Point-Counterpoint

Role of Dietary Fat in the Causation of Breast Cancer: Point

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Introduction

The question of whether or not a direct association exists between dietary fat and postmenopausal breast cancer risk has been the focus of numerous ecological, migrant, prospective cohort, case-control, and experimental studies conducted over the last several decades (1). No clear answer to this question, however, has yet been uncovered, and a considerable amount of controversy on the topic of dietary fat and breast cancer exists within the scientific community. When carrying out research studies in this area and interpreting their results, it is important to recognize that dietary fat is not a completely independent lifestyle risk factor. The effects of other lifestyle risk factors closely related to dietary fat—including caloric intake, weight gain, obesity, and physical activity—have a high probability of being intricately connected with the effects of dietary fat, *per se*. In fact, the expectation of separating the independent effects of these various factors on breast cancer risk may be unrealistic. Also, individual genetic susceptibilities may further cloud an existing dietary fat-breast cancer relationship. To illustrate, significantly increased breast cancer risk has been reported for postmenopausal women in the highest quartiles of exposure for total meat intake (a source of dietary fat) and for heterocyclic aromatic amines from cooked meats (2). Considering that polymorphisms in *N*-acetyltransferase 2—a xenobiotic metabolizing enzyme that influences detoxification rates of heterocyclic aromatic amines—determine whether postmenopausal women are slow acetylators or fast acetylators (3), measurement of the contribution to cancer risk by dietary fat from meat sources, particularly across studies, could readily be confounded by the acetylator status of the study population. Such differences in inherited genetic susceptibility, which result in environmental factors being a more important contributor to breast cancer in only some proportion of a study population, can limit the ability to detect associations because of misclassification of outcomes (4). Considering the integrated contributions to breast cancer risk stemming from individual genetic variations and the lifestyle factors noted above, there is little likelihood that epidemiological data alone can provide a definitive answer to what is undoubtedly a very complex relationship. In addition, methodological issues related to dietary assessment in epidemiological studies contribute further uncertainties to data interpretation. Although recognizing the limitations of an epidemiological approach to determining the true association between diet-related lifestyle factors and disease risk, epidemiological evidence, supported by consistent results from animal studies, has clearly suggested direct associations between breast cancer risk and total dietary fat, types of fat, obesity, weight gain, and physical activity.

Epidemiological Evidence

Dietary Fat. Epidemiological studies provide conflicting results regarding the association of dietary fat and breast cancer (1, 5). International correlation coefficients between fat intake and breast cancer incidence and mortality rates are high, generally ranging from 0.7–0.8 (6–8). Also, migrant and time-trend studies support an increased risk for breast cancer as eating patterns shift from a low-fat, high-fiber diet to a high-fat, low-fiber "Western" diet (9, 10). Individual case-control and cohort studies, comparing highest *versus* lowest quartiles/quintiles of fat intake, generally have not always found a clearly significant association between fat intake and breast cancer risk (1, 5). A combined analysis of the original data of 12 case-control studies found a significant direct relationship in postmenopausal women between breast cancer risk and both total fat intake ($RR^2 = 1.46$) and saturated fat intake (RR = 1.57; Ref. 11). One meta-analysis found a RR of 1.21 for breast cancer (for premenopausal and postmenopausal women combined), based on fat intake in 16 case-control studies (12). In contrast, large cohort studies generally have failed to demonstrate a link between dietary fat intake and breast cancer risk (1, 5). Two separate meta-analyses reported RRs of 1.01 for seven cohort studies (12) and 1.05 for seven cohort studies (13) investigating the impact of dietary fat on breast cancer development; five of the same cohort studies were included in both meta-analyses. One of these meta-analyses reported similar results for both premenopausal and postmenopausal women (13). Results of the Nurses' Health Study, which followed approximately 89,500 women for 8 years, indicated that total fat intake did not affect breast cancer incidence (14). One study of nearly 26,000 Norwegian women, however, reported a RR for breast cancer of 2.44 among women who ate meat at least five times a week, compared with those who ate meat no more than twice a week (15).

Although the relationship between total fat intake and breast cancer risk continues to be debated, a growing body of epidemiological literature suggests that the dietary fat-breast cancer association may be a result of the type of fat consumed rather than, or in addition to, total fat intake (1). International comparisons indicate that diets high in n-6 PUFAs (as found in corn oil) are associated with increased breast cancer risk (7). In contrast, consumption of oleic acid, a monounsaturated fatty acid found in olive oil, and n-3 PUFAs, which are present in certain fish and fish oils, do not increase and may even reduce risk of breast cancer (7, 16–18). A comprehensive assessment of evidence from animal, ecological, and analytic epidemiological studies linking olive oil and breast cancer concluded that a

Received 8/23/98; accepted 8/23/98.

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[2] The abbreviations used are: RR, relative risk; EURAMIC, European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Cancer; BMI, body mass index; FFQ, food frequency questionnaire; PUFA, polyunsaturated fatty acid.

modest protective effect of olive oil on breast cancer risk seems likely, but the evidence is not yet conclusive (18). Such evidence raises the question as to whether this observed protective effect is a result of the monounsaturated fat component of olive oil, other olive oil constituents such as polyphenolic compounds (19) or the hydrocarbon squalene (20), or some combination of these. To address this question, a prospective study was conducted to determine the effects of specific types of dietary fat on breast cancer risk in a cohort of more than 61,000 women in Sweden, a country with very low consumption of olive oil (21). Findings indicated that, for the highest *versus* the lowest quartiles of intake, monounsaturated fat was associated with reduced risk (RR = 0.8) and polyunsaturated fat was associated with increased risk (RR = 1.2). Saturated fat was not associated with breast cancer risk in this study.

Using data from the EURAMIC breast cancer study, the ratio of long-chain n-3 fatty acids in adipose tissue to total n-6 fatty acids showed an inverse relationship with breast cancer risk in four of five study centers (22), providing evidence that the balance between n-3 and n-6 fatty acids may be important in breast cancer. In this study, percentages of n-3 fatty acids, *per se*, were not associated with breast cancer risk. Findings from the EURAMIC study are supported by ecological mortality data for breast cancer for 24 European countries that show an inverse correlation with fish and fish oil consumption, when expressed as a proportion of animal fat (16). *Trans* fatty acids also have been investigated in relationship to breast cancer. Data for primarily postmenopausal breast cancer patients from the EURAMIC study found direct associations between increased breast cancer risk and the concentration of *trans* fatty acids (RR = 1.4; $P < 0.001$) and PUFAs (RR = 1.26) in gluteal adipose tissue. The most significant effect of *trans* fatty acids (RR = 3.65) was seen at the lowest tertile of PUFAs (23).

Caloric Intake/Weight Gain/Obesity. In general, diets high in total calories, which may contribute to weight gain and obesity, seem to increase the risk of breast cancer (1). Epidemiological studies have investigated the roles of factors related to caloric intake—including weight, body size (as measured through BMI), and weight gain—in relation to breast cancer risk, particularly in relationship to menopausal status (1, 5). In some studies, obesity before menopause seems to protect against breast cancer, whereas postmenopausal obesity is associated with increased risk (24, 25). With the onset of menopause, estrogen derived from the conversion of androgens in adipose tissue predominates. Thus, obese postmenopausal women, compared with their leaner counterparts, may have an elevated risk for breast cancer owing to higher levels of circulating estrogen secondary to the increased metabolic activity in adipose tissue (26, 27).

Gaining weight after age 18 and being overweight during the premenopausal years also seem to increase a woman's risk for breast cancer after menopause (25, 28, 29). In contrast, weight loss before, as well as after, menopause is associated with reduced risk (25). Some data suggest that high caloric intake and rapid growth during youth may increase breast cancer risk (30). A recent study reported that the risk of breast cancer in women who reached their maximum height when they were age 18 years or older was reduced by 30% compared with women who reached their maximum height when they were age 13 years or younger (31).

Physical Activity. A number of case-control and cohort studies have investigated the roles of either occupational, recreational, or total physical activity (energy expenditure) in relation to breast cancer risk (32, 33). Although the evidence for a protective effect of physical activity is inconsistent overall, some data are encouraging. A recent review of epidemiological studies published from 1966 to the present on the effect of physical activity on breast cancer risk reported that 11 of 16 studies found a decreased risk (12–60%) among premenopausal and postmenopausal women as their level of recreational exercise increased (33). Also, higher levels of occupational physical activity were associated with decreased risk in seven of nine studies. The reductions in breast cancer risk, however, were not statistically significant in some of these investigations (33). Findings from several studies have suggested that exercise protects against breast cancer regardless of menopausal status. For example, in one case-control study, women ages 20–74 years who expended more than 4000 kilocalories/week in recreational physical activity showed lower breast cancer risk (RR = 0.60, premenopausal; RR = 0.73, postmenopausal) than those who reported no recreational activity (34). Also, data from a large cohort study in Norway indicated that, compared with a sedentary lifestyle, regular exercise reduces risk in both premenopausal (RR = 0.53) and postmenopausal (RR = 0.67) women. Risk of breast cancer was lowest in lean Norwegian women (BMI = 22.8, premenopausal and postmenopausal combined) who exercised at least 4 h/week (RR = 0.28). Sustained physical activity, which leads to weight loss as well as loss of body fat, helps reduce circulating levels of estrogen and progesterone, and possibly cancer risk.

Methodological Issues

The totality of the epidemiological evidence that has been collected on breast cancer risk and lifestyle components—including dietary fat, caloric intake, weight gain, obesity, and physical activity—clearly supports a relationship between diet-related lifestyle factors and disease risk, although findings are not consistent across all studies. As noted previously, the independent effects of these lifestyle components likely are very difficult to separate, leading to some inevitable degree of confounding. In addition, several other factors may contribute to the inability of epidemiological studies to detect breast cancer risk associations for individual lifestyle components, including measurement error (both random and systematic) in dietary assessment, differences in methods of data collection and analysis among studies, insufficient variation within a study population, failure to distinguish between premenopausal and postmenopausal women, insufficient follow-up period, and the importance of diet and other lifestyle components before adulthood (8, 36–38).

Measurement Error. Both systematic and random errors can contribute to measurement error in dietary intake data (36, 37, 39). One source of random error is the natural variation in day-to-day eating patterns, which studies usually try to minimize by investigating dietary intake over a relatively extended period, using measures such as diet histories or FFQs (37). Use of such dietary assessment measures can introduce systematic error, frequently the result of either underreporting or overreporting of intake. Although incorrect reporting may be intentional in some cases, many individuals simply do not really pay close attention to what they eat and, thus, may be unable to report their dietary intake reliably, particularly past intake. Errors in food composition databases used to analyze the data collected by measures of dietary intake also can contribute to systematic error (37).

The FFQ, which is relatively inexpensive and easy to administer to large study populations, has been used widely in cancer epidemiology studies to assess dietary intake. In indi-

vidual studies, FFQs generally are validated against a reference method of dietary assessment, such as a diet record—that is, a detailed record of the types and quantities of all foods and beverages consumed during a specific period, usually between 3 and 7 days. Although such diet records are considered to be the "gold standard" for dietary assessment, research suggests that individuals keeping dietary records may underestimate their usual intake substantially. For example, free-living men and women in a controlled feeding/metabolic study, even when trained in keeping accurate records, underreported their energy intake by about 18%; age had no effect on reporting (40). An analysis of self-reported dietary intake data (24-h recall) from 11,663 adults in the Second National Health and Nutrition Examination Survey indicated that up to 31% of these individuals underreported their food consumption (41). Women were five times as likely as men to underreport their intake, and Caucasians more than twice as likely as non-Caucasians. The effect of BMI also directly influenced underreporting, with the odds of underreporting increasing by 16% for every 1 unit increase in BMI. In one study that used the doubly labeled water technique, which permits an accurate measure of energy expenditure, self-reported intakes of obese women, measured by weighed food records, were only about 73% of energy expenditure (42). Such underreporting in women may be a result, in part, of social desirability—the tendency to respond in such a way as to avoid criticism. For example, a higher social desirability score has been associated with underestimation of total fat and energy intakes in women, but not in men (43).

Underreporting has serious consequences in terms of misclassification in epidemiological studies; this is illustrated clearly by the following example. In the Nurses' Health Study 8-year follow-up, the reported daily caloric intake by women in the lowest quintile was only 1130 kilocalories, an unrealistically low value suggesting that some women in this study underreported their dietary intake substantially. Kuller (44) has pointed out that, according to the 1980 Recommended Dietary Allowances, a 130-pound woman who is moderately active would be expected to consume about 2000 kilocalories daily (45). Thus, there may be as many as 800 kilocalories missing from the caloric intake of the first (lowest) quintile of women in the Nurses' Health Study (44). Assuming the women followed a diet that had 30% of calories from fat, there may be as many as 27 grams of fat [$(800 \times 0.3) \div 9$] missing from the fat intake of the first quintile. This additional amount of fat could move a woman from the lowest to the highest quintile of fat intake (14, 44).

In a carefully designed validation study conducted by Willett *et al.* (46), 173 female nurses were requested to keep detailed dietary records for 7 days on four separate occasions, approximately 3 months apart. These women also completed a semiquantitative FFQ on two separate occasions. Using data from this study, Byar and Freedman (36) cross-classified quintiles of calorie-adjusted grams of fat for the second FFQ with the quintiles of average fat intake from the four 7-day food records. If the FFQ and the diet records measured exactly the same thing, with no measurement error, a direct correlation of 1.0 would result; that is, subjects classified in the lowest quintile of fat intake by the FFQ also would be in the lowest quintile for the diet record. However, the correlation between the lowest quintile (quintile 1) for fat intake by FFQ and the lowest quintile by diet record was 0.53. That is, only 53% of women in the lowest quintile by the questionnaire were also in the lowest quintile by diet record—indicating a measurement error of 47% for this quintile. The correlations were considerably lower—with correspondingly higher measurement errors—for the other quintiles, having values of 0.40, 0.29, 0.26, and 0.33 for quintiles 2, 3, 4, and 5 (highest), respectively (36). These low correlations are an indication of substantial measurement error and consequent misclassification. When a nondifferential measurement error in dietary assessment, which affects both cases and controls, is present in epidemiological studies, the RR will be underestimated such that values will be attenuated; that is, values will be biased toward 1.0, reducing the chances of finding an existing diet-cancer relationship (36, 47).

To investigate the effects of both systematic and random error in epidemiological studies on the likelihood of finding diet and cancer associations, Prentice (39) used data from FFQs and 4-day food records collected in the original Women's Health Trial to develop a new dietary measurement model. This model links measurement error parameters to BMI and incorporates a random underreporting quantity for self-report instruments. Application of this model to international correlation data on dietary fat and postmenopausal breast cancer showed that if both systematic and random errors in dietary assessment are overlooked, the projected RR is 4.00 for the FFQ and 3.08 for the 4-day food record, for the 90% *versus* the 10% fat intake percentiles. Acknowledging the presence of random error, but not systematic error, results in a projected RR of 1.42 for the FFQ and 1.54 for the 4-day food record. Acknowledging that both systematic and random measurement errors are present results in a projected RR of only about 1.10, for either the FFQ or the 4-day food record. These findings highlight the importance of measurement error in dietary assessment in epidemiological studies and clearly suggest that FFQs and diet records may not be adequate to determine a link between dietary fat and postmenopausal breast cancer, even if a strong association exists (39).

Other Issues

In addition to the uncertainty in epidemiological results introduced by measurement error, several other methodological issues likely contribute to the inconsistent results among studies investigating a relationship between either dietary fat or related lifestyle factors and breast cancer. For dietary fat, the issue of correlated variables is immediately apparent, considering that total caloric intake also may contribute to breast cancer risk, and that the correlation between fat intake and total calories is estimated to be about 0.88 in the general population (36). The statistical power of a study is decreased markedly when correlated variables are present so that it is difficult to detect real effects unless sample sizes are very large (36). Consequently, most studies attempt to adjust for correlated and other confounding factors such as BMI or physical activity by using various statistical methods. If the method selected differs among studies, however, interpretation of results across studies may not be straightforward.

Because of the high correlation of total fat with total energy, various methods for energy adjustment have been used in studies investigating the effect of dietary fat on breast cancer risk, including the standard multivariate method (48, 49), the residual analysis method (14, 50, 51), the energy partition method (52, 53), and the nutrient density method (48, 49). Use of different approaches to adjustment for energy intake may contribute to the inconsistency observed among study results and certainly contributes to the difficulty of comparing results across studies. Some researchers have concluded that, even with the use of energy-adjustment methods, it is impossible to separate completely the effects of energy and individual ma-

cronutrients in cancer etiology; however, the effect of change of macronutrient profile can be estimated (54).

Population variables can contribute to heterogeneity among studies, making comparisons among studies less meaningful. Often overlooked in epidemiological studies of diet and breast cancer is the range of fat intake, which may be too narrow for any significant effect to be observed. For example, fat intake (percentage of calories) for women in the validation study for the Nurses' Health Study ranged only from 32–44% (55). Furthermore, it is possible that a threshold level exists for the effect of fat on tumor promotion and that the lowest percentage of fat intake among individuals or groups in any particular study population is higher than the threshold (8).

Menopausal status of the study population also can contribute to the lack of a clear association between diet-related lifestyle components and breast cancer risk. Epidemiological studies of breast cancer that have included premenopausal women have discovered that factors associated with risk of breast cancer before menopause can have different and, as in the case of BMI, even reversed effects after menopause (56). It is possible that dietary components such as fat may influence breast cancer risk partly through hormonal connections; thus, menopausal status may contribute to inconsistencies in findings among epidemiological studies.

Meta-analysis, a statistical tool with both inherent strengths and weaknesses, has been used to combine outcomes from case-control and cohort studies on dietary fat and breast cancer risk (12, 13). Meta-analysis is an important innovation for increasing statistical power in epidemiological studies and for uncovering patterns among study results. However, it relies on previously published data that may be biased, to some degree, by both systematic and random measurement errors. Also, meta-analysis can introduce new bias by inappropriately pooling heterogeneous studies. Finally, various techniques for meta-analysis are available that have the potential to yield apparently conflicting summary estimates, even when combining results from the same studies (57–59). The summary RRs of 1.01 (12) and 1.05 (13) from meta-analysis of cohort studies on the association between total dietary fat and breast cancer risk suggest only a weak relationship. These results, however, are in agreement with projected RRs from the dietary measurement model proposed by Prentice (39) and do not rule out dietary fat—either alone or combined with other environmental and genetic factors—as a contributor to breast cancer risk.

Conclusion

Although recognizing that the evidence for a dietary fat-breast cancer relationship is not entirely consistent, it also must be recognized that the methodology generally used to determine dietary intake is far from perfect and that dietary fat is closely correlated with other lifestyle factors. Given these considerations, inconsistencies in results across epidemiological studies certainly are not surprising. In fact, it has been suggested that, in epidemiological studies, significant correlations likely are meaningful, because of the odds against finding such relationships (8, 60). The difficulty of finding diet-disease relationships was demonstrated dramatically by Kuller (61), who, using the same database as the follow-up epidemiological study of the First National Health and Nutrition Examination Survey—which found no relationship between dietary fat and breast cancer risk (50)—determined that the database also did not support a relationship between saturated fat/cholesterol intakes and either blood cholesterol levels or risk of coronary artery disease, although saturated fat and cholesterol are established risk factors for coronary artery disease.

It is not realistic to expect that all methodological problems will be solved in the near future. Some problems, such as elimination of dietary assessment error, may not be readily solvable. In fact, Beaton (37) argues that the lack of understanding and appreciation of measurement errors is a greater limitation than the errors, *per se*, and suggests that development of statistical methods to address measurement errors could be more valuable than improvements in dietary assessment methodology. Even meta-analysis of epidemiological studies, although a useful statistical technique in many respects, will not provide a definitive answer to the question of whether or not a direct association exists between dietary fat and breast cancer risk. The best hope of finding this answer rests with randomized, controlled clinical trials, such as the Women's Health Initiative (62, 63) and the Women's Intervention Nutrition Study (64, 65), both presently under way.

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