Methods for Studying the Relationship between Dietary Fat and Disease Risk

Dietary fat reduction is widely regarded as having major potential for reducing the risk of diseases, including coronary heart disease and several prominent cancers, that are among the most common in our society and among the most elevated relative to disease rates in other societies. Dietary fat reduction is advocated in dietary recommendations of the National Academy of Sciences (1), the American Heart Association, and the National Cancer Institute. The recent Surgeon General’s 1988 report on Nutrition and Health reportedly (2) “identified reduction in fat intake as the top priority for improving the diets of Americans 5 years or older” and “cites data from animal and epidemiologic studies that provide substantial evidence that dietary fat increases the risk for cancers of the breast, colon and prostate.” On the other hand, the scientific community, and particularly the epidemiologic community, appears to be quite ambivalent as to the strength of evidence in support of an association between fat intake and the cancers just listed. The National Cancer Institute’s Women’s Health Trial of dietary fat reduction for the prevention of breast cancer did not proceed to full implementation when peer reviewers questioned the rationale for the hypothesis (3, 4). Similarly, a recent review (5) of the fat and colon cancer literature questions the firmness of the evidence for this hypothesis, on the basis of equivocal or unsupportive analytical epidemiologic data. In fact, even though dietary fat is widely believed to be a strong risk factor for coronary heart disease on the basis of a clear association between saturated fat intake and blood cholesterol concentration, analytical epidemiologic studies of dietary fat and heart disease tend to suggest rather weak associations (e.g., Refs. 6 and 7).

The situation outlined above motivates an examination of the methods used to study the association between dietary fat and disease. Aggregate data studies, including international correlation, time trend, and most migrant studies, are typically regarded as having only hypothesis generating potential in view of the limited ability to control confounding and other biases and in view of limitations that attend available dietary data. Laboratory studies in animals can provide a major stimulus for a dietary fat and disease hypothesis and can allow valuable studies of mechanism, but these too cannot yield definitive results with respect to human disease. Hence, most attention is often directed to the results of analytical epidemiologic studies.

Analytical epidemiologic studies, i.e., cohort and case-control studies, properly play a central role in the study of many disease risk factors. There are, however, two major limitations to such studies in the context of dietary fat as a risk factor: (a) dietary fat intakes are rather homogeneous in populations that have been studied to date; and (b) instruments that are available for individual dietary assessment evidently involve substantial measurement error. It is the authors’ view that these two limitations combine with the potential biases that attend any observational study to imply that analytical epidemiologic studies may be unable to determine reliably the relationship between dietary fat and disease risks.

To illustrate the assertions of the preceding paragraph suppose that dietary fat has a relationship with a study disease that is of public health importance. For example, suppose that the relative risk is a linear function of percentage of calories from fat in the diet, with a 2-fold RR for 40% versus 20% calories from fat, i.e.,

$$\text{RR}(z) = \frac{z}{40}$$

where $z$ denotes the (lifetime) percentage of calories from fat in a person’s diet. Under these circumstances, what relative risk gradient can be expected across fat intake categories in an American cohort or case-control study using available dietary instruments? An answer to this question is provided by the excellent “validation” study (8) of Dr. Walter Willett and colleagues. In this study, 173 United States female nurses in the age range 34–59 years filled out food records for 28 days over the course of 1 year as well as a subsequent food frequency questionnaire that was intended to capture dietary intakes over the same 1-year period. The food records represent an unusually thorough attempt to collect individual dietary data, while the food frequency questionnaire is typical of the type of instrument that is practical for use in large-scale cohort or case-control studies. Let us suppose that the food records give the “true” percentage of calories from fat. Willett et al. (9) present quintile means for $z$ as 32, 36, 39, 41, and 44% based on the food record results. Hence, if such detailed food record information were available for each woman in an analytical study, one would expect relative risks of 0.80 (32/40), 0.90, 0.98, 1.03, and 1.10 across fat intake quintiles under the above relative risk function, and hence, a relative risk gradient of 38% (1.10/0.80 = 1.38). However, the relative risk as a function of the less accurate food frequency percentage of calories from fat, to an excellent approximation (10), is

$$\text{RR}(x) = \frac{E(z|x)}{40}$$

where $E$ denotes expected value. Among women in the lowest food frequency percentage of calories from fat quintile 53, 15, 12, 18, and 3% were in the lowest, second, third, fourth, and highest food record calorie adjusted fat quintiles (Ref. 9, Table 1), which are virtually identical to percentage of calories from fat quintiles. Hence, the average food record percentage of

$$3147$$
calories from fat for women in the lowest food frequency quintile is estimated as

$$32(0.53) + 36(0.15) + 39(0.12) + 41(0.18) + 44(0.03) = 35.6$$

The corresponding estimated average percentages of calories from fat (\(z\)) for women in the second through fifth food frequency quintiles are similarly 37.2, 38.4, 40.4, and 40.8. Hence, a dietary assessment instrument that is practical for use in an analytical epidemiological study defines fat intake categories that differ in actual fat intake by only about 5% across quintiles and for which the corresponding relative risks projected from the above model are 0.89 (35.6/40), 0.89, 0.96, 1.01, and 1.02.

Thus, a modest 15% gradient across quintiles (1.02/0.89 = 1.15) can be expected in an analytical epidemiological study using a dietary assessment instrument of similar accuracy to the Willett food frequency instrument. Such a gradient is in the same range as the types of biases that cannot be ruled out even in the most exemplary cohort or case-control study. Even if such biases are assumed to be totally absent, analytical epidemiological studies would need to be very much larger than those conducted to date in order to have acceptable power. For example, even though the study of Willett et al. (9), with 601 incident breast cancer cases, is the most powerful of existing analytical epidemiological studies of dietary fat and breast cancer, it has an estimated power of only 24% for detecting the relative risk gradient given above at the 5% level of significance, as was estimated by computer stimulation (“Appendix 1”). A cohort study would require about 1500 incident cases, and a pair-matched case-control study about 3000 cases and 3000 controls in order to have a 50/50 chance of detecting such a modest gradient. Since analytical epidemiological studies of cancer and heart disease thus far reported have mostly been based on a few hundred disease events, it is by no means surprising that they have yielded mixed results with many reporting nonsignificant relationships between disease rates and fat intake. Moreover, exercises of the type outlined above raise serious questions as to whether observational studies can, in principle, reliably identify dietary fat effects of major public health importance, regardless of their size or complexity.

Three additional points can be made to indicate that dietary measurement errors may have implications for the results of analytical epidemiological studies that are even more serious than is suggested by the above illustration. First, there is no “gold standard” for assessing the validity of any available dietary assessment instrument. Even the food records in Willett’s validation study (8) involve only 28 days of recording out of several years of fat intake that may be relevant to disease risk. The correlation between the food frequency fat intake estimate and the “true” fat intake may well be less than that between the food frequency and food record fat intake estimates, thereby giving an even more modest relative risk gradient than was indicated above. Equivalently, to the extent that fat intakes during the recording period of the validation study (8) were overestimated or underestimated on both the food record and food frequency instruments, the above projected 15% relative risk gradient will be too large.

Second, differential measurement error associated with fat components can affect analytical study results. For example, if a study disease is affected by polyunsaturated fat in the diet, but not other types of fat, and the pertinent dietary polyunsaturated fat history is uncorrelated with total fat as assessed by an instrument used in an analytical study (the estimated correlation of food record polyunsaturated fat grams with food frequency total fat grams in the Willett validation study is 0.19 with an approximate 95% confidence interval of 0.04 to 0.33), then no gradient at all can be expected between relative risk and total fat in the analytical study. Third, more complicated measurement error effects on relative risk coefficients, including possible sign reversals, may arise if potential confounding factors are also subject to measurement error (11). This may have major implications for the adjustment of relative risk by fat intake category, for total calories or for the intake of other nutrients, in analytical epidemiological studies, depending on the measurement properties of the dietary assessment instrument.

These considerations cause us to question whether or not there is any practical epidemiological method short of a randomized clinical trial that can reliably determine the effects of dietary fat on the major chronic diseases in our society. Certainly the onus should be on those reporting the results of analytical studies to elucidate the measurement properties of their dietary instruments and to convince the reader that confounding, even to the extent of affecting disease rate trends by 15 or 10%, is not present. While the present authors do advocate a large scale intervention trial to investigate the effects of dietary fat on prominent cancers and coronary heart disease, it should be remembered that any such trial is likely to be of such cost and logistical complexity that the public health rationale must be demonstrated in advance. What then can be done using existing observational epidemiological methods to solidify the rationale for a hypothesized relationship between fat intake and diseases of interest?

One important initiative could focus on methodology development. For example, can aggregate data methods be improved, perhaps by the inclusion of standardized dietary and risk factor survey data on appropriate samples of individuals, in order to strengthen their contribution? Can analytical epidemiological studies be improved by the selection of populations having greater heterogeneity of dietary habits, or by theoretical and applied work toward the understanding and accommodation of measurement errors? Might certain biomarkers obviate the need to rely exclusively on dietary recording or recall in analytical studies? In terms of existing data an effort aimed at the quantitative study of the consistency of the various types of epidemiological data pertinent to dietary fat and disease associations would seem well worthwhile. In particular, study of the agreement between relative risk estimates from international correlation studies and from cohort and case-control studies may be revealing with respect to possible strengths of association and sources of bias. Similarly, the disease rate adaptation of migrant groups in comparison to that projected from international comparisons or from analytical studies may be illuminating.

Such a quantitative comparison is attempted below for the study of breast cancer in relation to dietary fat. Breast cancer is selected as one of the most studied and most controversial diseases in its relationship to dietary fat. In fact, a significant number of epidemiologists appear to believe that the absence of association between fat and breast cancer, or at least the absence of any practically important association, has been virtually proved by the results of analytical epidemiological studies.

Analytical Epidemiological Studies of Dietary Fat and Breast Cancer and Their Consistency with International Regression Analyses

Some rather detailed regression analyses of international breast cancer incidence rates were recently presented (12) by
our group. These analyses were based on incidence rates averaged for the years 1973–1977 from Cancer Incidence in Five Continents (13) for 21 countries judged to have good cancer registration and on per capita food disappearance data from the Food and Agriculture Organization of the United Nations (14), averaged for the years 1975–1977. Per capita averages of certain potential confounding factors were obtained from various sources (12). A highly significant ($P = 0.0001$) approximate linear relationship between truncated (age range, 45–69 years) age-standardized breast cancer incidence rates and per capita disappearance of fat calories was observed, with a correlation coefficient of 0.76. Fat calories (or fat grams) showed a somewhat stronger correlation with breast cancer incidence than did percentage of calories from fat, as also turns out to be the case for a number of other cancer sites. The fat calories regression coefficient was virtually unchanged (in fact slightly increased) when nonfat calories were added to the regression equation. The result for nonfat calories was, however, far from significant ($P = 0.88$). A number of additional regression analyses were conducted to identify possible confounding by dietary and non-dietary factors, and to examine the relationship between components of fat and international breast cancer variations. Briefly, national estimates of per capita protein, alcohol, and carbohydrate calories did not relate significantly to corresponding breast cancer incidence rates after accommodating fat calories, while fat calories remained significant with virtually unchanged regression coefficient. Likewise, per capita supply of retinol and $\beta$-carotene did not explain significant international variation in breast cancer rates after accommodating fat calories, while fat calories remained highly significant with essentially unchanged coefficient. Similar results arose when per capita gross national product and national estimates of height, weight, and age at menarche were individually added to fat calories in a linear regression analysis. Finally, data compiled from Ref. 14 were used to examine fat components in relation to breast cancer incidence. Both polyunsaturated and saturated, but not monounsaturated, fat calories explained significant breast cancer variation. The polyunsaturated fat coefficient was about twice as large as the corresponding saturated fat coefficient.

In summary, the factors examined did not provide evidence of confounding. Qualitatively, the relationships between fat components and breast cancer incidence agreed rather well with expectations based on experimental studies in animals (e.g., Ref. 12). However, for reasons mentioned above, such analyses are far from definitive.

The regression analyses just summarized suggest a breast cancer relative risk function that is linear in fat calories. Upon rescaling the fat calorie disappearance data so that the United States value agrees with the average food record fat calories (617.5) in the Willett validation study (8) previously mentioned, one obtains

$$RR(z) = 1 + (z - 617.5)(0.00205)$$

as a breast cancer relative risk function from the international correlation data. For example, a reduction in fat calories by 60% from the mean value (617.5) gives a projected relative risk of 0.24. Such a 60% average reduction was recorded by intervention women in the Women's Health Trial attesting to the public health potential of a practical change in fat intake under the above relative risk function. Similar regression analyses have also been conducted using breast cancer rates from the age range 30–44 and 55–69 years. The regression coefficients from these altered age ranges differed little from that given above.

To evaluate the consistency of international correlational and analytical epidemiological studies one could attempt to project the relative risk function $RR(z)$ to the dietary fat categories used in case-control and cohort studies. In general, such analytical studies use a wide variety of dietary instruments, including various versions of food histories, records, recalls, or frequencies, and use a variety of reporting conventions including total fat intake quartiles or quintiles or other quantiles, as well as such quantiles with calorie adjustment. This diversity of instruments and intake classifications complicates any attempt to combine the pertinent analytical studies in a formal meta analysis.

Useful insight into anticipated results in analytical studies under the above relative risk function can, however, be obtained by again using data from the validation study (8), generously made available by Dr. Walter Willett. Upon identifying the food record fat calories with "true" fat calories in $RR(z)$ and assuming a joint normal distribution for $z$ and the corresponding food frequency fat calories $x$, with mean and variance matrix given in "Appendix 2," one obtains a good approximation

$$RR(x) = 1 + |E(z|x) - 617.5|(0.00205)$$

$$= 1 + (x - 504.7)(0.274)(0.00205)$$

as is elaborated in "Appendix 2." Hence the linear regression coefficient has been attenuated by the factor 0.274 (the covariance of $x$ and $z$ divided by the variance of $x$) in replacing $z$ by the less accurate food frequency measurement $x$. The normal distribution for $x$ mentioned above then leads to projected relative risks across food frequency fat intake categories. For example, the projected relative risks for quartile medians are 1, 1.10, 1.19, and 1.29 while those for quintile medians are 1, 1.06, 1.17, 1.27, and 1.33.

Some analytical studies have presented estimated relative risks for the so-called specific effect of fat; i.e., the effect of fat beyond its contribution to total calories, rather than relative risks for fat itself. For example, Willett et al. (9) present relative risks across calorie-adjusted grams of fat quintiles in which individual fat intakes are adjusted for corresponding calories via linear regression prior to forming quintiles.

As noted above, the international regression analyses do not suggest any relationship between nonfat calories and breast cancer incidence upon accommodating fat calories. Hence from this data source the estimated relative risks as a function of fat calories ($z_1$) and total calories ($z_2$) can be specified as

$$RR(z_1, z_2) = 1 + (z_1 - 617.5)(0.00205)$$

Upon identifying $z_1$ and $z_2$ with food record fat and total calories and assuming a joint normal distribution for those quantities and for food frequency fat ($x_1$) and total calories ($x_2$), one obtains the following projected relative risk as a function of food frequency fat and total calories

$$RR(x_1, x_2) = 1 + (x_1 - 504.7)(0.3624)(0.00205)$$

$$+ (x_2 - 1371.7)(-0.0409)(0.00205)$$

The details of this projection are given in "Appendix 2." It turns out that relative risks as a function of calorie-adjusted fat, as defined in Ref. 9, are virtually identical (see "Appendix 2") to relative risks for $x_1$ given that $x_2$ is equal to its mean (1371.7) in the above expression. It follows, for example, that projected relative risks at the medians of calorie-adjusted fat quartiles are
The above projected relative risks for either fat or calorie-adjusted fat appear to be rather insensitive to the joint normality assumptions, which cannot exactly hold since the relative risk functions must be nonnegative. However, a log-normality assumption for food record and food frequency fat and calories gives virtually identical relative risks to those projected above (see "Appendix 2").

The above projections can be summarized as follows. Under the strong associations between breast cancer and fat intake suggested by international disease rates one expects a relative risk gradient of about 30% across quartiles or quintiles of total fat, or about 18% across quartiles or quintiles of calorie-adjusted fat. Projected relative risk gradients in a given analytical study may differ somewhat from those projections according to the measurement properties of the dietary instrument and to the distribution of "true" fat intakes. The lack of validation study data for most dietary instruments used in analytical epidemiological studies precludes the development of more refined projections for the individual studies.

Before undertaking a review of the analytical studies it is instructive to consider the above projections in the context of a recent well-conducted case-control study. Hirohata et al. (15) summarize their study of 161 Caucasian and 183 Japanese breast cancer cases and pair-matched neighborhood controls, and the collective literature on dietary fat and breast cancer, as follows: "The findings from this study and others seem to indicate that there is an association of dietary fat with breast cancer, and it is a strong one." However, their study gave relative risk estimates across fat intake quartiles of 1, 0.9, 1.1, and 1.3 from the Caucasian pairs and 1, 0.7, 1.1, and 1.5 from the Japanese pairs. These relative risk trends are at least as large as projected from international comparisons (i.e., 1, 1.0, 1.1, and 1.29) under sensible dietary intake and dietary measurement assumptions. The appropriateness of these projections to both components of the Hawaiian study is suggested, but not proved, by the fact that the estimated means ± SD for fat calories were 516 ± 240, respectively, for the Caucasian controls and 437 ± 203 for the Japanese controls, in reasonable correspondence to 505 ± 198 from the Willett validation study. Fat intakes in Ref. 15 were based on histories of the frequencies and amounts of 43 food items that together include about 85% of total fat intake.

The modest projected relative risk gradients noted above imply that extreme care is necessary in the conduct and interpretation of analytical epidemiological studies of dietary fat. Specifically, it seems that the use of hospital-based control series is inadequate. Dietary fat is hypothesized to affect immunological, hormonal, and metabolic parameters that have implications for a broad range of human diseases, including prominent cardiovascular diseases and cancers. In the case-control study (15) described above, the estimated fat intake of hospital controls was more similar to that of the breast cancer cases than to the intake of neighborhood controls, even though patients with certain diagnoses were excluded from the hospital control series. Hence, case-control studies that rely solely on diseased controls may be essentially uninterpretable. Nevertheless, a brief description of such studies is given in the next paragraph.

The study of Graham et al. (16) found no difference between the fat intake of 2024 breast cancer cases and 1463 hospital controls based on a very abbreviated food frequency questionnaire. The Italian study of Talamini et al. (17) obtained food frequency data from 368 breast cancer cases and 373 hospital controls. A significant positive association with the intake of milk and dairy products was reported, but a quantitative estimate of fat intake was not calculated. A recent larger case-control study in this same region [LaVecchia et al. (18)] included 1108 breast cancer cases and 1281 hospital controls. Significantly elevated relative risks were reported at higher levels of fat intake, based on butter, margarine, and oil intakes and at higher levels of meat intake. In comparison, a recent study in Greece [Katsouyanni et al. (19)] found no association with the use of fats or oils, based on data from 120 cases and 120 hospital-based controls.

Now consider case-control studies that have included population-based controls. Some of these have not developed a quantitative estimate of fat intake but, like most of those just listed, have estimated risk as a function of the frequency of intake of selected foods. Lubin et al. (20) reported substantially higher relative risks among Canadian women frequently eating beef, pork, or sweet desserts, although potential interview bias, noted by the authors, requires that these results be very cautiously interpreted. Phillips (21) reported on a small case-control study among Seventh-Day Adventists which gave a positive association with intake of fried potatoes but evidently not with meat intake.

A recent sizable case-control study took place in Vancouver, British Columbia. Based on 846 cases and 862 neighborhood controls, Hislop et al. (22) reported increased breast cancer risk among women who more frequently consume high fat foods, specifically, with frequency of consumption of gravy, beef, and pork intake among premenopausal women, and with frequency of pork intake among postmenopausal women. Lubin et al. (23) recently reported the results of a noteworthy case-control study in Israel. The study involved 818 breast cancer cases and a comparable number of both neighborhood and surgical controls, each of whom provided a detailed food frequency history. Trend statistics were examined to relate breast cancer incidence to quartiles of an index of consumption of food items that contain at least 20% calories in the form of fat. These trend statistics indicate a nearly significant positive association between this rather unusual fat intake index and breast cancer, both for women less than and equal to or greater than 50 years of age, and both in relation to neighborhood and surgical controls.

Two cohort studies also studied breast cancer risk in relation to the frequency of intake of selected foods, without developing a quantitative estimate of fat intake. The study of Hirayama (24) gave, for women of ages 55 years or greater, a standardized breast cancer mortality ratio of 0.42 for no- or occasional-meat eaters versus daily meat eaters. Although this mortality reduction was reported to be significant it is worth noting that there were only 14 breast cancer cases among daily meat eaters. Similarly, a novel cohort study among Japanese living in Hawaii [Nomura et al. (25)] noted that men whose wives developed breast cancer were more likely to eat beef and certain other American foods and less likely to eat typical Japanese foods than were the remainder of the cohort, even though the two groups differed little in other "Oriental practices."

It is difficult to know how to interpret the case-control and cohort studies just listed. Multiple testing considerations along with a possible tendency to specifically report associations with high fat foods may imply that significance levels are not meaningful in these studies. On the other hand, certain eating behaviors, such as the frequent consumption of certain high fat foods or the liberal use of fat-containing condiments, may conceivably...
correlate more closely with "true" fat intake than do available quantitative estimates of fat intake. The fact that some studies report a significant relationship of breast cancer with the intake of certain high fat food items while others do not is to be expected in view of study sample sizes that are generally much smaller than would be necessary for definitive results. On the whole it appears that these studies provide some mild support for the hypothesis that high fat intake is associated with breast cancer risk.

Beyond the analytical studies mentioned above four population-based case-control and two cohort studies have been reported that develop a quantitative estimate of fat intake. We attempt here a quantitative analysis of the results of these studies with regard to both their consistency with the international regression analysis and their consistency with each other. For either purpose it is necessary to assume that measurement properties of the dietary instruments used are similar to those from the Willett food frequency instrument discussed previously and that the distribution of "true" fat intake histories is reasonably similar across studies. This latter assumption is likely inapplicable to the study of Hirohata et al. (26) which took place in Fukuoka, Japan. Hence, we will note only that this study, which involved 212 breast cancer cases and both neighborhood and hospital controls, failed to detect any relationship between the fat intakes of breast cancer cases and those for combined neighborhood and hospital controls.

Table 1 gives information on each of the other five studies. Relative risk estimates for total fat intake are provided along with corresponding relative risks projected from the international data. Table 1 also shows the results of a type of meta analysis in which the five relative risks listed for above versus below the median fat intake are combined and contrasted. As described in "Appendix 3" the summary log-relative risk is a variance weighted combination of the individual log-relative risk estimates. The summary relative risk estimate is 1.19, coincidentally identical to that projected from the international data, with a below the median fat intake, along with an approximate 95% confidence interval, with the method of imputation described in "Appendix 3." For comparison the international data analysis projects a relative risk estimate of 1.19 for above versus below the median fat intake upon using the Willett validation data to acknowledge regression coefficient attenuation due to dietary measurement errors.

The Hawaiian case-control study of Hirohata et al. (15) was discussed previously. Relative risks across fat intake quartiles are at least as large as projected from the international regression analyses.

The study of Miller et al. (27) included 400 cases and control neighborhoods, ages 35 to 74 years, drawn from four areas in Canada. Although several dietary instruments were used, relative risk estimates were based on a detailed dietary history that was intended to cover a 2-month period, 6 months prior to the time of interview. Relative risk estimates were given separately for postmenopausal and premenopausal women. Observed relative risk trends are quite consistent with those projected from the international data analyses. The recent Australian case-control study of Rohan et al. (28) included 451 case-control pairs ages 20-74 years. Fat intakes, based on a self-administered food frequency questionnaire, showed little evidence of any association with breast cancer incidence, although neither is there evidence of discrepancy with the relative risk estimates projected from the international data. Table 1 also shows the results of a type of meta analysis in which the five relative risks listed for above versus below the median fat intake are combined and contrasted. As described in "Appendix 3" the summary log-relative risk is a variance weighted linear combination of the individual log-relative risk estimates. The summary relative risk estimate is 1.19, coincidentally identical to that projected from the international data, with a

### Table 1 Observed and projected* breast cancer RR estimates for population-based case-control and cohort studies that develop a quantitative estimate of fat intake

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th>Study features</th>
<th>Fat classification</th>
<th>RR estimates by fat intake category</th>
<th>Imputed* RR for above vs. below median and approximate 95% confidence interval (numbers in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirohata et al. (15)</td>
<td>161 Caucasian case-control pairs (ages 45-74 yr)</td>
<td>Quartiles</td>
<td>Observed 0.9 1.1 1.3 1.3 (0.8, 2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.10 1.19 1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirohata et al. (15)</td>
<td>183 Japanese case-control pairs (ages 45-74 yr)</td>
<td>Quartiles</td>
<td>Observed 0.7 1.1 1.5 1.5 (1.0, 2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.10 1.19 1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al. (27)</td>
<td>213 postmenopausal case-control pairs</td>
<td>Approximate quartiles</td>
<td>Observed 1.7 1.2 1.8 1.1 (0.8, 1.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.10 1.19 1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rohan et al. (28)</td>
<td>88 premenopausal case-control pairs</td>
<td>Approximate median and upper quartiles</td>
<td>Observed 1.6 1.6 1.6 (0.9, 2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.12 1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary relative risk estimate and approximate confidence interval*</td>
<td></td>
<td></td>
<td></td>
<td>1.19 (1.01, 1.41)</td>
</tr>
<tr>
<td>Heterogeneity significance level*</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort studies</th>
<th>Case-control studies</th>
<th>Fat classification</th>
<th>RR estimates by fat intake category</th>
<th>Imputed* RR for above vs. below median and approximate 95% confidence interval (numbers in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willett et al. (9)</td>
<td>601 cases among 89,538 nurses, ages 34-59 yr</td>
<td>Quartiles</td>
<td>Observed 0.80 0.89 0.95 0.85 1.00 (0.85, 1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.06 1.17 1.27 1.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. (29)</td>
<td>99 cases among 5,485 women, ages 25-74 yr</td>
<td>Quartiles</td>
<td>Observed 0.78 0.95 0.47 0.80 (0.55, 1.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Projected 1.10 1.19 1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary relative risk estimate and approximate confidence interval*</td>
<td></td>
<td></td>
<td></td>
<td>0.97 (0.84, 1.12)</td>
</tr>
<tr>
<td>Heterogeneity significance level*</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.55</td>
</tr>
</tbody>
</table>

* Relative risks are projected from international breast cancer regression analyses using measurement error provisions as described in "Appendix 2."

* Details of relative risk imputation given in "Appendix 3."

* Details of summary relative risk calculations and test of heterogeneity among RR estimates given in "Appendix 3."
correlation between fat and calorie intake these calculations
trends. Relative risks by percentage of calories from fat quartiles
consistent with the 17% trend projected from the international
data. See "Appendix 1" for further study of the agreement
quintiles recorded by Willett et al. (9) do not appear to be
departure from the assumption that food records in Ref. 8 can
seem likely to be very sensitive to measurement characteristics
in Jones et al. (29) suggest a negative trend. In view of the high
results for total fat intake, relative risks by calorie-adjusted fat
distribution of fat to total calories, on disease risk. In line with the
aim to investigate the specific effect of fat, beyond the contri-
been adjusted for calories. As mentioned above such analyses
complexity.

The lower part of Table 1 gives similar results from two
American cohort studies. The study of Willett et al. (9) included
601 incident breast cancers detected during the 4-year follow-
up of 89,538 United States nurses. There was no evidence (P
= 0.50) of trend in breast cancer incidence across quintiles of total
fat intake as estimated by a food frequency instrument. There
is, however, evidence of discrepancy between the trend projected
from international comparisons and that observed in this study.
For example, the upper confidence limit for the imputed above
versus below median relative risk estimate is 1.17, smaller than
the projected value of 1.19. Similarly, the small cohort study of
Jones et al. (29), with 99 incident breast cancers, yields relative
risk estimates across fat intake quintiles that appear to be
discrepant with the international data analysis. This point is
somewhat difficult to judge, however, since this study used only
a 24-h recall for dietary assessment. Such an instrument may
have noticeably poorer measurement error properties than do
those used in the other studies. If this issue is overlooked the
two cohort studies combine to yield a summary relative risk
estimate of 0.97 for above versus below the median in total fat
intake with an associated 95% confidence interval from 0.84 to
1.12. A χ² test of equality of the summary relative risk estimates
from case-control and cohort studies gives a significance level
of P = 0.07, so that there is some evidence of disagreement
between the two types of analytical epidemiological studies.

The above analyses do not lead to any clear inference from
the best of the published analytical studies. The positive asso-
ciation between breast cancer incidence and fat intake indicated
by the case-control studies could be due, for example, to recall
bias. On the other hand, only very modest confounding (e.g.,
confounding that would affect the relative risk gradient by 10
or 20% across fat quintiles) would be necessary to bring the
cohort data into close agreement with the case-control studies
and with the international data projections. As mentioned
previously, it seems optimistic to think that observational stud-
ies can elucidate such minor biases regardless of their size or
complexity.

The two cohort study reports (9, 29) described above also
presented relative risk as a function of fat intakes that have
been adjusted for calories. As mentioned above such analyses
aim to investigate the specific effect of fat, beyond the contribu-
tion of fat to total calories, on disease risk. In line with the
results for total fat intake, relative risks by calorie-adjusted fat
quintiles recorded by Willett et al. (9) do not appear to be
consistent with the 17% trend projected from the international
data. See "Appendix 1" for further study of the agreement
between the results of Ref. 9 and very similar hypothesized
trends. Relative risks by percentage of calories from fat quartiles
in Jones et al. (29) suggest a negative trend. In view of the high
 correlation between fat and calorie intake these calculations
seem likely to be very sensitive to measurement characteristics
of the dietary assessment instrument. For example, modest
departure from the assumption that food records in Ref. 8 can
be taken to be a gold standard devoid of measurement error
could eliminate or reverse the projected trend across calorie-
adjusted quintiles in Ref. 9. Furthermore, it is interesting to
note that even under the above relative risk model, RR(zi,z2),
in which international regression analyses have been used to
hypothesize a major fat effect that is fully specific, the projected
relative risk across food frequency quintiles of total calories
using the method of Ref. 8 is very similar to that for total fat.
More specifically, even if it is assumed that calories have no
effect on breast cancer risk given the corresponding fat intake,
the induced relative risk as a function of food frequency calories
(x₀), obtained by taking expectations over the distribution of
food frequency fat calories (xᵣ) given x₀, is estimated to be

$$RR(x_0) = 1 + (x_1 - 1371.7)(0.000186)$$

from which relative risks across quintiles for total calories (xᵣ)
are, respectively, 1, 1.08, 1.13, 1.18, and 1.26, very similar to
those based on the corresponding fat intake. This exercise
points to the futility of trying to infer the comparative impor-
tance of two such highly correlated variables as fat and calories
based on marginal relative risk estimates, when both variables
are subject to important measurement errors.

Consistency of International Regression Analyses with Results
of Migrant and Other Population Studies

Studies of the disease patterns of migrant groups can provide
an important complement to the study of international disease
rate variations. Specifically, if the international regression anal-
yses of dietary fat are not seriously confounded then the extent
of disease rate adaptation following migration should be able
to be predicted from changes in dietary habits among the
migrants, at least after some years from migration. Unfortu-
nately, many migrant studies rely solely on mortality rather
than incidence data and collect no dietary data on the migrants
themselves, thereby severely limiting their specificity for this
purpose.

A lack of complete adaptation of breast cancer mortality rates
among Japanese and Chinese migrants to the United States
(30–32) is sometimes cited as evidence of a lengthy period of
time for disease rate change or of the importance of exposures
early in life or of nonenvironmental factors, in the determina-
tion of changes in disease risk. Studies of breast cancer inci-
dence, however, indicate that important adaptation toward the
higher United States rates takes place among first generation
Japanese migrants (33, 34). More quantitatively, the observed
ratio of age-adjusted breast cancer incidence rates for Japanese
in the United States compared to Japanese in Japan is 3.5, as
may be obtained from the data of Tominaga (35). This relative
risk can be compared with that projected from international
regression analyses upon taking the intakes of polyunsaturated
(P), saturated (S), and monosaturated (M) fat calories among
Japanese in the United States to be 82, 88, and 88% of corre-
sponding approximate 95% confidence interval of 1.01 to
1.41. Hence, the best of the available case-control studies appear
to be fully consistent with expectation based on international
breast cancer regression analyses. When combined these studies
provide evidence for a positive association between total fat
intake and breast cancer risk. The imputed relative risks from
these case-control studies seem to be quite consistent with each
other (P = 0.50). If the Fukuoka study (26) is included in spite
of the reservations mentioned above, the summary relative risk
estimate would be reduced slightly to 1.14, with an associated
95% confidence interval of (0.98, 1.33).

The two cohort study reports (9, 29) described above also
presented relative risk as a function of fat intakes that have
been adjusted for calories. As mentioned above such analyses
aim to investigate the specific effect of fat, beyond the contribu-
tion of fat to total calories, on disease risk. In line with the
results for total fat intake, relative risks by calorie-adjusted fat
quintiles recorded by Willett et al. (9) do not appear to be
consistent with the 17% trend projected from the international
data. See "Appendix 1" for further study of the agreement
between the results of Ref. 9 and very similar hypothesized
trends. Relative risks by percentage of calories from fat quartiles
in Jones et al. (29) suggest a negative trend. In view of the high
 correlation between fat and calorie intake these calculations
seem likely to be very sensitive to measurement characteristics
of the dietary assessment instrument. For example, modest
departure from the assumption that food records in Ref. 8 can
be taken to be a gold standard devoid of measurement error
could eliminate or reverse the projected trend across calorie-
adjusted quintiles in Ref. 9. Furthermore, it is interesting to
note that even under the above relative risk model, RR(zi,z2),
in which international regression analyses have been used to
hypothesize a major fat effect that is fully specific, the projected
relative risk across food frequency quintiles of total calories
using the method of Ref. 8 is very similar to that for total fat.
More specifically, even if it is assumed that calories have no
effect on breast cancer risk given the corresponding fat intake,
the induced relative risk as a function of food frequency calories
(x₀), obtained by taking expectations over the distribution of
food frequency fat calories (xᵣ) given x₀, is estimated to be

$$RR(x_0) = 1 + (x_1 - 1371.7)(0.000186)$$

from which relative risks across quintiles for total calories (xᵣ)
are, respectively, 1, 1.08, 1.13, 1.18, and 1.26, very similar to
those based on the corresponding fat intake. This exercise
points to the futility of trying to infer the comparative impor-
tance of two such highly correlated variables as fat and calories
based on marginal relative risk estimates, when both variables
are subject to important measurement errors.

Consistency of International Regression Analyses with Results
of Migrant and Other Population Studies

Studies of the disease patterns of migrant groups can provide
an important complement to the study of international disease
rate variations. Specifically, if the international regression anal-
yses of dietary fat are not seriously confounded then the extent
of disease rate adaptation following migration should be able
to be predicted from changes in dietary habits among the
migrants, at least after some years from migration. Unfortu-
nately, many migrant studies rely solely on mortality rather
than incidence data and collect no dietary data on the migrants
themselves, thereby severely limiting their specificity for this
purpose.

A lack of complete adaptation of breast cancer mortality rates
among Japanese and Chinese migrants to the United States
(30–32) is sometimes cited as evidence of a lengthy period of
time for disease rate change or of the importance of exposures
early in life or of nonenvironmental factors, in the determina-
tion of changes in disease risk. Studies of breast cancer inci-
dence, however, indicate that important adaptation toward the
higher United States rates takes place among first generation
Japanese migrants (33, 34). More quantitatively, the observed
ratio of age-adjusted breast cancer incidence rates for Japanese
in the United States compared to Japanese in Japan is 3.5, as
may be obtained from the data of Tominaga (35). This relative
risk can be compared with that projected from international
regression analyses upon taking the intakes of polyunsaturated
(P), saturated (S), and monosaturated (M) fat calories among
Japanese in the United States to be 82, 88, and 88% of corre-
sponding United States intakes. These fractions are obtained
by comparing the average fat intakes of Japanese and Caucasian
controls in the Hawaiian breast cancer case-control study (15)
described previously. Now international regression analyses
(Ref. 12, Table 1) give the following expression for projected
age-adjusted breast cancer rates (Y) as a function of P, S, and
M fat calorie disappearance:

$$Y = -77.924 + 0.475P + 0.260S + 0.0288M$$

from which the projected rate among Japanese in Japan is
DIETARY FAT AND BREAST CANCER

$Y = 56.76$ while that for Japanese in the United States is $Y = 168.18$. These calculations give a corresponding projected relative risk of 3.0, using the Japanese and United States fat disappearance data given in Table 1 of Ref. 12. Hence, the observed disease rate adaptation in breast cancer incidence among Japanese women in the United States appears to be at least as large as that projected from the international data under the assumption that dietary fat is fully responsible for such adaptation. These analyses then suggest that the relative increment in migrant breast cancer rates over those in Japan can be explained by changes in fat intakes and that the disease rate adaptation is rather complete among this migrant group in spite of varying ages at migration and times since migration. Note that the above exercise used dietary assessment data from Ref. 15 only to estimate (the ratio of) average fat intakes for the control groups, whereas the analytical studies depend intrinsically on the dietary intakes for individual study subjects.

Most other studies of breast cancer in migrant groups are based on mortality data. The Polish migrant mortality rates appear to adapt almost completely to the higher United States rates, at least up to about age 65 years, based on the study of Staszewski and Haenszel (36). Similar inferences can be drawn in respect to breast cancer mortality from the experience of Polish migrants to the United Kingdom (37) and from the experience of Polish migrants to Australia (38). The latter suggested complete adaptation of breast cancer mortality rates at least up to age 70 years with most migrants between 7 and 18 years from migration. The experience of Italian migrants to the United States is quite similar to that of Polish migrants in terms of the completeness of adaptation of breast cancer mortality rates to the higher United States rates up to about 60 years of age (39). Italian migrants to Australia have been shown to adopt high-fat eating patterns (40) and to have age-adjusted breast cancer mortality rates that are 43, 60, and 105% of Australian rates among women who are 0–6, 7–18, and 18 or more years from migration (41) based on a data set including 149 breast cancer deaths among women aged 40 years or older.

For completeness, it is also worth mentioning the results of some other population comparisons. For women aged 45 years or older Phillips et al. (42) report a standardized mortality rate of 0.85 for California Seventh-Day Adventists who eat little meat as compared to a demographically similar California comparison group. Kinlen (43) reported on the breast cancer mortality of British nuns who either eat no meat or eat some meat. The no-meat group evidently had a breast cancer mortality rate that was estimated to be 74% of that for the some-meat group, but the standardized breast cancer mortality for the no-meat group compared to the general population was close to unity (0.87). An assessment of consistency of these results with those of the international regression analyses is precluded by a lack of information on the fat intake distribution for these population groups.

Discussion

Several epidemiological data sources have been considered with respect to the relationship between dietary fat and breast cancer. International comparisons suggest an association of major public health importance with about a 4-fold risk reduction corresponding to a 60% reduction in total fat. To the extent that available data permit a quantitative analysis, migrant data also appear to be consistent with such a strong association. Under reasonable dietary measurement assumptions, available case-control studies suggest a positive relationship between total fat intake and breast cancer risk. These studies, as a group, appear to be fully consistent with the international data. Two cohort studies, on the other hand, are supportive neither of the strong association suggested by international data nor of any association between fat and breast cancer. Although not discussed here a positive association between fat intake and rodent mammary tumors is consistently observed under ad libitum feeding, although debate continues concerning the extent to which such an association with fat is specific (see Ref. 12 for a brief review).

Reduction in dietary fat presents an opportunity for disease prevention of major public health potential. International regression analyses suggest that 2- to 5-fold risk reductions may be possible after some appropriate period of time, not only for breast cancer but also for colon, prostate, ovary, endometrium, and rectum cancer and for coronary heart disease. Of course, international comparisons or other aggregate data analyses have inherent limitations that prevent them from establishing such associations. The perspective presented here, however, is that analytical epidemiological studies of dietary fat and disease must also be relegated to the hypothesis-generating category, leaving no reliable epidemiological method for pursuit of these topics of major public health importance. Methodological efforts to strengthen both aggregate and analytical study procedures seem warranted, but equally important, it seems to us, is the conduct of a dietary fat intervention trial. Although expensive and logistically complex, feasibility aspects of such an approach have largely been established. Furthermore, an intervention trial likely provides the only possible scientific approach to determining whether reducing fat intake during the middle or later decades of life can appreciably affect the risks of these prominent diseases.

Acknowledgments

The authors would like to thank Dr. Walter Willett for access to his validation study data and Drs. Walter Willett, Gilbert Omenn, and Larry Kessler for helpful comments.

Appendix 1. Numerical Study of Agreement between the Cohort Study (9) and Certain Relative Risk Functions

A series of additional calculations were carried out to more formally examine the results of the cohort study (9) of United States nurses in relation to a hypothesized risk function with a relative risk of 0.5 for 20% versus 40% calories from fat. Initially the transition matrix that links food record quintiles to food frequency quintiles was regarded as being known without error and trend statistic values for a cohort of similar characteristics (601 breast cancers among 89,538 study subjects) to that used in Ref. 9 were simulated using an IBM PC/AT microcomputer. At each step in the simulation a food frequency quintile $x$ was generated, with values 1 through 5 each having probability 0.2, and a corresponding breast cancer indicator was generated with probability a constant times the corresponding RR($x$) given in the text (i.e., RR(1) = 0.89, …, RR(5) = 1.02), the constant being chosen to give an expected 601 cases when 89,538 such values were generated. After generating these data a trend statistic, of the type used in Ref. 9, was calculated as a test of the hypothesis of no association between breast cancer and percentage of calories from fat. The distribution of the trend statistic was approximated by repeating the entire process 500 times. A total of 118 of the 500 trend statistics (24%) exceeded 1.96 indicating, as previously noted, that such a cohort study would have an estimated probability (power) of about 24% of rejecting the null hypothesis at the

---

5% significance level if, in fact, the hypothesized relative risk function obtains. Similarly, 53 of the 500 trend statistics (11%) were less than zero indicating that the observation of a negative trend statistic as occurred in the Willett study is not a particularly rare event. Note, however, that none of the 500 generated samples gave a trend statistic less than the actual value (~1.57) observed in Ref. 9 for calorie-adjusted fat. Note that percentage of calories from fat and calorie-adjusted grams of fat are virtually identical in Ref. 9. These calculations then indicate that the results of Ref. 9 are not in agreement with the hypothesized relative risk function, assuming that confounding and other biases are entirely absent.

The same conclusion was reached by generalizing the hypothesized relative risk function to

\[ RR(z) = (z/40)e^{\gamma z} \]

where \( \gamma_i \) is an additional parameter for the relative risk in the \( i \)th calorie-adjusted food record quintile \( i = 1, \ldots, 5 \), and conducting a score test of \( \gamma_i = 0 \). This test, under a Poisson approximation to the case counts within each calorie-adjusted food frequency quintile gives a \( \chi^2 \) statistic of value 14.86, leading to a rejection of the \( RR(z) = z/40 \) model with significance level \( P = 0.005 \). The score test for a common \( \gamma_i = \gamma = 0 \) takes value 12.12 on 1 d.f. \( (P > 0.001) \).

Note, however, that relative risk functions of nonlinear form that also specify a relative risk of 0.5 for 20% versus 40% calories from fat can be more consistent with the results of Ref. 9. As a rather arbitrary illustration a relative risk function of logistic form

\[ RR(z) = (50/48)(49)^{z/20-1}[1 + (49)^{z/20-1}]^{-1} - (48)^{-1} \]

would yield a \( \chi^2 \) statistic, derived as above, of value 2.16 \( (P > 0.50) \). This reinforces the point that the nurse study (9) is unable to estimate relative risks below 35% calories from fat.

The food record percentage of calories from fat quintile means and the transition probabilities from food record quintile to food frequency quintile were based on data from 173 subjects who participated in the validation study (8). Hence these estimates are subject to some random variation. Additional computer simulations were therefore carried out to acknowledge this random variation. At each step in this simulation, 175% calories from fat values were generated from a normal distribution with mean 39 and SD 4.5. Such a standard deviation is somewhat smaller than that imputed from the observed food record quintile means, to make some accommodation for measurement error in the dietary record fat intake estimates. We used 175 generated values rather than 173 (the number used in Willett’s dietary questionnaire validation study) so that quintiles were well defined. The quintile means were calculated. Similarly, for each quintile of diet record percentage of calories from fat, 35 values for questionnaire quintiles were generated using the transition probabilities estimated from the validation study. The transition frequencies were calculated. The remainder of the simulation step was carried out as in the previous simulations using the newly generated quintile means and transition frequencies and using \( RR(z) = z/40 \). Only 1 of the 500 simulated trend statistics fell below -1.57, the value generated in the nurses study \( (P = 0.002) \), confirming the discrepancy between the Willett data and the hypothesized relative risk function. In good correspondence with the simulations described previously 9.8% of trend statistics were equal or less than zero, and 25.0% exceeded 1.96.

### Appendix 2. Projections of International Regression Relative Risk Functions to Fat Intake Categories Used in Analytical Epidemiological Studies

Denote by \( z_1 \) and \( z_2 \) “true” fat calories and total calories and by \( x_1 \) and \( x_2 \) estimated fat calories and total calories in an analytical epidemiological study. Suppose that the mean and variance of \( (z_1^*, x_1^*) \) is \( (z_1, z_2, x_1, x_2) \), are, respectively, \( (\mu_{11}, \mu_{12}, \mu_{21}, \mu_{22}) \) = (617.5, 1,619.9, 504.7, 1,371.7) and

\[
\left( \begin{array}{cc}
\sum_{x_1} & \sum_{x_2}
\end{array} \right) = \left( \begin{array}{cccc}
21,496.7 & 41,942.9 & 10,717.2 & 21,116.6 \\
104,595.0 & 20,146.3 & 55,496.3 & 84,473.8 \\
39,099.6 & 232,376.0
\end{array} \right)
\]

the sample mean vector and sample variance matrix for food record fat and total calories and food frequency fat and total calories in the study of Willett et al. (8). Suppose now that the relative risk function is given by

\[ RR(z, x) = 1 + (z - \mu_1)\beta \]

which implies that the dietary measurements \( x \) have no ability to predict disease risk given the corresponding “true” dietary intakes \( z \), and that \( (z^*, x^*) \) is normally distributed. The induced relative risk as a function of dietary measurements is then to an excellent approximation (10)

\[ RR(x) = 1 + [E(z|x) - \mu_1]_\beta = 1 + (x - \mu_2)^T \Sigma^{1/2} \Sigma \beta \]

Hence the induced relative risk as a function of measured fat calories is

\[ RR(x_1) = 1 + (x_1 - 504.7)(39,099.6)^{1/2}(10,717.2)\beta_1 = 1 + (x_1 - 504.7)(0.274)\beta_1 \]

and the induced relative risk as a function of fat calories and total calories is

\[ RR(x_1, x_2) = 1 + (x_1 - 504.7, x_2 - 1,371.7)^T \Sigma^{1/2} \Sigma \beta_2 \]

where \( \beta_1 = (1, 0), \beta_2 = (0, 1), \beta^T = (\beta_1, \beta_2) \),

\[ \Sigma_{zz} = \left( \begin{array}{cccc}
0.05665 & 0.04248 & 0.03644 & 0.02457 \\
0.04121 & 0.02624 & 0.02590 & 0.12049 \\
0.015497 & 0.11953 & 0.00029
\end{array} \right) \]

the sample mean vector and sample variance matrix for the logarithms of food record fat and total calories and food frequency fat and total calories in Ref. 8. Note the above relative risk function can be rewritten

\[ RR(z, x) = 1 + [E(e^1 | w), E(e^2 | w)] - \mu_1^T \beta \]

from which, to a good approximation,

\[ RR(z) = 1 + [E(e^1 | w), E(e^2 | w)] - \mu_1^T \beta \]

where

\[
\theta_i^T = (1, 0), \quad \theta_2^T = (0, 1), \quad \beta^T = (\beta_1, \beta_2) \]

and where

\[ k_i = (\mu_i^T - \mu_2^T) \Sigma_{zz} \Sigma_{x1} \theta_1 + 0.5 \theta_1^T (\Sigma_{zz} - \Sigma_{x1x2} \Sigma_{zz}) \theta_1 \]

for \( i = 1, 2 \). Substitution for \( \mu \) and \( \Sigma \) then gives induced relative risk.
functions

\[ RR^*(x_i) = 1 + (|x_i^{1/3} - 1.81| - 617.5) \beta_i \]

and

\[ RR^*(x_i, x_2) = 1 + (|x_i^{1/3} - 1.81| + x_2^{1/3} - 35.16 - 1619.9) \beta_2. \]

In spite of the different appearance of these expressions from those arising under a normal rather than a lognormal assumption, the corresponding projected relative risks are virtually identical to those given above (e.g., in Table 1). This suggests some degree of robustness of dietary measurement error effects to the distributional form assumption.

Finally, it is of interest to consider the properties of the calorie-adjusted fat procedure used by Willett et al. (9) under the above normal or lognormal measurement assumptions.

Willett et al. (9) attempt to test the hypothesis of no specific fat effect (\( \beta_1 = 0 \) in above notation) by constructing a single index termed "calorie-adjusted fat." This index can be defined in terms of food frequency fat calories \( x_1 \), total calories \( x_2 \), and an estimate \( \overline{S} \) of their variance matrix, as the "residual"

\[ r_i = x_i - \hat{a}x_2 \]

where \( \hat{a} = \overline{S}_{12} \overline{S}_{22}^{-1} \) and where, for example, \( \overline{S}_{12} \) denotes the element in the first row and second column of \( \overline{S} \). Typically, \( \overline{S} \) would be the sample variance matrix for the entire cohort in a prospective study, or the sample variance for the controls in a case-control study. Also denote \( r_2 = x_2 \) so that \( x^T = r^T \hat{A} \)

where

\[ \hat{A} = \begin{pmatrix} 1 & 0 \\ \hat{a} & 1 \end{pmatrix} \]

Now if \( x^T \) is normally distributed with mean \( \mu \) and variance \( \Sigma \), the above relative risk function \( RR(x_i, x_2) \) can be rewritten, for specified \( \hat{a} \), as

\[ RR(r_i) = 1 + (r_i - \mu)^T \Sigma_{xx}^{-1} \Sigma_{ru} \beta \]

where \( \mu = \mu \hat{A}^{-1} \). The relative risk as a function of calorie-adjusted fat (\( r_i \)) is then obtained by taking expected values over the distribution of \( r_2 \) given \( r_1 \). Upon noting that \( r_i \) is normally distributed with mean \( \mu_i \) and variance \( \Sigma_i = (\hat{A}^{-1})^T \Sigma_{xx} \hat{A}^{-1} \), this expectation can be written

\[ RR(r_i) = 1 + (r_i - \mu_i)(1,1) + \Sigma_{rr}(1,2)(\hat{A}^{-1})^T \Sigma_{ur} \Sigma_{ur} \beta. \]

The coefficient for \( r_i - \mu_i(1) \) in the expression for \( RR(x_i, x_2) \) given above from the term

\[ \Sigma_{rr}(1,1)^{-1} \sum_{(1,2)(\hat{a},1)} \sum_{(1,2)\beta} = (a - \hat{a}) \sum_{(1,1)} - 2 \hat{a} \sum_{(1,2)} + \hat{a}^2 \sum_{(2,2)^{-1}} \sum_{(2,2)(\hat{a},1)} \sum_{(2,2)\beta} \]

which is a function of \( (a - \hat{a}) \), the difference between the true regression coefficient \( \alpha = \sum_{(1,2)} \sum_{(2,2)^{-1}} \) and its estimate, \( \hat{a} \), used in forming the calorie-adjusted fat residuals. Hence bias or sampling variation in \( \hat{a} \) may cause some attenuation or bias in the coefficient of \( r_i \). However, setting \( \hat{a} = a \), as would appear to be reasonable in Ref. 9 because of the size of the cohort, and substituting for \( \mu_i \), \( \sum \) gives

\[ RR(r_i) = 1 + (r_i - 6.04)(0.3624 \beta_i - 0.0033 \beta_2) \]

Under these normality assumptions \( r_i \) has estimated mean 6.04 and variance 8391.51 so that one obtains relative risk estimates for quintile medians of \( r_i \) that are identical to those of the previous section for \( x_i \) given \( x_2 \) is equal to its mean, thereby giving the projections noted in the text.

Evidently Willett et al. (9) log transformed their food frequency fat and calorie data in order to improve a normality approximation, before applying their calorie-adjusted procedure. Hence their data analysis procedure involved the formation of quintiles on the basis of

\[ s_i = w_i - \hat{b} w_2 \]

where, as above, \( w_i = (\log x_i, \log x_2) \) and \( \hat{b} = \overline{S}_{12} \overline{S}_{22}^{-1} \) where \( \overline{S} \) is an estimate of the variance of \( w^T \). Upon ignoring sampling variation in \( \hat{b} \) and assuming \( w^T \) to be normal with mean and variances as given above, the estimated relative risk as a function of \( s_i \) and \( s_2 = w_2 \) is obtained by substituting in the expression of \( RR^*(x_i, x_2) \) given above. Hence, one obtains

\[ RR^*(s_i) = 1 + |exp(0.3316s_i + 0.4541s_2)(196.1) - 617.5| \beta_i \]

+ \( |exp(0.0151s_i + 0.2149s_2)(351.6) - 1619.9| \beta_2 \)

Under the assumptions just mentioned, \( s_i \) and \( s_2 \) are statistically independent so that the relative risk as a function of \( s_i \) alone is estimated as

\[ RR^*(s_i) = 1 + |exp(0.3316s_i)(640.3) - 617.5| \beta_i \]

+ \( |exp(0.0151s_i)(1644.2) - 1619.9| \beta_2 \)

Also under these assumptions \( s_i \) has a normal distribution with mean \( -0.9588 \) and variance \( 0.03638 \). The estimated relative risks at quintile medians of the calorie-adjusted fat quantity \( s_i \) are now easily calculated and, once again, agree closely with those arising from a normal rather than a lognormal assumption.

Note that these calculations indicate that the calorie-adjusted fat trend test used in Ref. 9 does not, in general, provide a valid test of the hypothesis of no specific association between fat and breast cancer (\( \beta_i = 0 \)) but rather it tests a hypothesis concerning a rather complicated function of \( \beta_1 \) and \( \beta_2 \), where \( \beta_1 \) is the linear regression coefficient for total calories.

Appendix 3. Relative Risk Imputation and Summarization Methods

This appendix provides notes on the calculations on the right side of Table 1. Consider first the imputed relative risk estimates for the study of Hirohata et al. (15). Estimated fat intake was divided into quintiles based on the control group data. Let \( r_1, r_2, \) and \( r_3 \) denote respective relative risk estimates for the second, third, and fourth quartile relative to the first. The imputed relative risk estimate for above versus below the median in estimated fat intake was then defined simply as \( RR = (r_1 + r_2)/(1 + r_3) \). This quantity is precisely the above versus below median odds ratio estimator if no stratification or other standardization were involved in calculating \( r_1, r_2, \) and \( r_3 \) and is expected to provide a good approximation to an appropriately standardized odds ratio more generally. The variance of the logarithm of \( RR \) was estimated by

\[ \ln \langle RR \rangle = \ln \langle r_1 + r_2 \rangle - \ln \langle 1 + r_3 \rangle \]

where \( n_0 \) and \( n_i \) are the total numbers of controls and cases, respectively. This is the standard variance formula for the logarithm of the odds ratio estimator in the absence of stratification or other standardization in the computation of \( r_i \), \( i = 2,3,4 \). In the presence of the type of standardization considered in the studies of Table 1 this standard error formula can be expected to involve some, presumably slight, underestimation, in which case the approximate 95% confidence intervals on the right side of Table 1 may be slightly too narrow.

In applying these formulae to the data of Miller et al. (27) the four given categories of fat intake for postmenopausal women were regarded as approximate quartiles, while the three categories for premenopausal women were taken to define the approximate median and upper two quartiles.

The above versus below median relative risk estimate from percentage of calories from fat quartiles in the cohort study of Jones et al. (29) was imputed exactly as described above. The variance of the logarithm of this relative risk estimate was approximated as the sum of the reciprocals of the above median and below median number of cases.

The imputed relative risk estimate for above versus below the median calorie-adjusted fat procedure used by Willett et al. (9) under the above normal or lognormal measurement assumptions.
corresponding imputed log-relative risk estimates. The estimated variance can be expected in this estimator in view of the manner of handling the one-half the third fat intake quintile. Some very slight bias toward unity divided by the sum of the relative risks for the first and second and one-half the third fat intake quintile. Some very slight bias toward unity.

The logarithms of the summary relative risk estimates given in Table 1 were calculated as a variance-weighted linear combination of the corresponding imputed log-relative risk estimates. The estimated variance of this log-relative risk estimate is the reciprocal of the sum of the individual log-relative risk variance estimates. The approximate 95% confidence intervals are found by regarding such log-relative risk estimate as being normally distributed. The heterogeneity test statistics are calculated as the sum of the squared difference of each individual log-relative risk estimate from the corresponding summary log-relative risk estimate divided by the estimated variance of the individual log-relative risk estimate.

References


Dietary Fat and Breast Cancer: A Quantitative Assessment of the Epidemiological Literature and a Discussion of Methodological Issues

Ross L. Prentice, Margaret Pepe and Steven G. Self


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/49/12/3147.citation

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.