative, women will be counseled to adopt an eating pattern that is not only low in total and saturated fat, but also high in fruits, vegetables, and grains. Thus, not only may any observed effects due to total and saturated fats be confounded by the increased consumption of fruits, vegetables, and grains, but also weight loss that may result from the more healthful eating pattern if these factors were also related to breast cancer risk. Although the investigators of the Women's Health Initiative did modify their primary specific aims to address this issue, it is worth noting that it may be difficult to design an intervention study to study the independent effect of dietary fat.

Other sources of confounding can be attributed to the inability to adequately assess and control for other factors, such as alcohol intake, physical activity levels, and body size, which are all proposed risk factors for breast cancer and are also related to dietary fat consumption.

Effect Modification/Interaction

In addition to inadequate adjustment for confounding factors, the results from both case-control and cohort studies may not have been adequately controlled for effect modification by other factors. For example, in the meta-analysis of data from 12 case-control studies, Howe and colleagues (45) showed that although there was virtually no effect of total fat among premenopausal women (OR = 1.1), the effect was large and statistically significant among postmenopausal women (OR = 1.5). Like body weight, the effect of fat on breast cancer may be different by menopausal status. The interaction between dietary fat and menopausal status is biologically plausible, as the effect of fat on breast cancer risk may be mediated through the same estrogen mechanism as endogenous body fat. However, among the studies presented in Tables 1 and 2, only a handful of the reported risk estimates were stratified by menopausal status.

Statistical Adjustment for Total Energy and Other Related Dietary Components

In multivariate regression models, energy adjustment is used to separate the independent effects of a specific macronutrient (e.g. fat) from the other macronutrients (e.g. carbohydrate and protein). The regression coefficient from such models is interpreted as the increase in risk of substituting some defined unit of fat for an equal amount of energy from carbohydrate and/or protein (99). Many researchers question using such models to interpret an independent effect of fat separate from other energy sources on disease risk (30, 99). In addition, there are several different ways to statistically adjust for the effect of energy from sources other than fat (46, 104). It has been demonstrated that the magnitude of the effect of fat differs depending on the statistical method used (62, 77, 97, 107). Thus, our current methods of statistically analyzing specific nutrients in epidemiological studies

may limit our ability to understand the true effect of dietary fat on breast cancer risk.

Measurement Error

Measurement errors can be classified as differential and nondifferential. Nondifferential measurement error, in which misclassification of exposure occurs randomly across groups defined by disease/nondisease status, results in an underestimation or attenuation of the risk estimate from its true value (56, 89). These types of error generally can be attributed to inaccuracy in measurement. The impact of nondifferential measurement error can be illustrated with the RR estimated from international correlational studies before adjustment for measurement error (RR = 1.9), and after adjustment for measurement error (RR = 4) (48, 80). On the other hand, differential measurement error, in which misclassification in exposure occurs differentially between cases and controls or persons with disease and without disease, results in risk estimates that can deviate from its true value in either direction (56, 88, 89). Differential misclassification can be attributed to errors such as recall bias. There are also indications in the literature of differential under-reporting of nutrient intake, in particular fat and total energy, among overweight and less-educated women (80, 110).

Variation in Exposure

The inability of epidemiologic studies to consistently detect a link between fat and breast cancer has also been attributed to an insufficient variation in exposure (i.e. dietary fat intake) within the study population (30, 31, 47, 58, 68, 80, 110). In particular, relatively high intakes of dietary fat are generally found within the US population, as compared with a greater variation in fat intake in lower-risk populations. In addition to a lack of sufficient variation in exposure, in view of the high consumption of fat within the Western population, an "overexposed control group" may also contribute to an inability to detect a significant association between fat and breast cancer (69, 110). To overcome an inability to detect a significant effect of dietary fat due to insufficient variations in exposure, investigators should consider including in future studies a sufficient number of women who consume very-low-fat diets.

Assessment Tools

Much has been written about constructing, validating, and improving on existing food-frequency questionnaires, the most commonly used instrument to assess levels of dietary nutrients in questionnaire-based epidemiologic studies. The food-frequency questionnaire has been criticized for not being able to adequately assess true levels of dietary intake in validation studies. Therefore, even if an association between fat and breast cancer truly exists, it may not be detected using current methodology (30, 80, 110). Greenwald (30) supported this point with the

observation that although an association between dietary fat and breast cancer was not detected using food-frequency questionnaires in the First National Health and Nutrition Examination Survey, neither was one found between fat and risk of cardiovascular disease, a well-established association (30). Thus, the currently available dietary instruments may be inadequate for any epidemiologic analytical studies of dietary fat and breast cancer risk because of the inherent measurement error biases.

Dietary History

Most food-frequency questionnaires usually focus on a narrow time period prior to interview, generally one year. Such tools do not capture cumulative diet over a lifetime, or diet at different periods of life, which may be more relevant to breast cancer causation (48). The relevant periods in influencing dietary fat on breast cancer risk may occur during adolescence, earlier childhood, or even in utero (10, 14, 102). In addition, cohort studies have been criticized for having insufficient follow-up periods, such that the period of maximal influence of exposure, and possible relevant lifestyle and reproductive factors at different periods of life (e.g. during adolescence), may not have been captured (48). The inability of cohort studies to detect a causal association between fat and breast cancer may be attributed to insufficient follow-up periods or not having assessed the relevant period. This is supported by the observation that results from cohort studies of fat intake and colon and prostate cancers have also been inconsistent (110).

Research on the role of adolescent exposures of dietary fat and nutritional status, perhaps the most important in terms of critical time period for breast cancer risk, are needed.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, data from epidemiologic studies have been equivocal in supporting an association between fat and breast cancer risk in humans, with the strongest evidence coming from the studies with the weakest designs (i.e. correlational), and with studies with the most compelling designs (i.e. cohort) overwhelmingly indicating no association. It has been suggested that any associations between fat and breast cancer is likely small or weak and, therefore, undetectable using our existing methodologies in epidemiologic studies. Only a few case-control studies reviewed have assessed childhood or adolescent fat intake on subsequent risk of breast cancer (39, 78). During adolescence, fat intake may promote body growth and earlier onset of menarche, which in turn are risk factors for breast cancer. Because of the possibly long latent period between initiation, promotion, and detection of cancer and the role of dietary fat in this mechanism, researchers suggest using intermediate end points, such as changes in serum estrogen levels or mammographic density, to look for an effect of fat (5, 81).

Taken together, analytical epidemiological studies do not strongly support the etiologic link between high dietary fat in adult life and breast cancer; however, increased risk has been consistently observed in animal and correlational studies. A recent report from the American Institute for Cancer Research suggests that diets high in total fat and saturated fat may possibly increase the risk of breast cancer. The report also affirms that those diets high in monounsaturated fat per se, or polyunsaturated or vegetable fats, possibly have no relationship with the risk of breast cancer, independent of any contribution of total fat (1).

The type of fat may be an important distinction to be considered. In particular, there may be a potential benefit of monounsaturated fat. The observed low rates of breast cancer in southern European countries maybe due to their high use of olive oil in cooking, as indicated by several case-control studies (1, 63, 64, 96). Moreover, it is important to know that dietary history is very complex and we cannot focus on one single item, such as dietary fat. Dietary recommendations should not be based solely on fat reduction, but the number of servings of fruits and vegetables containing specific micronutrients needs to be considered as well so that a combination of protective effects of dietary factors can be achieved. Furthermore, we need to be concerned with the question of what kind of dietary recommendation to offer women who have been diagnosed with breast cancer (41, 42, 69).

Currently, the hypothesis relating dietary fat to breast cancer risk remains viable but unproven. The apparent discrepancies between case-control and cohort studies have often been emphasized, and results from these studies need to be interpreted with proper caution. Measurement errors and recall biases are the major concerns for case-control studies. Lack of follow-up time or not assessing diet during adolescence, which represents the most relevant period of time of breast tissue development and presents a window of vulnerability for later development of breast cancer, are the major concerns for cohort studies. Given the current knowledge of study designs, dietary assessment tools, and statistical methods, additional case-control or cohort studies would likely not provide more useful information. If fat intake can be assessed without much error, appropriate consideration of the proper methods for analyzing dietary data and adjustments for energy intake in epidemiological studies should become a priority area of research.

Markers of susceptibility to breast cancer that can detect women at higher risk for breast cancer or genetic polymophorisms explaining individual differences in fat metabolism may be helpful in clarifying the role of dietary fat. DNA repair proficiency, as Helzlsouer et al (34) have hypothesized, may be a susceptibility factor that predisposes women to breast cancer through increased sensitivity to carcinogenic damages from environmental exposures, such as to dietary fat. The search for genetic markers has been relentless in the past decade (57). Genetic testing of BRCA1 and BRCA2, familial breast cancer genes, appear to be promising; however, this only accounts for less than 10% of breast cancer cases. Subtle defects in DNA repair or apoptosis genes can place women at increased cancer risk. Other candidate genes may also contribute to breast cancer risk. These high-penetrance

genes are not likely to account for breast cancer in the general population, as the majority of breast cancer occurs sporadically; more than 90% of breast cancer cases involve women who do not have strong genetic predispositions (9).

Dietary fat intake in the general population has slightly declined over the past 20 years because the adverse effects of fat, cholesterol, and heart disease are in the forefront of media stories (7). As a result of more healthy eating habits, health benefits may occur, as we may expect to see a decline in breast cancer incidence in the future if indeed the relationship between dietary fat and breast cancer holds true.

Given the challenge of measuring dietary habits more accurately and the debates over the validity of the case-control, cohort, and clinical studies, whether to confirm or to refute the dietary fat hypothesis with breast cancer remains an on-going dilemma. However, the fact that reducing dietary fat intake helps to prevent other major chronic diseases, such as cardiovascular disease, colon and rectal cancers, and possibly prostate cancer, almost makes the point moot.

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