# Critical Appraisal of the Evidence That Dietary Fat Intake Is Related to Breast Cancer Risk in Humans [1]

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ABSTRACT—A critical appraisal was undertaken of the evidence that dietary fat intake is related to breast cancer risk by application of the criteria for causal inference proposed by Bradford Hill to the published evidence that relates dietary fat to breast cancer risk in humans. These criteria concern the consistency, strength, and temporal relationships of possible causative associations and also require the existence of a biologic gradient and examine the extent to which the proposed causal association is in keeping with other biological and epidemiological knowledge. The published reports were inconsistent in their ability to detect a significant association between dietary fat and breast cancer risk, correlation studies that examined the effect of fat over large ranges being largely positive, and studies with stronger designs (case-control, cohort) that examined fat intake over much smaller ranges being largely negative. It was postulated that methodologic limitations associated with the design of the latter studies, in particular the small ranges of fat intake examined and inaccuracies in the measurement of fat intake, may have obscured any relationships between dietary fat and breast cancer that did exist. The remaining criteria, with the exception of temporality and epidemiological coherence, were not satisfied. Insufficient evidence existed to conclude a causal association existed between dietary fat and breast cancer risk in humans. A need for further study was identified in several areas, and it was concluded that intervention studies that examined the effect of fat over large ranges were most likely to yield the information required to determine whether dietary fat intake was causally related to breast cancer risk.—JNCI 1987; 79:473-485.

Cancer of the breast is the most prevalent cancer among women and a leading cause of female cancer deaths in North America (*1*). Research into the treatment of breast cancer has failed to significantly reduce mortality from this disease during the 20th century, and a shift in research priorities toward breast cancer prevention has been advocated (*2*). The development of preventive strategies has in the past been hampered by lack of knowledge concerning potentially reversible etiologic factors. However, recent publications have focused attention on one potentially reversible factor in humans, a high intake of dietary fat, as a possible causal factor in the development of breast cancer that could be manipulated and that might modify cancer risk.

The association between dietary fat and the development of breast tumors was first proposed by Tannenbaum (*3*) in 1942. Since that time, studies using animal models have confirmed an effect of fat on the development of mammary tumors that is independent of total caloric intake and that appears to be related to intake of both saturated and unsaturated fats. Experiments involving the administration of carcinogens have demonstrated that dietary fat exerts its effect during the promotional stage of carcinogenesis (*4*).

Numerous epidemiological studies in humans, which used different study designs and which were undertaken in different geographic locations, have examined the relationship between dietary fat and breast cancer risk and have provided inconsistent support for such an association. The results of these studies, in conjunction with those of animal studies, have, however, been considered to provide sufficient evidence to conclude that a relationship exists between high fat intake and breast cancer risk in humans. As a result, guidelines for changes in dietary fat consumption in the general population have been developed recommending that dietary fat intake be reduced from the present level of approximately 40% of total caloric intake to approximately 30% of total caloric intake (*5*). The Committee on Diet, Nutrition, and Cancer of the National Research Council, which developed these dietary guidelines, stated that they were based on an assessment of the "overall strength of all the evidence combined" rather than on "a detailed critique of the results and methodology of each report." Thus their recommendations were not based on a critical appraisal of the available evidence, and it appears that such an appraisal has not yet been undertaken.

This lack of a critical appraisal of the evidence in the past, combined with the continued publication of investigations that fail to confirm a significant association between dietary fat and breast cancer risk (*6-12*), and controversy in the medical community regarding these dietary recommendations (*13*) have prompted us to review the evidence relating dietary fat intake to breast cancer risk in humans. The purpose of this review was to summarize the present level of knowledge, to assess the strength of the evidence that dietary fat is causally related to breast cancer risk in humans, and to identify deficiencies in the evidence that might provide directions for future investigations.

For the purposes of this evaluation, we have focused on the relationship between dietary fat and breast cancer risk and have considered the effects of other dietary constituents only insofar as they bear on the independent

ABBREVIATIONS USED: CI=confidence interval; RR=relative risk; WWII=World War II.

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effects of fat on breast cancer risk. We have not considered associations between dietary fat and other diseases, since this is not germane to our current evaluation, although we recognize it is quite likely that dietary fat is related to other diseases and that these relationships have an important effect on the general health of the population. The basic strategy adopted has been to apply to the published evidence the following criteria for causal inference as proposed by Bradford Hill (*14*): 1) consistency of the evidence, 2) strength of the association, 3) relationship in time, 4) biological gradient, 5) specificity, 6) coherence of the evidence, 7) biological plausibility, 8) reasoning by analogy, and 9) experimental evidence.

These criteria provide a framework for assessing evidence relating to a potential causal association when the evidence is obtained by use of observational, rather than experimental, methods. The extent to which these criteria are met provides a measure of the strength of existing information, and criteria that cannot be met provide guidance for future investigations.

## METHODS

*Assembly of literature.*—A computerized search of the literature by use of Medline and Cancerlit was undertaken to identify reports in the English language published between January 1981 and January 1987 that dealt with diet and breast cancer risk. Additional reports were identified through references in the studies found in this way and through references in a 1982 report by the Committee on Diet, Nutrition, and Cancer of the National Research Council (*5*). Additional searches were conducted when necessary. Reports that examined the relationship between total dietary fat or specific fatty foods (including meat) and breast cancer risk were included in this report. Abstracts and letters were excluded.

*Classification of study design.*—Three study designs (cohort, case-control, and correlation) were used to examine the relationship between dietary fat intake and breast cancer risk. Reports were classified according to the following criteria.

Cohort studies: Reports were classified as cohort studies if they examined breast cancer risk in a group of women, initially free of breast cancer, whose dietary intake was determined and who were followed forward in time and observed for the development of breast cancer. The risk of breast cancer associated with a particular level of intake is given by dividing the number of women at that level who develop breast cancer by the total number of women at that level. The RR of breast cancer for a given level of intake is simply the ratio of its risk to the risk associated with a predetermined base-line level.

Case-control studies: Reports were classified as case-control studies if they assembled a group of patients with breast cancer and a comparative group free of breast cancer. In these studies the RR of breast cancer is approximated by an odds ratio.

Correlation studies: Reports were classified as correlation studies when groups or entire populations rather than individuals formed the basis for the determination of dietary intake and/or breast cancer rates. In some reports dietary information was obtained from individuals considered to be representative of the general population, and this information was correlated with breast cancer rates in the general population; in other reports dietary information was derived from per capita estimates of intake for the entire population.

Three types of correlation studies were identified: international, national or regional, and time trend. Reports were classified as international correlations when dietary fat intake and breast cancer incidence or mortality were correlated across countries. Reports were classified as national or regional correlations when dietary fat consumption in two or more areas of a country were correlated with breast cancer rates in the same areas. In time-trend studies, changing dietary practices in a given population during a specified period of time were correlated with changing breast cancer rates during the same time period.

## RESULTS: APPLICATION OF CRITERIA FOR CAUSAL INFERENCE

### Consistency of the Association

#### *Criterion*

Consistency refers to the extent to which studies by different investigators, using different study designs, in different places, agree that dietary fat is related to breast cancer risk.

#### *Results of Applying the Criterion*

Tables 1-3 summarize the results of studies that have examined the relationship between total fat intake or the intake of fat-containing foods and breast cancer risk. Significant relationships reported between specific sources of fat in the diet (either specific foods or specific types of fats) are also shown in these tables.

*Cohort studies.*—Four cohort studies (table 1) were identified, one of which examined the relationship between total fat intake and breast cancer risk (*6*). In this study 89,538 American nurses were followed 4 years, and dietary fat intake at one point in time was correlated with the development of breast cancer over the following several years. No relationship was seen between total fat intake and breast cancer risk, the risk of breast cancer for those in the highest quintile of fat intake relative to that for those in the lowest quintile being 0.82 (95% CI=0.64-1.05). Mean fat intake in the highest quintile was 44% of total calories; in the lowest quintile it was 32%.

The other three cohort studies examined the relationship between meat intake and breast cancer risk, and two Japanese studies (*15, 16*), one with 1,330,382 person-years of observation, showed a positive association between the two; however, an American study by Phil-

TABLE 1.—*Cohort studies*

| Source | Group studied | Food | Comparisons | Results: breast cancer[a] |
|---|---|---|---|---|
| Willett et al. (*6*) | United States—nurses | Total fat | Highest vs. lowest[b] quintile | RR=0.82 (95% CI=0.64-1.05) (Trend: $P$=.11) |
| Hirayama (*15*) | Japan—study in 29 health center districts | Meat | Daily vs. occasional, rare, none | 40-54 yr old vs. SMR=1.26<br>55 yr old vs. SMR=2.38 |
| Hirayama (*15, 16*) | Japan—adult health study (Hiroshima) | Meat | Almost daily vs. <1/wk | RR=3.83 |
| | | Eggs | Almost daily vs. <1/wk | RR=2.86 |
| | | Butter, cheese | Almost daily vs. <1/wk | RR=2.10 |
| Phillips and Snowdon (*17*) | United States—California Seventh-Day Adventists | Meat | Non-meat eater<br>Meat 1-3 times/wk<br>Meat >4 times/wk | 47.8 deaths/100,000<br>58.3 deaths/100,000<br>56.9 deaths/100,000<br>(No significant differences) |

[a] SMR=standardized mortality ratio.
[b] Mean fat intake: highest quintile=44% calories; lowest quintile=32% calories.

lips and Snowdon (*17*) was not able to confirm this result in a group of Seventh-Day Adventists followed for 21 years. One of the Japanese studies (*16*) also demonstrated an association between intake of eggs, butter, and cheese and breast cancer risk.

Thus two cohort studies carried out in the United States, where dietary fat intake is high, were unable to demonstrate an association between intake of fat or meat and breast cancer risk, while two studies in Japan, where fat intake is lower and probably more heterogenous, were able to show an association between intake of meat and fatty foods and breast cancer risk.

*Case-control studies.*—Table 2 summarizes the results of 14 case-control studies that examined the relationship between intake of total fat or fat-containing foods and breast cancer risk.

Analysis of total fat: Eight studies examined the relationship between fat intake and breast cancer risk. Only one (*23*) found a statistically significant association; however, the control group in this study was derived

TABLE 2.—*Case-control studies*

| Source | No. of cases | No. of controls | Source of controls | Total fat evaluated | Significant association between breast cancer and total fat | Other results (excluding subgroup results)[a] |
|---|---|---|---|---|---|---|
| Phillips (*18*) | 77 | 231 | Population and hospital | No | — | + fried potatoes |
| Nomura et al. (*19*) | 86[b] | 6,774 | Population | Yes | No | + butter, margarine, cheese, meat<br>− green tea, nori and other seaweeds |
| Miller et al. (*20*) | 400 | 400 | Neighborhood | Yes | No[c] | + total calories, saturated fat, oleic acid |
| Lubin et al. (*21*) | 577 | 826 | Population | No | — | + beef, pork, sweet desserts, butter and margarine for frying, butter at table |
| Graham et al. (*22*) | 2,024 | 1,463 | Hospital | Yes | No | |
| Kolonel et al. (*12*) | 268 | 591 | Hospital and neighborhood | Yes | No | |
| Talamini et al. (*11*) | 368 | 373 | Hospital | No | — | + milk and dairy (trend), alcohol |
| Zemla (*10*) | 328 | 585 | Friends | No | — | |
| Nomura et al. (*8*) | 344 | 688 | Neighborhood and hospital | Yes | No | |
| Sarin et al. (*23*) | 68 | 33 | Hospital[d] | Yes | Yes | + calories |
| Hirohata et al. (*9*) | 212 | 424 | Neighborhood and hospital | Yes | No | + animal protein from shellfish (hospital controls) |
| Hislop et al. (*24*) | 846 | 862 | Friends | No | — | + visible fat on meat, whole milk, beef |
| Lubin et al. (*7*) | 818 | 1,556 | Neighborhood and hospital | Yes | No[e] | |
| Katsouyanni et al. (*25*) | 120 | 120 | Hospital | No | No | − vegetables |

[a] Significant at $P$<.05. +=positive association with breast cancer; −=negative association with breast cancer.
[b] Husbands of cases.
[c] $P$=.05 (one-sided), postmenopausal subgroup.
[d] Those with fat-related diseases excluded.
[e] Women >50 yr old with high fat intake, $P$<.05 when compared to hospital controls.

TABLE 3.—*Correlation studies*

| Source | Incidence (I) or mortality (M) | Total fat evaluated | Significant association between total fat and breast cancer risk | Other significant results[a] |
|---|---|---|---|---|
| **International studies** | | | | |
| Hirayama (*15*), 28 countries | M | No | — | + pork, beef |
| Lea (*26*), 33 countries | M | Yes | Yes | + specific fatty foods, sugar |
| Carroll et al. (*27*), 21 countries | M | Yes | Not tested | |
| Wynder (*28*), 18 countries | M | No | — | |
| Hems (*29*), 22 countries | M | Yes | Yes | + sugar |
| Drasar and Irving (*30*), 37 countries | I | Yes | Not tested | + specific fatty foods |
| Armstrong and Doll (*31*), 32 countries | I, M | Yes | Yes | + specific fatty foods, sugar, calories<br>− cereals |
| Howell (*32*), 37 countries | M | Yes | Not tested | + specific fatty foods, sugar[b]<br>− cereals, pulses |
| Hems (*33*), 41 countries | M | Yes | Yes | + specific fatty foods, sugar, calories |
| Gray et al. (*34*), 34 countries | I, M | Yes | Yes | + specific fatty foods, sugar |
| Correa (*35*), 41 countries | M | Yes | Yes | + specific fatty foods, beer<br>− rice, maize, beans |
| Knox (*36*), 20 countries | M | Yes | Yes | + meat, sugar, calories |
| Maruchi et al. (*37*), 18 countries | M | No | Not tested | + sugar |
| **National or regional studies** | | | | |
| Hirayama (*15*), Japan | M | Yes | Yes | |
| Maruchi et al. (*37*), Japan | M | No | — | + fats and oils, milk and dairy products, vegetables |
| Stocks (*38*), United Kingdom | M | No | — | + specific fatty foods<br>− margarine, other fats |
| Gaskill et al. (*39*), United States | M | Yes | Yes | + specific fatty foods |
| Hems (*40*), United Kingdom | M | Yes | No | + animal protein |
| Kolonel et al. (*41*), Hawaii | I | Yes | Yes | + groups of fatty foods |
| Kinlen (*42*), United Kingdom | M | Yes | No | |
| Boing et al. (*43*), Federal Republic of Germany | M | Yes | Yes | + vitamin C, fiber, cholesterol, lipids |
| La Vecchia and Pampallona (*44*), Italy | M | No | — | + specific fatty foods |
| **Time-trend studies** | | | | |
| Hirayama (*15*), Japan | M | Yes | Not tested | |
| Hems (*33*), international | M | Yes | Yes | + animal protein |
| Hems (*40*), United Kingdom | M | Yes | Not tested | Maximum correlation with fat or sugar one decade earlier |
| Pawlega and Wallace (*45*), Iowa | I | Yes | Not tested | |
| Ingram (*46*), United Kingdom | M | Yes | Yes | + meat, sugar<br>− cereal |

[a] $P \leq .05$ or $r \geq 0.50$. +=positive correlation with breast cancer. −=negative correlation with breast cancer.
[b] Factor analysis.

from hospital out-patients and patients with cancer, diabetes mellitus, coronary artery disease, and gallstone disease (all of which may be associated with high dietary fat intake) were excluded, while no such exclusions were made from the group of cases. It seems likely that the result of this exclusion will be to lower the average fat intake in the control group relative to that in the cases and bias the results in favor of an association between dietary fat and breast cancer.

Of the remaining seven studies, one found a significant association between dietary fat and breast cancer risk in postmenopausal women (*20*), and one found in increase in breast cancer risk in women over 50 years of age who had the highest level of fat intake when compared to the fat intake of neighborhood but not to that of hospital controls (*7*). One study found an increased fat intake among cases that was not statistically significant (*19*), and two (which may have had cases in common) found a nonsignificant increase in fat intake among cases in 3 of 4 subgroups and a nonsignificant decrease in the fourth (*8, 12*). One study found lower dietary fat intake among cases than either hospital or neighborhood controls (*9*); however, this difference was not statistically significant. The remaining study (*22*) found fat intake to be virtually identical in cases and controls. Thus the results of these case-control studies are inconsistent and provide only weak evidence in support of an association between total fat and breast cancer risk.

Analysis of fat-containing foods: Six investigators (*11,*

*18–21, 24*) demonstrated significant associations between breast cancer risk and one or more specific dietary sources of fat—in particular, meat, butter, and margarine. None of these studies found all sources of fat examined to be significantly associated with increased breast cancer risk. Miller et al. (*20*) demonstrated a significant association between the intake of saturated fats and breast cancer risk, which appeared to be greatest in postmenopausal women. [A subsequent reanalysis by Howe (*47*), using both 24-hr recall and food frequency data to estimate fat consumption, has demonstrated that this association is strongest in premenopausal women.] An association between total caloric intake and breast cancer risk was demonstrated in two studies (*20, 23*), but neither study examined the independent effects of dietary fat and caloric intake on breast cancer risk.

*Correlation studies.*—Twenty-seven correlation studies were identified among the international, national or regional, and time-trend studies.

International: Thirteen international correlation studies were identified. Many of these studies used similar sources of information for the estimates of dietary fat and breast cancer risk; although some differences exist between the methods used, the studies cannot be considered independent. Ten of these studies examined the relationship between total dietary fat and breast cancer risk (*26, 27, 29–36*). All demonstrated an association between breast cancer mortality or breast cancer incidence and per capita intake of fat. Three studies (*27, 30, 32*) did not formally test the statistical strength of this association. Several studies (*15, 29–36*) demonstrated an association between consumption of specific fatty foods and breast cancer risk. Negative associations were demonstrated for cereals and pulses in two studies (*32, 35*).

National or regional: Nine national or regional studies were identified. Six of these studies examined the relationship between total fat intake and breast cancer risk. Four demonstrated a positive association (*15, 39, 41, 43*), while two did not (*40, 42*). The positive association between regional consumption of fat and breast cancer risk in the United States demonstrated by Gaskill et al. (*39*) disappeared when the Southern States were excluded from the analysis or when the 48 States were grouped into four regions and diet and breast cancer mortality rates were averaged for States within these regions. Several studies demonstrated an association between specific fatty foods and breast cancer risk (*15, 37, 39–41, 43, 44*).

Time trend: Five time-trend studies were identified. All examined the relationship between total fat intake and breast cancer risk, and the two that tested this association (*33, 46*) for statistical significance found it to be significant. Hems (*40*) and Ingram (*46*) found that the correlation between breast cancer risk and dietary fat was stronger if diet 10 or 12 years previously was used in the analysis.

All of these correlation studies have several limitations that are inherent in their design and cannot be overcome by modifying the methodology used. First, information is based on populations, not on individuals, and one must assume that those at increased risk of breast cancer are also those whose dietary fat intake is greatest. Secondly, the dietary information used in the international studies was usually based on per capita disappearance of foodstuffs and did not always take into account home production of food and the consumption of food by livestock. Estimates of per capita fat consumption thus obtained do not necessarily agree with those obtained from surveys of dietary practices of the same population (*48*). Dietary information in national correlation studies was usually derived from household surveys, which may have been more accurate; however, food consumed outside the home was not always considered and fat intake may have been underestimated. Finally, it is possible that the results of these studies are influenced by other factors that may be causally related to breast cancer and act as confounders in the apparent association between fat and breast cancer.

In summary, the only cohort study that examined total fat intake failed to find an association between fat intake and breast cancer risk; however, two of three cohort studies that examined the relationship between meat intake and breast cancer risk found the association between the two to be significant. Only one of the eight case-control studies that evaluated the association between total fat and breast cancer risk found it to be significant; however, this result was probably biased due to a methodologic flaw in the design of the study. Seven other case-control studies demonstrated a significant association between specific fatty foods and breast cancer risk. All of the international and time-trend correlation studies that formally tested the association between per capita total fat intake and breast cancer risk found it to be statistically significant, as did four of the six national correlation studies that tested the association.

### *Conclusion*

When the strongest study designs were used, investigators failed to consistently demonstrate a significant association between dietary fat and breast cancer risk. Several investigators found a significant association between dietary fat and breast cancer risk in certain subgroups or between specific sources of fat in the diet and breast cancer risk, and several were able to demonstrate nonsignificant positive associations between fat intake and breast cancer risk. Possible reasons for these largely negative results are discussed in the following section. International correlation and time-trend studies consistently demonstrated an association between fat intake and breast cancer risk, but weaknesses inherent in the design of these studies outlined above limit the value of these results.

## Strength of the Association

### *Criterion*

The stronger the association between dietary fat and breast cancer risk, the more likely it is to be causal.

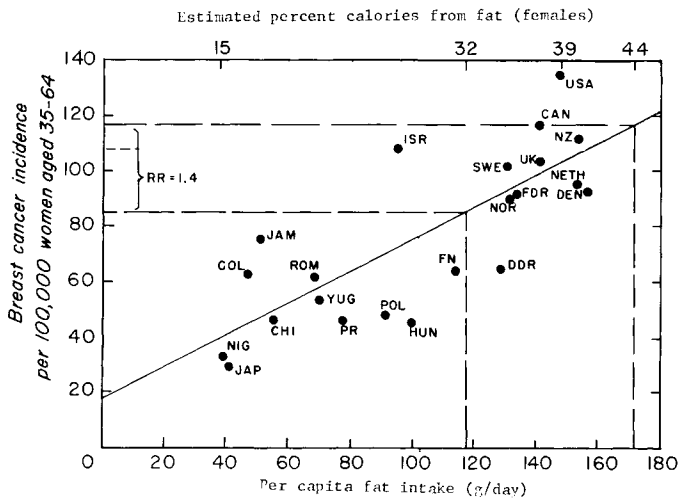
*Results of Applying the Criterion*

It follows from the foregoing discussion of consistency that the association between dietary fat consumption and breast cancer risk is strong only in international correlation studies. The relationship is weaker in correlation studies carried out within countries and is either weak or absent in cohort and case-control studies.

The principal difficulty posed by this conflicting evidence is to know which of the several sources of information is more likely to be in error. Reference has been made to the potential shortcomings of correlation studies. Cohort and case-control studies may also give misleading results. In the present context a particularly important feature of their design is the range of fat intake observed in the populations included in these studies.

Epidemiological investigation of the role of fat in breast cancer differs from most other etiological studies in that there is no group available that has not had some exposure to the agent under study. Investigators are, therefore, only able to examine the risk of breast cancer in relation to the extent of exposure, as assessed by the quantity of fat ingested. If, in cohort and case-control studies, populations are examined whose fat intake is systematically less variable than the variation in fat consumption between countries, then the associations found between fat intake and breast cancer risk will be weaker than those found in international correlation studies, if they can be identified at all.

The potential effects of this methodologic limitation are illustrated in text-figure 1. In this text-figure the variability in fat intake seen in the most rigorous cohort study reported to date (*6*) that examined the relationship between fat intake and breast cancer incidence is contrasted with that seen in the only international correlation study that provided data on both fat intake and breast cancer incidence (*34*). Breast cancer incidence and per capita fat intake in the 22 countries included in Gray's correlation study were plotted, and the least squares regression line was fitted to the data. The scale on the abscissa showing percentage calories as fat was fitted by establishing two points, 39% of calories from fat from the data of Willett et al. (*6*) for the United States and 15% of calories from fat from the data provided by Kagawa (*49*) for Japan. A linear scale was then constructed between these points.




TEXT-FIGURE 1.—Estimate of the breast cancer risk detectable within the Western population in association with dietary fat. CAN=Canada; CHI=Chile; COL=Colombia; DDR=German Democratic Republic; DEN=Denmark; FDR=Federal Republic of Germany; FN=Finland; HUN=Hungary; ISR=Israel; JAM=Jamaica; JAP=Japan; NETH=The Netherlands; NIG=Nigeria; NOR=Norway; NZ=New Zealand; POL=Poland; PR=Puerto Rico; ROM=Romania; SWE=Sweden; UK=United Kingdom; USA=United States; YUG=Yugoslavia.

As shown in the text-figure, the approximately fivefold international variation observed in breast cancer incidence is strongly associated with differences in estimated fat consumption ($r=0.78$). To estimate the differences in cancer incidence that might be found in association with fat intake within a country, if the international data indeed do indicate a causal association, we have projected onto the regression line the range in fat intake reported in the cohort study of Willett et al. Fat intake varied from 32% of calories (mean of lowest quintile) to 44% of calories (mean of highest quintile). As shown in the text-figure, this range of fat intake would be expected to be associated with relatively small differences in cancer incidence, and the ratio of the risks in the highest and lowest quintiles would be approximately 1.4. This risk ratio would be even smaller if other methodologic limitations existed, such as measurement error.

The influence of measurement error on the largest RR of breast cancer that is likely to be detected in association with dietary fat can be estimated from data provided by Willett et al. The questionnaire used by Willett et al. to collect dietary information from the nurse cohort was a semiquantitative method of retrospective inquiry. This method of inquiry had been validated by comparing fat consumption as determined by questionnaire and as determined by food records maintained over 7 days (*50*). Data were then given showing the distribution of patients according to both methods.

To examine the influence of measurement error associated with use of the questionnaire, we have assumed that diet records provide a "true" description of dietary fat intake and that if they were used to collect dietary information from the cohort, the RR of 1.4 between highest and lowest quintiles, whose derivation is described above, would be identified. Each quintile of fat intake would then be associated with a 10% increment in risk of breast cancer.

Data from table 1 of the paper by Willett et al. give the distribution of subjects in the highest and lowest quintiles of fat intake according to the questionnaire classified in regard to fat intake as assessed by diet records. In table 4 we estimate the effects of such misclassification on the cancer risk associated with the highest and lowest quintiles of fat intake as determined by questionnaire. Misclassification will reduce the apparent difference in risk between the upper and lower

TABLE 4.—*Estimates of the effects of error in dietary measurement on the assessment of breast cancer risk [from Willett et al.]*[a]

| Quintile of diet questionnaire | Diet record quintiles | | | | | Apparent risk |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| "True" RR | 1.0 | 1.1 | 1.2 | 1.3 | 1.4 | |
| Lowest | 53 | 14 | 12 | 18 | 3 | 1.115 |
| Highest | 3 | 12 | 21 | 32 | 33 | 1.292 |
| | | | | Apparent RR | | 1.159 |

[a] *See* text for explanation.

quintiles compared to the "true" difference in risk, so that a true difference of 1.4 will appear to be only 1.16.

It is likely that other sources of error, such as the error in measurement associated with the diet records themselves, will further reduce the detectable risk.

### *Conclusion*

The association between dietary fat consumption and breast cancer risk is strong in international correlation studies, but it may not be causal. Weaker associations found in other studies may be due to the restricted range of fat intake in the populations studied and to difficulties in measuring small differences in fat consumption.

## Relationship in Time

### *Criterion*

For dietary fat intake to be causally related to breast cancer, it must be shown to precede the development of breast cancer.

### *Results of Applying the Criterion*

Exposure to dietary fat invariably occurs prior to the development of breast cancer. Most studies included in this report examined the relationship between recent or current consumption of fat and breast cancer risk. In the two correlation studies that examined dietary fat intake and breast cancer risk on several occasions, it was found that breast cancer mortality correlated most closely with fat intake one decade (*40*) or 12 years (*46*) previously. In the only case-control study that examined diet at different times, Hislop et al. (*24*) demonstrated a positive association between childhood consumption of visible fat on meat and premenopausal but not postmenopausal breast cancer. They also found that recent adult consumption of fatty foods was more predictive of breast cancer risk than was childhood consumption.

### *Conclusion*

The temporal relationship between dietary fat intake and breast cancer risk is consistent with a causal association. Dietary fat intake approximately 10–12 years previously appears to be most predictive of subsequent breast cancer risk. Additional information relating to secular changes in diet and breast cancer risk is included in the section "Coherence of the Evidence Criterion."

## Biological Gradient

### *Criterion*

The presence of a biological gradient or dose-response relationship between dietary fat and breast cancer risk would strengthen the evidence for a causal relationship.

### *Results of Applying the Criterion*

*Cohort studies.*—Willett et al. (*6*) were unable to demonstrate a dose-response gradient between total fat intake and breast cancer risk, and Phillips and Snowdon (*17*) found no gradient in association with meat consumption. Hirayama (*15, 16*) found steadily increasing breast cancer risk with increasing consumption of meat and eggs.

*Case-control studies.*—Two case-control studies have examined the association of total fat intake and breast cancer risk for a dose-response relationship. Neither Miller et al. (*20*) nor Hirohata et al. (*9*) were able to demonstrate a significant dose-response relationship between total fat intake and breast cancer risk.

Several case-control studies have reported dose-response relationships between consumption of specific types of fat or fat-containing foods and breast cancer risk. Talamini et al. (*11*) demonstrated a significant dose-response gradient of breast cancer risk for meat, milk, and other dairy products. Lubin et al. (*21*) demonstrated significant dose-response gradients for beef, pork, and sweet desserts, whereas Hislop et al. (*24*) found significant gradients in premenopausal women for gravy, beef, and pork and in postmenopausal women for pork. Lubin et al. (*21*) found a significant dose-response gradient of breast cancer risk in association with consumption of sweet desserts, animal fat, animal protein, and several groups of fatty foods (e.g., meat, eggs, cheese). Lubin et al. (*7*) found a marginally significant dose-response gradient of breast cancer risk with foods containing greater than 20% fat, particularly in persons over 50 years of age. Howe's reanalysis (*47*) of Miller's data demonstrated a significant gradient of breast cancer risk with increasing intake of saturated fat in premenopausal women. Katsouyanni et al. (*25*) found a significant inverse gradient between the intake of vegetables and breast cancer risk.

*Correlation studies.*—International correlation studies provide evidence for a steadily increasing rate of breast cancer with increasing fat intake, in keeping with a linear dose-response relationship between these two entities; however, because of the methodologic limitations of these studies outlined above and the possible confounding effects of factors such as socioeconomic status, this provides only weak support for the presence of a biologic gradient.

The failure of most investigators using strong study designs to demonstrate significant dose-response gra-

dients may be related to the restricted range of fat intake studied, a methodologic limitation discussed in detail in the section "Strength of the Association."

### *Conclusion*

Although some studies provide evidence of a biological gradient between dietary fat and breast cancer risk, this gradient is not consistently demonstrated and further investigation using stronger study designs and larger ranges of fat intake is necessary before one can conclude that such a gradient exists.

## Specificity of the Association

### *Criterion*

A causal association between dietary fat and breast cancer risk should be specific for dietary fat; i.e., dietary fat should be associated with breast cancer risk after the effects of other dietary components and known risk factors for breast cancer are considered.

### *Results of Applying the Criterion*

*Cohort studies.*—The inability of Willett et al. (*6*) to demonstrate an association between dietary fat and breast cancer risk was unchanged by adjustment for the effects of several recognized risk factors for breast cancer (family history, parity, age at first birth, history of benign breast disease, menopausal status, smoking history, alcohol consumption). In view of the methodologic limitations of this study outlined above and the apparent lack of association between fat intake and breast cancer risk that was demonstrated, however, it cannot be concluded that the effect of fat intake is independent of these other factors.

*Case-control studies.*—The effect of dietary fat on breast cancer risk after consideration of the effects of other recognized risk factors for breast cancer was examined in six case-control studies. The findings of a nonsignificant increase in dietary fat intake among cases in 3 of 4 subgroups demonstrated by Kolonel et al. (*12*) and Nomura et al. (*8*) and of a significant association between specific fatty foods (beef/pork, fat used for frying, animal fat, animal protein) and breast cancer risk reported by Lubin et al. (*21*) were unchanged after consideration of various risk factors, including reproductive and anthropometric variables, family history of breast cancer, and history of benign breast disease. Lubin et al. (*7*) found that the nonsignificant associations between fat, animal protein, and fiber and breast cancer risk were only slightly diminished when several risk factors for breast cancer were considered, and they concluded that intake of these nutrients independently affected breast cancer risk. When Talamini et al. (*11*) controlled for "all identified potential distorting factors" (including various foods and breast cancer risk factors), a previously significant dose-response relationship between meat intake and breast cancer risk became nonsignificant, although a significant dose-response gradient between milk and dairy products and breast cancer risk persisted. When Hislop et al. (*24*) controlled for the effects of several risk factors for breast cancer (age, education, history of benign breast disease, parity, age at first birth, family history) as well as several foods, they found that the majority of their results were unchanged; several fatty foods remained significantly associated with breast cancer risk, particularly in premenopausal women.

The effect of dietary fat, independent of other dietary constituents, has been difficult to determine because the consumption of different foods is often closely related. In particular, total fat intake is highly correlated with intake of protein, animal fats, and total calories. Lubin et al. (*7*) found that fat had a greater effect on breast cancer risk than either animal protein or fiber, but high fiber intake appeared to exert a minor protective effect when intake of both fat and animal protein was high. Miller et al. (*20*) found that the risk ratio for total fat intake in premenopausal women rose from 1.6 to 2.0 when intake of saturated fat was controlled. Talamini et al. (*11*) and Hislop et al. (*24*) found little change in their results when they controlled for various dietary components.

*Correlation studies.*—Five international correlation studies (*30, 31, 33, 34, 40*) found a strong association between fat intake and breast cancer risk, which persisted after consideration of at least one of the following variables—reproductive factors (parity, birth rates, family size, age at menarche), marital status, anthropometric factors (height, weight), and measures of socioeconomic status (per capita income, gross national product, motor vehicles per capita).

Hems (*29*) found total fat intake to be significantly correlated with breast cancer risk after the effects of other dietary constituents (sugar, total calories, total carbohydrates, meat protein) were considered, and he found that 75% of the variation in breast cancer rates in women 65-69 but only 50% of the variation in those 40-44 years old were explained by changes in fat intake. In a subsequent study (*33*) he found total fat intake as well as intake of fat from either animal or vegetable sources to be correlated with breast cancer risk. La Vecchia and Pampallona (*44*) found that cheese and milk remained significantly correlated with breast cancer mortality in several regions of Italy after controlling for several other foods and breast cancer risk factors.

When different components of total fat are examined with the use of any study design, associations with breast cancer were more often demonstrated for saturated than for unsaturated fats, for fats from animal sources than from vegetable sources, and for animal proteins than for vegetable proteins. The evidence currently available is not sufficient to determine whether total fat or a specific component of total fat is responsible for an association with breast cancer risk.

### *Conclusion*

The association of dietary fat with breast cancer risk appears to be independent of other risk factors for breast

cancer. The effect of dietary fat on breast cancer risk after consideration of the effects of other foods is difficult to determine, since intake of many foods is correlated with fat intake. Further investigation is necessary to determine whether particular components of dietary fat are related to breast cancer risk.

## Coherence of the Evidence

### Criterion

A causal association between dietary fat and breast cancer risk should be consistent with the known facts about the epidemiology and natural history of breast cancer.

### Results of Applying the Criterion

*Secular changes in fat intake and breast cancer risk.*—Secular changes in breast cancer mortality in England during and after WWII correlate with changes in dietary fat intake during the same time period (*46*); however, these correlations may be due to changes in reporting practices (*51*) rather than a true association between these two entities. Correlations between changes in fat intake and changes in breast cancer mortality have been noted in Japan in recent years (*15, 49*), where dietary fat intake rose approximately twofold to threefold between 1950 and 1975 to approximately 25–30% of total calories; this was associated with a twofold rise in breast cancer mortality. Since younger individuals may have altered their diets to a greater extent than older persons, the full impact of these dietary changes may not be seen until the younger cohort reaches an age when breast cancer mortality is more prevalent. Changes in fat intake in the United States during the 20th century do not correlate well with changes in breast cancer incidence. The average fat intake of Americans rose 27% between 1913 and 1976, with increases in intake of total fat, separated fats and oils, unsaturated fats, and fats from vegetable sources and was associated with little or no change in breast cancer incidence (*13*). This inconsistency may be due to the lack of an association between these types of fat and breast cancer risk or to changes in reporting procedures for breast cancer; it should be investigated further.

*Changes in breast cancer risk in migrant populations.*—Populations that migrate from an area of low breast cancer risk to one of high risk develop the breast cancer risk of the adopted country, as would be expected if an environmental factor such as dietary fat was related to breast cancer risk. Migrants from Poland to the United States reached the higher breast cancer risk seen in American natives within one generation (*52*). Japanese migrants to Hawaii experienced a slower rise in breast cancer risk. Incidence rates for native Japanese, Issei (first-generation Japanese in Hawaii), Nisei (second-generation Japanese in Hawaii), and Caucasians in Hawaii of 13.0, 35.9, 57.2, and 66.2 per 100,000, respectively (*53, 54*), demonstrate a stepwise increment in breast cancer risk with each generation, the Nisei having rates almost equal to those of Hawaiian natives. The lag may be explained by the persistence of previous cultural habits in Japanese migrants and, to a lesser extent, in their first generation offspring.

*Relationship of breast cancer risk factors to nutritional factors.*—Several risk factors for breast cancer appear to be related to nutritional factors. Early age at menarche and late age at menopause, both of which are associated with an increased risk of breast cancer, have been shown to be related to improved nutrition and to increased body weight (*55, 56*). Increased body weight, which is related to the above risk factors, is also associated with an increased risk of postmenopausal breast cancer in Western societies (*57*). In Japan, where the average postmenopausal body weight is less than 50 kg (110 pounds), the postmenopausal rise in breast cancer mortality characteristic of Western societies does not occur (*57*). At autopsy, benign breast disease characterized histologically by epithelial hyperplasia is more prevalent in Nisei (51.4%), who are at increased risk of breast cancer and who have better nutritional status as evidenced by their higher Quetelet index ($wt/ht^2$) than in native Japanese (18.7%), who are at lower risk of breast cancer and who tend to have lower Quetelet indices (*58*). Family history of breast cancer varies internationally and is less common in areas where dietary fat intake is low; this variation appears therefore to be related to environmental factors (*59*). Age at first live birth (or parity, which is closely related) does not appear to be related to nutritional factors.

### Conclusion

The majority of the epidemiologic evidence is consistent with a causal association between dietary fat and breast cancer risk. Most of the recognized risk factors for breast cancer appear to be related to nutritional factors, in keeping with a causal association of dietary fat and breast cancer risk. The lack of correlation between changes in fat intake and breast cancer mortality in the United States during the 20th century is inconsistent with a causal association and should be investigated further.

## Biological Plausibility

### Criterion

The association of dietary fat and breast cancer risk would be biologically plausible if experiments in whole animals confirmed an association between dietary fat and breast cancer risk and if dietary fat could be shown to be associated with histologic changes that are known to be associated with an increased risk of breast cancer. While the purpose of this review is to consider the available evidence in humans, no human experimental data are available, so relevant animal experiments are reviewed briefly. Comprehensive reviews of animal data may be found in (*60*).

*Results of Applying the Criterion*

In 1942 Tannenbaum (*3*) reported the first experimental evidence demonstrating that dietary fat enhanced the development of chemically or spontaneously induced mammary tumors in mice. Subsequent studies (*4*) have demonstrated that increasing levels of dietary fat intake are associated with an increase in the number of animals that develop tumors, the number of tumors that develop per animal, and, in experiments involving the administration of carcinogens, a shortening of the latent interval before the appearance of the tumors. Dietary fat, rather than total caloric intake, appears to be responsible for enhancing tumorigenesis. These studies have also demonstrated that dietary fat acts as a tumor promoter in experiments in mice when 7,12-dimethylbenz[*a*]anthracene is administered as a tumor initiator. Further investigation has shown that small amounts of polyunsaturated fat, providing sufficient amounts of essential fatty acids, must be present for the effect of dietary fat on tumorigenesis in mice to occur (61). There is continuing controversy as to whether polyunsaturated fat exerts a greater effect on tumor growth than saturated fat once the requirements for essential fatty acids have been satisfied (*62*). Further, Welsch et al. (*63*) have shown that dietary fat influences the proliferative activity of mammary epithelium in vivo.

Knazek et al. (*64*) demonstrated that dietary fat had an effect on mammary gland development in mice when they found that linoleic acid was required for the normal development of ductal and alveolar structures in the developing mammary gland and for maintenance of alveolar structures in the adult gland. Wicha et al. (65) demonstrated an effect of fats on the growth of normal and neoplastic mammary cells in culture; unsaturated fats stimulated the growth of both cell types when added to the cell culture medium, whereas the addition of saturated fats inhibited growth.

Thus experiments in animals have demonstrated an effect of dietary fat on mammary tumorigenesis in mice, on the normal development of mammary structures in mice, and on the growth of normal and neoplastic mammary cells in culture. Evidence relating fat to histologic changes leading to the development of mammary tumors is lacking.

*Conclusion*

Experimental evidence supports a causal association between dietary fat and the development of mammary tumors in mice and provides preliminary evidence of an effect of fatty acids on the normal development of mammary structures and on the growth of normal and neoplastic cells in culture. Further investigation is required to determine whether dietary fat induces histologic changes associated with breast cancer.

### Reasoning by Analogy

*Criterion*

The relationship between dietary fat and breast cancer risk should be analogous to other causal associations.

*Results of Applying the Criterion*

There are several examples of causal associations between ingested substances and cancer risk (e.g., the association between alcohol ingestion and head and neck cancer or the relationship between the ingestion of aflatoxins and hepatic cancer). There is no proved association between an essential component of the diet and cancer, although overnutrition is associated with an increased risk of cancer in general (*57*).

*Conclusion*

A causal association between dietary fat and breast cancer risk is not analogous to any previously proved causal association involving an essential component of the diet. Further investigation is necessary to determine whether analogous associations exist.

### Experimental Evidence in Humans

*Criterion*

A causal relationship is most directly demonstrated by showing that changes in the consumption of dietary fat result in changes in breast cancer risk.

*Results of Applying the Criterion*

To date, there is no published experimental evidence in humans that relates dietary fat intake to breast cancer risk.

*Conclusion*

Evidence regarding the effect of alteration of dietary fat intake on breast cancer risk in humans is lacking but, if present, it would provide important information regarding a causal association between dietary fat and breast cancer risk.

## DISCUSSION

The results of applying the criteria for causal inference to the evidence relating dietary fat intake to breast cancer risk are summarized in table 5.

The most important criteria, relating to the consistency of the evidence and the strength of the association, were not satisfied. International correlation studies consistently demonstrated a strong positive correlation between dietary fat and breast cancer risk. When stronger study designs were used (case-control and cohort), a significant association between increased dietary fat intake and breast cancer risk could not be consistently demonstrated, although a weak association may have been present. This failure to demonstrate a significant association may be due to methodologic limitations, in particular, the inaccuracies inherent in measuring past dietary practices and the relatively small ranges of fat intake studied. As shown above, the restricted range of fat intake observed in Western populations and the dif-

TABLE 5.—*Summary of application of Bradford Hill criteria* (14)

| Criterion | Result |
|---|---|
| Consistency | Inconsistent—weak designs positive, strong designs variable. Further investigation required. |
| Strength | Strength maximum when large ranges of fat intake examined. Further investigation required. |
| Time | Consistent with causal association. |
| Biological gradient | Weak support, further investigation needed. |
| Specificity | Dietary fat probably independent of other risk factors, independence from other dietary components not demonstrated. Further investigation necessary. |
| Coherence | Consistent with a causal association. |
| Biology | Further investigation required to relate high-risk histological changes to dietary fat intake. |
| Analogy | Further investigation required. |
| Experiment | Further investigation required. |

ficulty in measuring dietary fat consumption mean that even if the international correlational data do indicate a causal association, observational studies within populations can only be expected to show weak associations. The tendency toward the demonstration of positive associations between specific fatty foods and breast cancer risk in these studies is in keeping with a causal association between fat and breast cancer risk but is not sufficient to confirm that such an association exists.

Given the inconsistency of the published studies and the uncertainty regarding the strength of the association between dietary fat and breast cancer risk, application of the remaining criteria is difficult and serves mainly to identify areas in which further investigation is necessary. Considerable support is available for coherence of the evidence and for the presence of a temporal relationship between dietary fat and breast cancer risk that is consistent with a causal association; however, further evidence relating to the remaining criteria is needed before it can be concluded that a causal association exists between dietary fat intake and breast cancer risk in humans. It is important to note that none of the currently available evidence is sufficient to exclude such an association, and it appears possible that such an association will be confirmed in future studies; however, if the Bradford Hill criteria for causal inference are used as a standard, this association cannot be considered proved in the light of present evidence.

Evidence relating to the consistency and strength of the association between dietary fat and breast cancer risk and to the presence of a biologic gradient could be obtained from future observational studies in humans; however, these studies should examine breast cancer risk over large ranges of fat intake and, ideally, should attempt to measure diet prospectively in order to minimize uncertainty in the measurement of fat intake. Replication of case-control and cohort studies in populations whose dietary practices are relatively homogeneous (e.g., within individual countries) is unlikely to provide much information in addition to that already available. Using the regression model illustrated in text-figure 1, it can be seen that intervention studies that examine fat intake over a large range, say from 15% of caloric intake, which is common in Japan, to 40% of caloric intake, which is normal in Western societies, would have the potential to identify a risk ratio for breast cancer of 4.8. This represents a considerable improvement over the maximum potential RR of 1.4 that could be identified in a large, well-designed cohort study (*6*). The effects of errors in classification of dietary fat intake would also be minimized in such intervention studies, since different levels of dietary fat intake would be assigned and compliance would be measured in a prospective fashion. Thus the use of intervention studies would minimize the limiting effects of two major methodologic problems that are inherent in the investigation of the association between dietary fat and breast cancer risk in Western populations.

The specificity of the association between dietary fat and breast cancer risk, particularly the effect of fat independent of other dietary constituents, would be difficult to determine in observational studies. Intake of fat, protein, and total calories is closely correlated, and it may not be possible to separate their effects in observational studies, regardless of the rigor of the methodology. The manipulation of fat intake in the context of a randomized study, while maintaining caloric intake constant, has been shown to be feasible (*66*), and this approach is more likely to provide useful information regarding the specificity of the association between dietary fat and breast cancer risk. It is unlikely that either observational or intervention studies will differentiate the effect of reduction of dietary fat intake from a compensatory increase in carbohydrate intake. Similarly, the independent effects of fat and protein intake may be difficult to identify with the use of either approach. The specificity of the association with respect to other risk factors for breast cancer could be addressed in an intervention study by balancing treatment groups with respect to important risk factors.

Thus it appears that an intervention study that examines the effects of alterations in dietary fat intake on breast cancer risk would be an appropriate and useful method to obtain most directly the information needed to determine whether a causal association exists between dietary fat and breast cancer risk and is the study design that is most likely to yield unbiased information. The use of an intervention design would have the additional benefit of providing information regarding the effects of changes in fat intake in relation to changes in breast cancer risk.

Concurrent with such intervention studies, investigation of the histologic effects of dietary fat reduction on normal and abnormal breast tissues in the women enrolled in these studies could provide evidence relating to the biologic basis of an association between dietary fat and breast cancer risk, and determination of changes in the levels of hormones, lipids, and their receptors in women enrolled in these studies might provide insight

into the biologic mechanisms by which dietary fat affects breast cancer risk.

The role of many potential causal factors for cancer cannot be investigated using experimental methods, since exposure of human subjects to potential carcinogens is unethical. An experimental approach is feasible in the study of the relationship between dietary fat and breast cancer risk, since exposure to high dietary fat is ubiquitous in our society and the consequences of decreasing this exposure are being examined. Since this approach is the one that is most likely to yield useful information in a reasonable period of time, it is recommended as a means of resolving many of the uncertainties regarding the relationship between dietary fat and breast cancer risk. Successful resolution of these uncertainties could lead to the development of prevention programs for breast cancer that have a major impact on the burden of illness resulting from this disease in our society.

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