Role of Dietary Fat in the Causation of Breast Cancer: Counterpoint[1]

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Evaluating the hypothesis that dietary fat intake in adult life is positively related to breast cancer risk has been a major challenge in nutritional epidemiology since the 1970s. The fact that we are still debating the issue in 1998 illustrates how difficult it is to obtain agreement on epidemiological evidence when hypothesized RRs[3] are modest. The debate also depends on beliefs about the relative merits of animal experimental data and ecological studies compared with observational data from humans in assessing diet-disease associations.

A large body of cohort data indicates that any relation between total dietary fat intake and breast cancer risk is at most very weak, and that an inverse relation is as likely as a positive relation. The arguments used to support a positive relation break down into the following general categories: (*a*) exposure misclassification (*i.e.*, measurement of intake of total dietary fat) is sufficiently high that RRs in observational studies are biased to the null; (*b*) the range of fat intakes studied in Western populations is too narrow to reliably detect a difference in risk; (*c*) ecological study designs are superior to prospective cohort studies of this issue; and (*d*) a randomized trial design is the only way to reach valid conclusions for this and other nutritional hypotheses.

In this review, I will address the above arguments in turn and conclude by briefly reviewing the evidence on two modified hypotheses relating the type of dietary fat and dietary fat intake at a young age to breast cancer risk.

Measurement of Dietary Fat Intake

Nondifferential misclassification of any nutritional variable can substantially attenuate the relation between the exposure and the outcome. Standard theory predicts that if the correlation between measured intake of a nutrient and true intake is $r = 0.50$ (and both measures of intake have the same SD, as occurs when using quintiles), then a true RR of 3.00 will be observed as a RR of 1.73; a true RR of 1.5 will be observed as a RR of 1.22 (1). Thus, the accuracy of current methods of measuring total dietary fat intake is the crux of the question of how to interpret the available epidemiological evidence.

No perfectly valid reference or gold standard method for measuring true fat intake exists. The conventional method is to use multiple days or weeks of dietary records in which partic-

ipants weigh and record their food intake. Alternatively, a large number of 24 h recalls (*i.e.*, subjects are asked to recall everything they have consumed in the previous 24 h) are used. Estimates of nutrient intake from these methods are then compared with estimated intakes from the same subjects using the methods used in large epidemiological studies, typically, a food frequency questionnaire. Many studies of this nature have been done in many diverse populations (1). The correlations between total fat intake measured by food frequency questionnaire and diet records are typically between $r = 0.40$ and $r = 0.60$ (1). This correlation is likely to underestimate the true correlation between observed total fat intake and true intake, because the reference method is clearly inaccurate. Another source of inaccuracy in the reference standard is that only a limited number of days or weeks of intake are sampled. Within-person variability in intake ensures that the correlation of the estimates derived from the period sampled with true long-term intake is less than $r = 1.0$. Fortunately, if the period is sampled at random, methods exist to correct for the attenuation in the correlation due to this within-person variability (2). Typically, with 1–2 weeks of diet records, these deattenuated correlation coefficients are about 0.1 higher than the uncorrected correlations; *i.e.*, typical deattenuated correlations between observed and true dietary fat intake are about $r = 0.5$ to $r = 0.7$. Similar methods can be used to deattenuate RRs for the relation of dietary fat intake and breast cancer in studies for which the correlation between the food frequency estimate of dietary fat intake and a reference method is known (3).

Assuming that reporting of dietary fat intake is nondifferential, this degree of misclassification can substantially affect our ability to detect modest RRs. International correlation studies that relate per capita fat intake with national breast cancer incidence suggest a RR of 1.9 comparing the 90th with the 10th percentile of percent energy from fat (4). Using the above assumptions about nondifferential measurement error, we should observe typical RRs of 1.38. In fact, the pooled RR for this difference in fat intake from a study that pooled data from the six largest prospective studies of this issue was 1.05 (95% CI, 0.94–1.16; Ref. 5). The upper bound of this CI excludes all but a small increase in risk and is clearly incompatible with the RRs projected from the international correlation.

Another argument used to suggest that measurement error of total fat intake is extreme is that studies of cardiovascular disease have "failed" to observe a positive relation between total fat intake, or saturated fat intake, and cardiovascular disease, allegedly because the estimates of fat intake have low validity. Metabolic studies indicate that this "failure" reflects the complexities of the relations between different types of fat and atherosclerosis. In fact, recent studies have demonstrated that food frequency estimates of the Key's score (based on the response of serum cholesterol in metabolic studies to changes in saturated, monounsaturated, and polyunsaturated fatty acids) predict coronary heart disease incidence (6).

Thus, nondifferential measurement error is highly unlikely to explain the lack of association between total fat intake and breast cancer incidence in prospective studies. The above dis-

cussion assumes independence of measurement error in the food frequency questionnaire and the reference method. This independence has been challenged, and the argument has been made that some subjects may underestimate their total fat intake in both methods. Few data exist for this assertion. Even fewer data exist for the additional assertion that this phenomenon is more likely among obese people. If this were true, a positive relation between total fat intake and breast cancer may be obscured because overweight women (who are at modestly higher risk of postmenopausal breast cancer; Ref. 7) may underreport calories from fat. Prentice (4) has developed a measurement error model that assumes a strong inverse correlation between body mass index and self-reported total fat intake. However, this correlation was not observed in any of the six component studies of the Pooling Project of Diet and Cancer (8). In this study, the relation of energy-adjusted dietary fat and breast cancer risk was consistently null across strata of body mass index, strongly refuting the likelihood of bias due to underreporting of fat intake associated with obesity. An additional argument that reporting of calories from fat is differential according to body mass index proceeds from the data that suggest that obese people underestimate their true caloric intake (9). The existence of this phenomenon is not in dispute, the key question is whether the proportion of calories from fat is related to body mass index; on this point, most studies suggest that it is not (10, 11).

Most of these questions could be put to a direct empirical test if we had a valid biochemical indicator of total fat intake. Unfortunately, no such indicator exists. However, it is well established that exogenous fatty acids such as linoleic acid, *trans* fatty acids, and ω-3 polyunsaturated fatty acids are stored in adipose tissue and reflect the dietary intake of these types of fat (as opposed to saturated and monounsaturated fats that can be produced endogenously from carbohydrates). Multiple studies have shown that correlations of 0.5 and higher are typical (12, 13) when food frequency questionnaire estimates of exogenous fats are compared with the concentration of these fats in adipose tissue. It is unlikely that subjects would report these particular fats relatively accurately and report the other fatty acids so inaccurately as to completely invalidate estimated intakes of total dietary fat.

Range of Total Fat Intake in Observational Studies

The range of fat intake in a study conducted within a single population will of course be less than that which occurs across populations. Studies of the dietary fat hypothesis have been criticized as having too narrow a range of observed dietary fat intakes (14). Typically, however, the range of intake between the top and bottom quintiles of observed total fat intake in a North American study is about 15% of calories from fat, which is not, in fact, a small difference. One of the principal motivations of the pooling project referred to above was to stabilize estimates for more extreme comparisons. In that study (5), the RR for an estimated fat intake of 30–35% of calories from fat was 0.94 compared with an intake of <20% of calories from fat. The RR for highest (>45% of calories from fat) *versus* lowest (<20% of calories from fat) fat intake was 0.99. These data suggest that if the populations studied are sufficiently large, a sufficient number of women with extremely low and high total fat intakes can indeed be observed, even in Western populations.

Study Design

Proponents of the dietary fat hypothesis have consistently pointed to ecological studies of dietary fat intake and breast cancer incidence and mortality rates as strong evidence for the hypothesis (15). Even the investigators who originally described the positive correlation between estimated per capita dietary fat intake and breast cancer rates pointed out the key flaw of ecological studies: confounding by other correlated variables. The prevalence of breast cancer risk factors such as low parity, late age at first birth, late age at menarche, increased height, and postmenopausal obesity is higher in developed countries with higher fat intake, predicting higher breast cancer incidence in these countries. The relation between estimated per capita gross national product and national breast cancer rates is actually slightly stronger than the relation with dietary fat intake (16). Supporters of the fat hypothesis still use this ecological argument because other supportive human data are lacking. It is hard to think of other areas of epidemiology in which ecological correlation studies are still offered as important evidence of likely causality almost 25 years after they were conducted.

The intuitive appeal to the public of an ecological correlation is strong and is presumably the reason why the dietary fat-breast cancer hypothesis has become accepted wisdom in some quarters. We teach students of epidemiology, however, that ecological studies should be used for hypothesis generation and have severe limitations for testing etiological hypotheses (17). In view of the consequences of having to retract guidelines for disease prevention that have been widely believed by the public, it is unfortunate that ecological studies for this particular issue have been so heavily promoted as credible evidence of causality.

Animal Studies

It is clear from animal studies that a restriction of energy intake substantially lowers the incidence of mammary and other tumors (18). Thus, controlling for energy intake in animal experiments is crucial. Meta-analyses of the animal literature reach different conclusions with respect to the influence of dietary fat after controlling for energy. Albanes (19) concluded that after adjustment for energy intake, experiments in mice showed essentially no relation of fat intake and mammary tumor incidence. A review by Freedman *et al.* (20) concluded the association was positive. Perhaps the major limitation of animal studies is the uncertain generalizability to humans of results generated in models in which animals are given chemical carcinogens to increase tumor yield.

Case-Control Studies

Until recently, most epidemiological data on dietary fat and breast cancer risk have been from case-control studies. In a pooled analysis of 12 studies, Howe *et al.* (21) observed statistically significant heterogeneity of the estimates of the association between total fat intake and breast cancer. In a subset of eight of these studies, the estimate of the RR for the fifth quintile *versus* the first quintile was 1.46, with a highly significant trend across quintiles ($P = 0.0002$). However, this pooled analysis did not include the largest available case-control study in which there was no relation between total fat intake and breast cancer risk (22). Case-control studies of diet and cancer are difficult to interpret; reporting of past diet could be influenced by a dietary change after diagnosis or beliefs about the aspects of diet that may have been associated with the occur-

rence of cancer. Few studies have been able to compare the past diets of individuals reported before and after breast cancer diagnosis. Giovannucci *et al.* (23) asked women in a prospective study who had been diagnosed with breast cancer after completing a food frequency questionnaire to fill in another food frequency questionnaire after the diagnosis. Compared with controls who completed questionnaires at the same time, there was no material association of dietary fat intake with breast cancer risk prospectively. However, using questionnaires completed after diagnosis, a positive relation was present. In a similar exercise, Friedenreich *et al.* (24) did not observe evidence of this phenomenon. The best interpretation of these data is that case-control studies of diet and cancer are unreliable sources of evidence, and a very high degree of consistency across studies (which does not exist in the instance of dietary fat and breast cancer) is necessary before they can be used as strong evidence for a diet-cancer relation.

Cohort Studies

In recent years several cohort studies have published prospective data; the number of cases (4980 cases) in a pooled analysis of these studies (5) was actually larger than the number of cases (4427 cases) in the previous pooled analysis of case-control studies (21). As described above, no association was observed across a wide range of dietary fat intakes. Of particular importance, the association was very close to the null comparing dietary fat intakes of <20% with 30–35% of calories from fat (RR, 1.06; 95% CI, 0.83–1.37). Some studies have reported positive relations only in certain subgroups, such as women with a family history or another risk factor; in the pooled analysis, the association was essentially null within strata of established breast cancer risk factors (25). Most epidemiological studies have measured dietary fat intake on one occasion (with a reference period for the dietary intake averaged over several weeks or up to 1 year). In the Nurses' Health Study, Holmes *et al.* (26) were able to average dietary fat from up to four questionnaires administered over a period of up to 10 years; no relation between total dietary fat intake and breast cancer was present. Thus, the evidence from cohort studies is that there is unlikely to be an important positive relation between total fat intake and breast cancer risk.

Intervention Studies

The paradigm for epidemiological study design is the randomized controlled trial. For the limited number of issues for which it is feasible and ethically appropriate to randomize exposure, a body of controlled clinical trials is to be preferred to observational studies. However, even in drug trials in which the exposure can be accurately measured and masked, randomized trials of the same drug do not always reach the same conclusion, and meta-analyses of multiple studies are needed. The dietary component of the WHI was undertaken as the study to answer the question of dietary fat and breast cancer. Even if the investigators can cope with the difficulties that have marred other large complex trials in the past, such as noncompliance in the intervention arm and secular trends in the comparison arm toward the intervention group, a single key problem remains: the trial, as conceived, will not answer the question it set out to answer. The investigators state that "Women in the dietary intervention group will be counseled to adopt a dietary pattern this is high in fruits, vegetables, and grain products and low in total fat and saturated fat" (27). Although evidence is very limited that fruits and vegetables are as protective against breast cancer as they are against cancer at other sites, the WHI diet cannot be interpreted as a test of the dietary fat hypothesis; if the WHI diet is beneficial, it is possible that replacing carbohydrates with fruits and vegetables may be equally beneficial. The WHI investigators conceded this point some time ago, calling the trial a test of the "low fat eating pattern" and stating that the randomized design "will not permit estimation of the separate effects of fat, micronutrients, and fiber" (28). A general dietary pattern is being tested, not total fat intake specifically.

An additional potential difficulty in interpreting the intervention studies is that pilot data on the effect of low-fat diets show a consistent tendency toward lower caloric intake in the intervention arms, with subsequent weight loss. In the WHI feasibility study (29), the mean caloric intake as measured by 4-day food records was 22% lower at 2 years than at baseline in the low-fat diet group, compared with 5% lower in the control group. Not surprisingly, weight dropped by 1.9 kg in the low-fat diet group compared with 0.1 kg in the control group. Given the established relation between weight gain and postmenopausal breast cancer (7), any diet that causes long-term weight loss or prevents weight gain will decrease breast cancer incidence, regardless of whether fat, carbohydrates, or protein restriction or a combination of these was responsible for the reduction in caloric intake.

What Is the Mechanism by Which High Dietary Fat Intake May Cause Breast Cancer?

Given the continuing enthusiasm for this hypothesis, it is surprising that there is also little in the way of plausible mechanisms by which total fat intake would be expected to increase breast cancer risk. There is strong evidence that plasma estrogen levels predict breast cancer risk. One would expect it to be fairly simple to establish which dietary factors predict plasma estrogen levels. Unfortunately, measurement of plasma hormone levels among premenopausal women is complicated by variability over the menstrual cycle. Among postmenopausal women, the levels are stable but very low and subject to substantial laboratory error in measurement (30). Several studies have examined whether altering dietary fat intake alters plasma estrogens among postmenopausal women. In a crossover study comparing a standard diet (40% of calories from fat) with a low-fat diet (20% of calories from fat), Ingram *et al.* (31) showed reductions in serum cholesterol but not in estrogens in postmenopausal women. Prentice *et al.* (32) reported a 17% reduction in the average estradiol concentration after 10–22 weeks of a low-fat diet, but these women had also lost an average of 3.4 kg in weight, reflecting a large decrease in caloric intake. Furthermore, this study had no control group, and the participants were early postmenopausal women in whom estradiol levels would be expected to be falling. Rose *et al.* (33) conducted a randomized trial of a low-fat diet and reported that women with higher baseline estradiol concentrations experienced a significant reduction in serum estradiol. However, this reduction was due to regression to the mean among women with initially high values (1); overall, there was no change in estradiol levels. Boyd *et al.* (34) observed that estradiol levels declined more often over 2 years among women in their low-fat intervention group than among controls. However, these women also reported a 7% reduction in caloric intake and maintained stable weight over 2 years, whereas women in the control group reported a 4% increase in caloric intake and an average weight gain of 1.3 kg. Several large cross-sectional studies of determinants of blood estrogen levels

have not observed positive relations with dietary fat intake, although a strong positive relation with body mass index is consistently observed (35–37). Thus, there is little evidence from these studies for a specific effect of dietary fat intake on raising blood estrogen levels.

Are There Alternative Hypotheses Worth Testing?

Type of Fat. Like entrenched hypotheses in other fields, concentrating on the total fat hypothesis may have limited our thinking on other promising areas of research. Cardiovascular researchers have usually been at pains to disentangle the different metabolic effects of types of fat, at least at the level of saturated, monounsaturated, and polyunsaturated fatty acids. Some recent evidence supports a similar direction with respect to breast cancer, notably the hypothesis that monounsaturated fatty acid intake may be inversely related to breast cancer risk. In Greece, for instance, breast cancer rates have been among the lowest in Europe, despite a relatively high intake of dietary fat (mainly monounsaturated fatty acids due to the olive oil-based cuisine). In case-control studies in Greece (38), Italy (39), and Spain (40), women who consumed more olive oil had a significantly lower risk of breast cancer. In Northern European and North American studies, the analysis of type of fat is substantially complicated by the fact that the major dietary contributors to monounsaturated fat intake are animal products; thus, saturated and monounsaturated fatty acid intakes tend to be highly correlated. The Southern European studies raise the specter that dietary guidelines that focus mainly on total fat intake, for instance, urging Greek women to replace monounsaturated fatty acid intake with carbohydrates, may actually do harm.

Age of Exposure. An important caveat to all discussions of the epidemiological evidence is that most studies have only assessed the relation of dietary fat intake in the recent past or with up to about 5 years of follow-up. It is important to note that this limitation also applies to intervention studies, because the studies are predicted to be run for no more than 10–15 years. Thus, we do not have observational epidemiological evidence to evaluate the hypothesis that total fat intake 20 or more years in the past influences breast cancer risk.

A plausible hypothesis is that diet during childhood and adolescence may affect breast cancer risk much later in life. This is a period when the breast undergoes maximum growth and before the cells are exposed to the potentially protective effects of pregnancy. Any exposure that is genotoxic would be expected to exert its maximum influence during this period. The fact that girls exposed to ionizing radiation around the time of puberty have a higher increase in breast cancer risk than women exposed in their 20s is an example of this phenomenon. Dietary fat intake during youth may influence subsequent breast cancer risk; however, there is little reason to assume that calories from fat are deleterious rather than that calories themselves are culprit. Height is a risk factor for breast cancer (41); the concept that a caloric supply sufficient to permit women to attain their full genetically attainable height also increases risk of breast cancer would explain much of the geographic variability in breast cancer risk.

If energy intake during growth is the culprit, it does not lead to an obvious dietary intervention; we are not likely to wish to stunt young women's growth to achieve a potential reduction in future breast cancer risk. The recent observation that plasma levels of the powerful mitogen insulin-like growth factor I are positively correlated with premenopausal breast cancer risk (42) may have important implications for breast cancer prevention. Reducing insulin-like growth factor I levels

through diet or other means may be a future means of breast cancer prevention, if this can be achieved without side effects.

Conclusion

As we end the century, the dietary fat and breast cancer discussion illustrates some key aspects of the state of development of the field nutritional epidemiology. There is continuing concern about the measurement error associated with estimates of food and nutrient intakes using the techniques available for use in large studies. This concern is shared by all who work in the field, and efforts to refine, improve, or replace existing methods are ongoing. Concern about measurement error has caused some to entirely reject the body of evidence that suggests that the most plausible true relation between dietary fat intake in adult life and breast cancer risk is that it is null or, at most, very weak. However, the large number of prospective studies that make up this body of data suggest that it is very unlikely that an important relation between total dietary fat intake and breast cancer risk exists. The major intervention trial in this area will not answer this specific hypothesis, but it should shed light on whether a 5–10-year exposure to a diet that is relatively rich in fruits, vegetables, and grains has any salutary effect.

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