

The Dietary Fat–Breast Cancer Hypothesis Is Alive

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Data from animal experiments and human correlation studies strongly support the dietary fat–breast cancer hypothesis. Moreover, a causal relation between dietary fat and breast malignancy is biologically plausible. Negative findings from recent analytic epidemiologic studies of dietary fat and breast cancer, however, have fueled the notion that the hypothesis is no longer viable. We argue that only limited conclusions should be drawn from epidemiologic studies to date because of the narrow range of dietary fat intake among subjects and the substantial measurement error in dietary assessment. Although many doubts remain about the dietary fat–breast cancer hypothesis, the question is of such importance that intensive efforts at designing better studies of the hypothesis are urgently needed. Such studies might include (1) laboratory investigations in humans that examine possible mechanisms for the effects of fat, (2) large, prospective epidemiologic studies, and (3) randomized, controlled diet trials.

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IT IS estimated that in 1989 in the United States 143 000 women will be diagnosed with breast cancer and that 43 000 will die of the disease.¹ One of 10 women in this country will develop a breast malignancy during her lifetime.¹

The hypothesis that women can reduce their risk of breast cancer by cutting their intake of dietary fat not only fits certain experimental and epidemiologic observations, but also provides a realistic possibility for modifying breast cancer risk. Of late, though, enthusiasm for the hypothesis seems to have waned, largely on the basis of recent epidemiologic studies that report no positive association between dietary fat and breast cancer. Some might even have the impression that the dietary fat–breast cancer hypothesis has become a dead

issue. We argue herein that the hypothesis is very much alive.

ANIMAL EXPERIMENTS

Animal experiments on dietary fat and mammary cancer have shown the following:

1. Increasing the amount of dietary fat increases mammary tumorigenesis, whether measured in terms of incidence, multiplicity of tumors, or latency.²
2. The production of tumors is enhanced when a high level of fat is fed after, not before, initiation, suggesting a promotional effect for dietary fat. The importance of dietary fat in carcinogenesis might extend at least to midlife in rodents.³
3. The tumor-enhancing effects of high levels of saturated or polyunsaturated fat are similar when the diets contain a minimal amount of polyunsaturated fat to provide essential fatty acids.⁴ The effect of various types of dietary fat

on mammary carcinogenesis is an area of current research interest.

4. Finally, dietary fat and total caloric intake seem to have separate tumor-enhancing effects. Figure 1, derived from one of the early studies by Tannenbaum,⁵ illustrates two important points. First, at every level of total caloric intake, animals that consumed a high-fat, compared with a low-fat, diet had an increased incidence of mammary tumors after administration of a chemical carcinogen. Second, total caloric intake enhanced mammary tumorigenesis even when the level of dietary fat was held constant. The precise relative contributions of fat and calories remain a matter of controversy. It is indisputable from the animal studies, though, that animals fed ad libitum a high-fat, high-calorie diet have a substantially higher incidence of mammary tumors than animals fed a low-fat, calorie-restricted diet.

ECOLOGICAL STUDIES

Ecological studies examine relations among grouped data. Because these studies do not examine relations among individuals, they have been regarded traditionally as useful for generating, rather than definitively testing, hypotheses.

Figure 2 depicts the relation of national breast cancer mortality rates to average national levels of estimated per capita fat consumption. These international comparisons of per capita fat consumption are based on food disappearance data derived from food balance sheets⁶ and might tend to overestimate the quantity of fat actually eaten. Per capita estimates of consumption are measures of food that has disappeared

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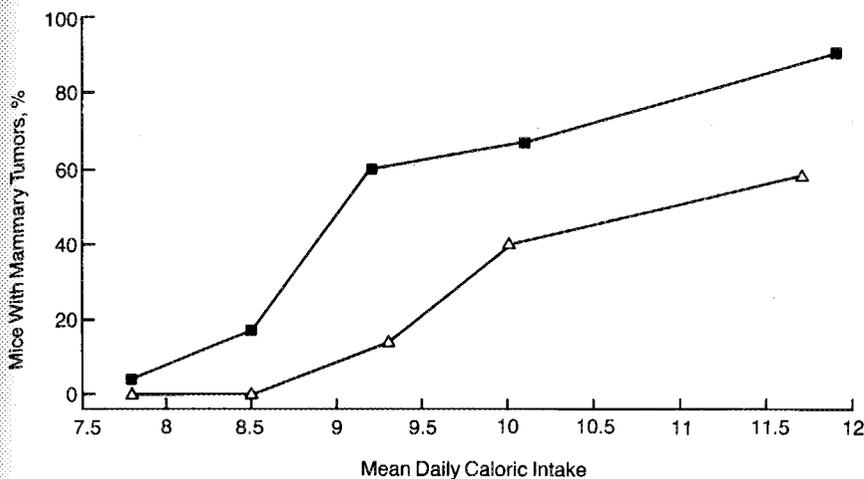


Fig 1.—Relation of dietary fat and caloric intake to incidence of spontaneous mammary tumors in C3H virgin female mice. Closed squares indicate high fat; and open triangles, low fat (adapted from Tannenbaum⁵).

into the food supply and are calculated by adding the total quantity of food produced in a country to the quantity of food imported, and then subtracting the sum of food exported, fed to livestock and pets, and put to nonfood uses. These estimates are then divided by the total population to yield per capita consumption. Food disappearance data provide useful information when used within their appropriate limits of interpretation and have been valuable in providing leads for further research.

As Fig 2 demonstrates, breast cancer rates vary over more than a fivefold range between those countries with the highest and lowest rates. There is also a wide international variation in per capita fat consumption. The fat consumption-breast cancer relation here is direct, strong, and linear, with a correlation coefficient of .8 to .9.⁹ Thus, countries with relatively high estimated fat consumption have high rates of breast cancer, those with low fat consumption have low breast cancer rates. Prentice et al¹⁰ recently showed that the strong international correlation with breast cancer rates holds for total calories from fat but not for nonfat calories.

In light of the wide international variation in breast cancer frequency, breast cancer rates have been studied among persons migrating from areas with low rates to areas with high rates. In general, breast cancer rates change toward those of the country to which women migrate. For example, the incidence of breast cancer has been increasing in successive generations of Japanese women in Hawaii compared with women in Japan to the point that the inci-

dence among second-generation Japanese women in Hawaii is similar to that for whites in Hawaii.¹¹ Among Italian-born women migrating to Australia, breast cancer mortality increased in direct relation to the duration of residence in the adopted country.¹² Dietary acculturation, including the adoption of a diet higher in fat content than that in the country of origin, is a possible explanation for the change in breast cancer rates.

A third ecological approach to this question is the time-trend study, in which investigators examine the relation between changes over time in fat intake and breast cancer rates. In Japan, for example, mean per capita daily fat intake rose from 23 g/d in 1957 through 1959 to 52 g/d in 1973.¹³ During the same period, overall breast cancer mortality rose approximately 30%,¹⁴ with the sharpest increase (>50%) in women aged 45 to 54 years.¹⁸

These ecological studies have two major strengths. First, there is a fairly wide range of fat intake when countries are the units of analysis. This contrasts with studies of individuals within a given country, where variability of fat intake is much more limited. Second, we can be reasonably certain that a country classified as having high fat consumption can be differentiated clearly from a country with low fat consumption.

A potential problem with correlation studies, however, is that relations at the group or aggregate data level might not accurately reflect relations among individuals.¹⁵ There might exist a confounding environmental factor, X, that is associated with dietary fat intake and is

the real causative agent in breast cancer. Since countries with higher fat intake also would have higher exposure to X, the international association between dietary fat and breast cancer would reflect merely this true causal link between X and breast cancer. No such X-factor has yet been identified, though, and the ecological association between dietary fat and breast cancer might mirror a true cause-and-effect relation in individual women.

ANALYTIC EPIDEMIOLOGY

Studies that involve comparisons of individuals have been regarded by epidemiologists traditionally as the strongest type of observational evidence in human populations. In cohort studies, diet is assessed at the beginning of follow-up, before breast cancer develops. The case-control study, which can be viewed roughly as a slice of the experience unfolding in the cohort setting, begins with women who already are diagnosed with breast cancer and one or more groups of control women who do not have the disease. A potentially serious limitation of the case-control study is that diet is assessed in the cases after diagnosis, when they might unintentionally overestimate or underestimate fat intake. While it is not yet established how the accuracy of dietary reporting is affected by this retrospective data gathering, this problem of recall bias can be of sufficient magnitude to invalidate a case-control study.

The most commonly used methods to assess diet in epidemiologic studies are the 24-hour recall and the food frequency questionnaire.¹⁶ For the 24-hour recall method, a trained nutritionist asks a subject to recall everything eaten in the previous 24 hours. With the food frequency questionnaire, subjects are asked how often, usually in the previous year, they consumed various foods. Portion size can be assessed with each of these methods. Data on foods consumed are then converted by means of a food composition database into nutrients such as grams of total fat, saturated and unsaturated fat, protein, and carbohydrates.

More than 20 epidemiologic studies of diet and breast cancer have been completed and recently reviewed.^{17,18} Slightly more than half estimated total fat intake; the others assessed the intake of meat, fried foods, dairy products, and other food groups. Results from 16 published case-control studies of dietary fat and breast cancer have been inconsistent.^{17,18} One cohort study from Japan showed a positive association between meat intake and subsequent breast cancer,¹³ while a cohort study conducted in

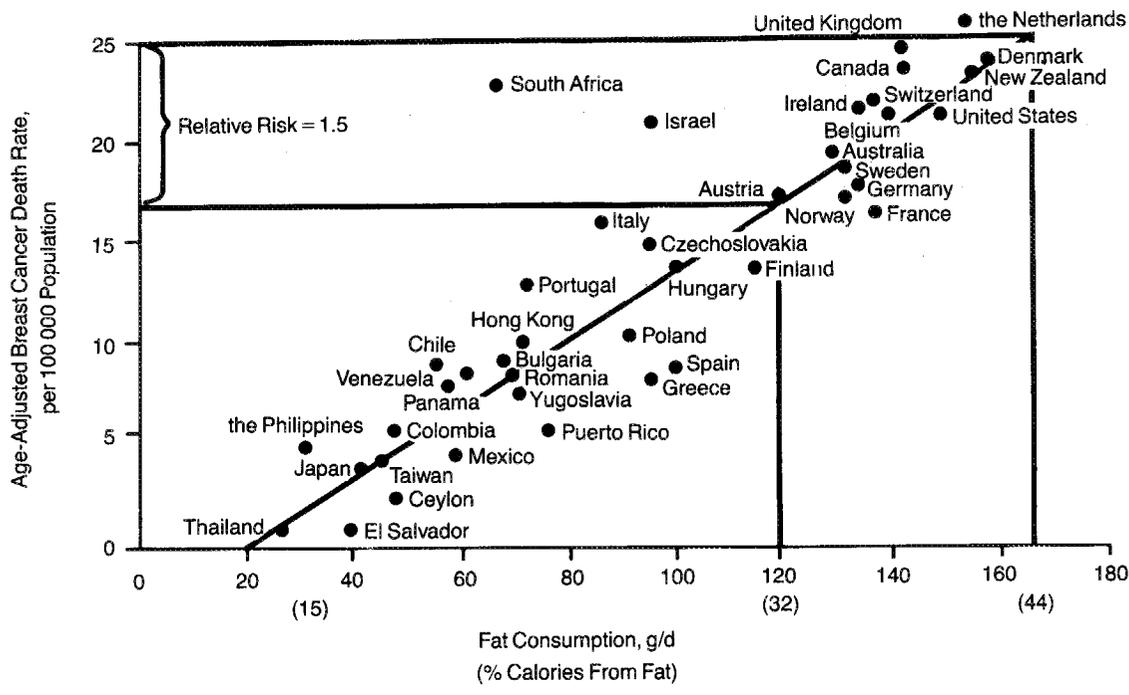


Fig 2.—Relation between age-adjusted breast cancer mortality rates and per capita fat consumption (adapted from Carroll and Khor⁶ and Willett et al⁷).

the United States found no association between meat intake and breast cancer.¹⁹ Data from two recent cohort studies in the United States that assessed fat intake revealed no association or even an inverse association between dietary fat and breast cancer.^{7,20}

LIMITATIONS OF ANALYTIC EPIDEMIOLOGY

Two criticisms have been directed at the findings of cohort and case-control studies of dietary fat and breast cancer. First, the analytic studies often are carried out in populations with a fairly narrow range of fat intake. This makes it difficult to show a dietary fat effect, especially if the real protective effect of a low-fat diet emerges only at a level below that eaten by virtually everyone in the study population. If one looks at only those countries in Fig 2 with 32% or more of total calories from fat (the mean of the lowest quintile of fat intake in the Nurses Health Study⁷), one finds that the breast cancer rates in those countries with the highest fat intake (44% of calories from fat) are only 1.5 times the rates in those countries with 32% of calories from fat. Suppose that these international data reflect a true association between dietary fat and breast cancer and that women in an epi-

demologic study consume between 32% and 44% of calories as fat. Then the relative risk of breast cancer for women in the highest, compared with the lowest, fat category would be only 1.5. A study with the statistical power to detect a relative risk of 1.5 would require a sample size much larger than one with the power to detect a relative risk of 5.0.

Second, there is considerable error in the assessment of diet because people often forget what they eat. Even if people do remember accurately, they might not be aware of the exact components of their meals unless they prepared the food themselves. Interpretation of the 24-hour recall is hampered by the fact that what people eat on a given day might not be typical of their usual diet. The food frequency questionnaire is designed to assess usual diet, but it is difficult to reconstruct precisely how often particular foods were eaten over an extended period. As a result of the dietary measurement error, a substantial proportion of subjects in epidemiologic studies are misclassified. That is, some individuals considered to be in one of the higher categories of fat intake really belong in one of the lower categories, and vice versa.

When misclassification occurs without respect to disease status (as it would

in the cohort studies described previously herein), the observed relative risk is attenuated toward 1.0 (no association). In other words, even if dietary fat truly elevated the risk of breast cancer, with sufficient misclassification a study would fail to reveal that elevated risk.

Some authors have attempted to quantify the magnitude of error by correlating dietary intakes from the food frequency questionnaire (or the 24-hour recall) with intakes from dietary records collected over several days.²¹ For example, Willett et al⁷ reported correlation coefficients of .39 (not adjusted for calories) and .53 (calorie adjusted) for total fat intake estimated from a food frequency questionnaire vs total fat intake assessed from four 7-day food records. These correlations indicate a substantial amount of measurement error. It can be shown that if the correlation between the "imperfect" and "true" exposure is only .5 when the relative risk was truly 2.0, one would observe a relative risk of 1.4 for a unit change in the observed exposure.²² Thus, marked attenuation of relative risk can result from the measurement error that plagues dietary assessment studies. A number of researchers are attempting to use the results of validation studies to develop "misclassification-adjusted" estimates

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of the relative risk of breast cancer in relation to various levels of dietary fat intake.

When the limited range of dietary intake is compounded by the relative risk-attenuating effect of dietary misclassification, severe constraints are placed on the ability of observational epidemiologic studies to demonstrate a true direct relation between dietary fat and breast cancer (should one exist). As a consequence of these methodological constraints, data from case-control and cohort studies to date have not been decisive in resolving the dietary fat-breast cancer question.

BIOLOGIC PLAUSIBILITY

It is reasonable to ask at this point whether the dietary fat-breast cancer hypothesis "makes sense." That is, biologically plausible mechanisms exist by which dietary fat can increase the risk of human breast cancer? The answer is, yes. On the basis of at least some experimental evidence, several mechanisms have been proposed. Perhaps the leading candidate for a mechanism is one that involves hormones, especially estrogens.²³ Dietary fat might modulate ovarian hormonal production directly. Alternatively, dietary fat might alter estrogen-metabolizing intestinal flora or affect the quantity and composition of adipose tissue, which plays a role in steroid hormone metabolism. Other proposed mechanisms include the effects of dietary fat on membrane permeability, prostaglandin synthesis, immune function, DNA repair, and metabolism of chemical carcinogens.²⁴ Thus, while the mechanisms for the dietary fat-breast cancer link are still speculative, it is reasonable to conclude that a causal relation between dietary fat and breast cancer is biologically plausible.

FUTURE RESEARCH

It remains to be seen whether the major thrusts in breast cancer prevention research will be toward (1) large-scale prevention trials, perhaps a modification of a trial that has completed a feasibility phase¹⁰ or a trial with multiple disease end points and changes in more than one dietary component; (2) large

cohort studies with intensive efforts toward improving dietary assessment methods, including identification of biochemical markers of dietary intake; or (3) laboratory-based human studies of intermediate markers that reflect earlier stages in breast carcinogenesis (though a definite correspondence between the intermediate markers and cancer per se will need to be documented).

Studies of dietary fat and breast cancer face a number of difficulties. First, certain nutrients "travel" together. It is not always feasible to disentangle the effects of fat, calories, fiber, and other dietary components. Second, nutrients might interact with each other. That is, dietary fat might have an effect on breast cancer only in the presence, or absence, of certain micronutrients or other dietary factors. This possibility of nutrient interactions might be particularly important in light of recent studies that suggest a positive relation between alcohol consumption and breast cancer.²⁵ Third, specific types of fat, not just total fat, might be critical. It is possible that effects of certain fatty acids are not reflected clearly by measures of total fat.

Finally, dietary fat or other dietary factors consumed in early life—at puberty, for example—might influence the development of subsequent breast cancer. Studying this possibility in human populations is a daunting prospect, given that we would have to determine what women ate many years in the past or else follow up young women for several decades until sufficient numbers developed the disease. We might have to rely, at least in part, on such circumstantial evidence as cross-cultural comparisons and metabolic studies in young women.

The dietary fat-breast cancer hypothesis is viable and important. It deserves vigorous investigation.

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