Table 1. Response duration, time to progression and survival

	Median follow-up	
	16 months	39 months
Mean duration (range)		
CR	6.2 (1–11)	13.7 (1–31+)
PR	7.2 (2–16)	10.0 (2–36+)
CR+PR	8.2	11.1
Median time to progression	1.5	3.0
Median survival (months)	8.0	9.0
Patients alive	38%	11%

their variation after a longer follow-up. No delayed toxicity has been detected.

DISCUSSION

The update of our original work seems to emphasise that some patients responding to chemotherapy for advanced malignant melanoma may have a prolongation of their response as a consequence of adding IFNs to the cytotoxic treatment.

Indeed, in our series we have observed 4/19 objective responses lasting for more than 2 years and this observation is confirmed by other authors, reporting with IFN with or without chemotherapy in malignant melanoma a disease stabilisation in 24% of cases for up to 12 months [5]. Furthermore, in other reports some long-term responses have been found similar to ours [5, 6].

Certainly, these observations need confirmation by ongoing clinical trials in which a treatment randomisation (dacarbazine vs. dacarbazine + IFNs) is proposed, in order to observe any advantage between the different treatment groups in terms of response rate, response duration and survival [5, 7].

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Additional Ecological Evidence: Lipids and Breast Cancer Mortality Among Women Aged 55 and over in China

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That dietary fat increases breast cancer risk has been strongly supported by international data collected among developed countries during the past few decades. Population aggregates with elevated lipid intake have tended to report elevated breast cancer incidence and mortality. This study is an ecological analysis of the association of various indicators of lipid intake with breast cancer mortality in 65 county-wide population aggregates in the People's Republic of China. Although the result is consistent with a positive association between lipid intake and breast cancer risk, the observed association is weaker than the association previously observed. This finding provides only modest support for the possibility of a diet–breast cancer link.
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INTRODUCTION

WHETHER WOMEN in the USA might materially alter their risk of breast cancer by lessening their lipid intake has proven an elusive question, and one that continues to provoke sharp debate. Any proposed answer must address the problem of the ambiguous evidence derived from different research arenas. International variation in fat intake and in breast cancer risk tend to coincide; countries with higher per capita fat intake report higher breast cancer incidence and mortality [1, 2]. As the fat intake of countries increases, the breast cancer rate of those countries tends to increase [3]. Animal experiments are said to consistently indicate that dietary fat increases breast cancer risk [4]. Individual-based human data are less consistent, several well-designed and executed case–control studies apparently failing to show any association [5, 6]. Although Howe *et al.*'s sophisticated meta analysis suggests that the weight of the

case–control evidence supports a dietary lipid–breast cancer association [7], there remains significant variation among case–control studies in support of this association. Two prospective studies reveal little or no association [8, 9]. Howe *et al.*'s prospective study results provide, at best, ambiguous evidence of a positive association between fat intake and breast cancer risk [10].

The interpretation of this human evidence has been widely contested. Willett [11] has suggested that the weakness of support for the hypothesis argues against it, his argument hinging on the ability of epidemiological inquiries to link other putative dietary substances to cancer risk. As carotenoids have been identified as protective against many epithelial cancers, alcohol has been linked to increased breast cancer risk, and dietary fat to increased colon cancer risk, Willett has asserted, any true association of dietary fat intake and breast cancer should have been more consistently revealed by the studies reported thus far.

A particularly vexing problem in interpretation of the human data—the epidemiological data—is that inability to assess diet could obscure the association of dietary practice with breast cancer risk. While random error will not completely obscure even a weak effect in a large, well-executed study [12, 13], such error could readily obliterate the significance of a weak association in a smaller study; patterned error could cause the disappearance of a substantial relative risk from even a large study [14].

It is in light of the debate over interpretation of this evidence that Schatzkin *et al.* [4] have argued that ecological data deserve more attention. Unfortunately, the ecological studies reported thus far have in large part been iterations of the analysis of one data set: the association, among approximately 40 countries with well-developed census, cancer incidence and mortality data, of food disappearance records regarding fat and breast cancer incidence and mortality. Whether the bulk of cancer incidence matches the geographical region from which the food data are derived can be argued. Willett and Stampfer [15] have suggested that this correlation is largely spurious, that apparent variation in diet among these countries is an artifact of variation in reporting errors due largely to wastage. Errors in these data would not be well behaved; they would be concentrated in the more affluent countries and thus positively associated with the risk of breast cancer. The evaluation of additional ecological data sets might help to place that ecological datum in context. This paper provides one such ecological analysis.

METHODS

This study considers the associations among lipid status indicators and breast cancer risk among 65 rural and semirural counties in the People's Republic of China. The counties were selected to provide a broad range of mortality due to the cancers most common in China [16].

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A nationwide mortality survey was conducted in 1976 in 2312 counties on causes of death during 1973–1975. The data collection procedures were rigorously standardised to assure complete and comparable death-cause ascertainment in each county. The 1973–1975 cancer mortality rates were first reported as part of a nationwide cancer atlas [16]. We used these data along with information on the age structure of each county to construct crude breast cancer mortality rates for women aged 55 and older. We wished to use these 55+ rates to approximate postmenopausal breast cancer mortality rates. The menopausal status of cases and residents was not ascertained; these rates only approximate a postmenopausal rate. As the average age at menopause in China is 50, and very few counties had average ages at menopause higher than age 53, these rates probably provide a good description of postmenopausal breast cancer.

In 1983, detailed ascertainment of nutritional status and dietary practices in the 65 counties took place. Two communes were randomly sampled from each county and, in each commune, random samples of 25 males and 25 females aged 35–64 were selected for study. Each subject contributed a 10-ml fasting blood sample and responded to a questionnaire regarding history of dietary practices, alcohol intake, smoking and reproductive experience.

The blood samples were drawn from the subjects between 6:00 a.m. and noon, placed in light-free, insulated jars, and transported on ice to county laboratories. They arrived within 4 h of the last blood drawing of the day. Upon arrival, the samples were fractionated into plasma and red blood cells and preserved at −15°C. The samples were then shipped by air, on dry ice in insulated transport boxes, to Beijing. There they were combined in sex-specific pools for each commune and frozen at −15°C. Thus, two female plasma and two female red blood cell pools were assembled for each of the 65 counties. The pooled samples were transported to Cornell together, on dry ice, in February 1984; the temperatures in the transporter boxes upon arrival at Kennedy Airport in New York City were between −18 and −30°C. At the Cornell Laboratory in Ithaca, New York, the samples were sonicated once to disperse a flocculent precipitate [17], and partitioned into small quantities so that subsequent thawing and refreezing would be unnecessary. Subsequent lipid analysis is described in Chen *et al.* [16]. The plasma and red blood cell data were used to provide summary descriptors of lipid status. As the plasma, red blood cell and questionnaire data were drawn from two communes within each county, they can be regarded as repeat measures. Thus, the correlation between the two measures describes their reliability as descriptors of county lipid status; it can be interpreted as the ratio of true to total variance in the separate measures [18]. The reliability of the scale based on combined indicators from both communes for each county was estimated by Cronbach's coefficient α [18].

In one randomly chosen commune in each county, 30 households were selected for a diet survey composed of 3-day food records. The households were randomly selected from each of two work teams. A nutritionist observed the household during this 3-day diet-survey period, recording total food intake, keeping track of purchases and of food discarded. Children under 2 years of age were excluded. The data were used to index the intake of 25 individual foods and of 14 nutrients. Intake was standardised to a reference man of weight 65 kg, aged 19–59 years, undertaking light, physical labour. The standardisation was designed to ensure comparability among counties. As the data were analysed together for each commune, it is not possible to derive reliability coefficients for measures based on the diet

survey. There is some overlap between these data based on the diet survey and those based on the questionnaire. However, the questionnaire data, which focuses almost exclusively on food frequency and not on quantity, do not lend themselves readily to straightforward construction of nutrient intake indices. The survey data are our sole source of direct information on nutrient intake.

Over 250 blood and dietary variables were recorded. Of these, a few represent especially direct descriptors of the lipid status of human populations. These include six plasma and three red blood cell membrane indicators, and three intake indicators drawn from the dietary survey. Because of its possible pertinence, alcohol intake was considered. Anthropometric status, age at menarche, and history of parity were considered because they represent potential confounders of the lipid–breast cancer association.

The data were analysed using correlation and regression procedures with data transformations for non-linearity, and maximum likelihood techniques that adjust for measurement error in representation of county lipid status [19–21]. We relied heavily on the use of standardised regression coefficients. Although some objection to their use has been registered, Newman and Browner [22] have recently pointed out that standardised coefficients are quite useful for comparing predictors that are measured on different scales. The coefficient describes the number of standard deviation increases in breast cancer corresponding to a single standard deviation increase in lipid status as variously measured.

RESULTS

Table 1 summarises the 65 counties in terms of key variables. The mean county breast cancer mortality rate for women aged 55 years and older is 18.1/100 000. The breast cancer mortality rate for USA women 55 and older, directly adjusted to the age structure of China, is 57.3/100 000, or about three times the Chinese rate (USA rate derived from [23]). The mean total cholesterol and low density lipoprotein (LDL) cholesterol levels in China are well below those of the USA, while the high density lipoprotein (HDL) cholesterol levels are comparable [16]. The mean lipid intake in China is about half that of the USA, although the mean caloric intake is higher. The percentage of calories derived from lipids, therefore, is correspondingly much lower in China than in the USA. The alcohol intake of Chinese women is about one-sixth the mean of USA women [24]. The mean age at menarche in China is 17 years, that in the USA around 12.5. The mean age of first pregnancy in China is comparable to that of the USA, the mean completed parity in China much higher than in the USA [16]. The r values presented are the Pearson correlations between commune levels of each county for each indicator, and the alpha levels refer to Cronbach's α for a scale composed of the average of both commune levels. The alpha coefficient can be interpreted as the ratio of

Table 1. Age 55+ breast cancer mortality, lipid and other risk indicators: the 65 counties

	Mean	S.D.	Min	Max	r	α
Age 55+ breast cancer (mortality rate/100 000)	18.1	10.5	0.0	55.0	—	—
Plasma						
Total cholesterol (mg/dl)	127	16	84	171	0.62	0.77
High density lipoprotein cholesterol (mg/dl)	43.4	5.6	30.8	54.8	0.32	0.48
*Low density lipoprotein cholesterol (mg/dl)	84.0	15.0	49.3	123.8	0.61	0.76
Triglyceride (mg/dl)	103.9	22.2	61.1	172.9	0.56	0.72
Apolipoprotein A-1 (mg/dl)	121	10	96	139	0.44	0.61
Apolipoprotein B (mg/dl)	58	6	41	75	0.33	0.50
Red blood cell						
Total lipid saturates (% of total fatty acid by weight)	40.1	3.0	33.0	48.7	0.13	0.23
Total lipid polyunsaturates (% of total fatty acid by weight)	30.5	3.1	23.4	38.0	0.14	0.25
Ratio: total lipid polyunsaturates/saturates	0.77	0.13	0.53	1.21	0.18	0.31
Diet survey						
Total lipid intake (gm/day)	44.2	22.5	11.9	185.8	—	
Total caloric intake (Kcal/day)	2636	408	1808	3722	—	
Percentage calorie intake from lipids	15.0	6.1	5.9	44.9	—	
Questionnaire						
Height (m)	1.5	0.0	1.5	1.6	0.64	0.78
Weight (kg)	48.6	3.2	43.0	56.8	0.79	0.88
Quetelet index	20.6	1.0	18.5	23.4	0.71	0.83
Alcohol (g/person/day)	1.5	2.8	0.0	17.8	0.53	0.69
Age at menarche (years)	17.0	0.8	15.8	18.9	0.66	0.80
Age at first pregnancy (years)	21.9	1.4	19.6	25.4	0.71	0.83
Total live births	4.3	0.7	3.0	6.9	0.73	0.84

* LDL cholesterol = total cholesterol − HDL cholesterol.

true to total variance in the combined scale indicator. It can be seen that, for total cholesterol, LDL and triglyceride, over 70% of variance is true variance, generated by actual variance in the indicator. The questionnaire data exhibit even higher ratios of true to total variance. On the other hand, the red blood cell data appear to provide extremely unreliable measures of county status. It is important to emphasise that this poor reliability is not necessarily a reflection of the quality of the red blood cell assays; the low alpha coefficient reveals substantial within-county variance relative to between-county variance in red blood cell saturates [18].

Table 2 presents the estimated association of each factor with the breast cancer mortality rate. The first data column contains the standardised bivariate regression coefficient, with the t statistic for that coefficient in parentheses. In the third column, the R^2 statistic describes the proportion of variance in the county breast cancer mortality rate explained by the variable. The table indicates that, of the plasma lipid indicators, cholesterol, low density lipoprotein and apolipoprotein A-1 are the strongest predictors of risk. For each of these, an increase in lipid is associated with an increase in risk. None of the red blood cell fat indicators, on the other hand, is associated with an even approximately substantial alteration of risk. Increased red blood cell saturated fat is associated with an insignificantly lower risk of breast cancer.

The diet survey data provide the most convincing evidence of a positive bivariate association with risk: total lipid, total kilocalorie and the ratio of lipid to kilocalorie intake are each associated with increased risk. The kilocalorie variable is significant only at the 0.10 level but both lipid and the ratio of lipid to total kilocalories are significant at the 0.05 level.

Table 2. Regression estimates: lipid and control factors as predictors of breast cancer risk: the 65 counties study

Predictor	Breast Cancer	
	Standardised regression coefficient*	r^2
Plasma		
Cholesterol	0.24 (1.96)†	0.06
HDL	0.11 (0.86)	0.01
LDL	0.21 (1.72)†	0.04
Triglyceride	−0.11(−0.86)	0.01
Apo A1	0.30 (2.50)‡	0.09
Apo B	−0.01(−0.11)	0.00
Red blood cell		
Saturated fat	−0.16(−1.26)	0.02
Polyunsaturated fat	0.04 (0.28)	0.00
Ratio: poly/sat	0.08 (0.62)	0.01
Diet survey		
Total lipid	0.35 (2.92)†	0.12
Total Kcalories	0.24 (1.94)†	0.06
Ratio: lipid Kcal/total Kcal	0.31 (2.57)‡	0.09
Questionnaire		
Height	0.22 (1.81)†	0.05
Weight	0.19 (1.55)	0.04
Quetelet	0.12 (0.94)	0.01
Alcohol	0.08 (0.66)	0.01
Age at menarche	−0.32(−2.64)‡	0.10
Age at first pregnancy	−0.17(−1.40)	0.03
Parity	0.09 (0.71)	0.01

* t statistic in parentheses.
† $P < 0.10$; ‡ $P < 0.05$.

Table 3. Plasma lipids as predictors of breast cancer rates

Adjusted for	Standardised regression coefficient (t statistic)		
	Cholesterol	LDL	Apo A-1
Cholesterol	—	−0.10(−0.30)	0.26(1.71)*
LDL	0.34(0.97)	—	0.28(2.01)†
Apo A1	0.11(0.81)	0.12 (0.95)	—
Lipid	0.17(1.38)	0.13 (1.09)	0.23(1.97)*
Kcal	0.24(1.99)*	0.20 (1.67)*	0.28(2.41)†
Ratio	0.17(1.43)	0.15 (1.18)	0.24(2.03)†
Height	0.20(1.59)	0.17 (1.30)	0.30(2.56)†
Weight	0.22(1.79)	0.19 (1.46)	0.29(2.42)†
Quetelet	0.24(1.96)*	0.21 (1.66)*	0.29(2.41)†
Age at menarche	0.29(2.46)†	0.25 (2.17)†	0.29(2.56)†

* $P < 0.10$; † $P < 0.05$.

Of the anthropometric data gathered, height is associated with an increase in risk at the 0.10 level, while age at menarche is associated with lower risk. This association of higher age at menarche with lower risk is strong and significant.

On the basis of these Table 2 results, we evaluated the lipid variables with the strongest bivariate associations with risk—cholesterol, LDL, apolipoprotein A-1, lipid, kilocalories and ratio of lipid to total calories—considering the strength of these with control for the other major lipid and anthropometric factors.

Table 3 evaluates the partial association of cholesterol, LDL, and apolipoprotein A-1 with risk, with adjustment for the other lipid and anthropometric variables. It can be seen that the strength and significance of cholesterol level is variable. It persists with control for the anthropometric measures, weight, and age at menarche. It is also statistically significant with control for total kilocalorie intake. The association of LDL levels and risk is less convincing. The strongest and most consistent predictor of risk is apolipoprotein A-1; higher levels are consistently associated with greater breast cancer risk, and this association persists with control for each control factor considered. As mentioned, none of the blood cell fatty acids was associated with risk significantly at the bivariate level, so we did not pursue these with adjustment for other factors.

Table 4 considers the associations of lipid and kilocalorie intake, and the ratio of lipid to total kilocalorie intake, with risk, with adjustment for the other lipid and anthropometric indicators. It can be seen that lipid intake is consistently and significantly associated with risk, its significance declining only with control for the ratio of lipid to total kilocaloric intake. Even with adjustment for total kilocalories, the lipid level is significantly associated with increased risk. Although kilocalorie intake is associated significantly and consistently with risk, that association is weaker than that for total lipid intake. In fact, the association of kilocalorie intake and risk adjusted for lipid intake is insignificant, the t statistic being only 0.92. The ratio of lipid to kilocalorie intake—a mark of the centrality of lipids to the

Table 4. Lipid and calorie intake and breast cancer rates

Adjusted for	Standardised regression coefficient (*t* statistic) Lipid	Kcal	Ratio
Cholesterol	0.31(2.53)†	0.23(1.96)*	0.27 (2.16)†
LDL	0.31(2.55)†	0.23(1.89)*	0.27 (2.22)†
Apo A1	0.29(2.46)†	0.22(1.83)*	0.25 (2.11)†
Lipid	—	0.12(0.92)	−0.08(−0.27)
Kcal	0.30(2.31)†	—	0.29 (2.47)†
Ratio	0.42(1.34)	0.21(1.82)*	—
Height	0.32(2.69)†	0.22(1.85)*	0.29 (2.42)†
Weight	0.33(2.78)†	0.22(1.79)*	0.30 (2.55)†
Quetelet	0.34(2.90)†	0.23(1.85)*	0.31 (2.62)†
Age at menarche	0.28(2.33)†	0.19(1.62)†	0.25 (2.05)†

* $P < 0.10$; † $P < 0.05$.

Table 5. Fitted breast cancer risk patterns: China and USA

Lipid intake (quintile)	Mean lipid intake (calories)	Predictor variables: Lipid calories [risk (RR)]*	Lipid calories, Age at menarche [risk (RR)]†
China			
1	223	14.9(1.0)	15.5(1.0)
2	292	16.2(1.1)	16.5(1.1)
3	369	17.5(1.2)	17.6(1.1)
4	450	19.0(1.3)	18.8(1.2)
5	655	22.6(1.5)	21.7(1.4)
USA			
1	423	18.5(1.0)	35.2(1.0)
2	531	20.4(1.1)	36.7(1.0)
3	612	21.8(1.2)	37.9(1.1)
4	675	22.9(1.2)	38.8(1.1)
5	882	26.6(1.4)	41.7(1.2)

* Crude, post-menopausal risk, age 55+, rate/100 000.
† Based on multivariate model of breast cancer, with mean age at menarche in China, 17 years; in USA, 12 years.

total dietary profile—is nearly as significantly related to risk as is simple lipid intake. As can be seen by a comparison of *t* statistics, the association of the ratio with risk is a bit weaker than the association of lipid levels with risk. It is worth noting that, with total kilocalories taken into account, the ratio of lipid to total kilocalories is statistically significant. On the other hand, if total lipid intake is held constant, the ratio of lipid to total kilocalories becomes nonsignificant—insignificantly negative.

The characteristics of these lipid indicators as measures of the status of individuals are relatively well understood; the degree to which the mean values of the indicators, based on a sample of subjects, typify the lipid status of the counties from which they were drawn is less well understood. Thus, to evaluate the salience of these lipid indicators requires consideration of possible attenuation due to measurement error, or inability of the indicators to completely summarise the lipid status of the counties they represent. The effects of control variables must also be adjusted for attenuation [19, 20]. Several additional analyses based upon structured equation modeling were used to adjust for attenuation of the associations in these data. The reliability coefficients used for this attenuation adjustment are those presented in Table 1 [20, 21]. The results changed little, however, the size of the coefficients increasing but the statistical significance of the indicators actually diminishing with adjustment for less than perfect reliability (results not shown).

Table 5 uses the results of the Tables 2 and 3 regression analyses to interpolate the breast cancer risk for Chinese women age 55+ according to the mean fat intake for the county of their residence. The right-column multivariate risk estimates are based also on adjustment for age at menarche. Also presented are extrapolations to USA women according to their fat intake (mean quintile estimates from [8]) and age at menarche. As noted, the average age at menarche in China is over 17 years, while that in the USA is approximately 12 years.

The data suggest that the relative risk at the top Chinese fat intake quintile rises as high as 1.5, with a similar though slightly weaker pattern if age at menarche is taken into account. Extrapolation to women age 55+ in the USA, based only on fat intake, displayed in the left column, suggests that risk is elevated to approximately the same degree, with a top-quintile relative risk of 1.4. If the equation adjusting for age at menarche is used to extrapolate to women in the USA, the top fat-intake quintile risk is approximately 1.2.

What is also noteworthy is the degree to which these results approximate the actual risk of USA women. With age at menarche not taken into account, the predicted top quintile rate is about half the actual USA rate. If age at menarche is taken into account, the predicted top quintile rate, 41.7/100 000, is about two-thirds the actual. In fact, the lowest predicted quintile rate with age at menarche taken into account (35.2/100 000) exceeds that of the top quintile with age at menarche not taken into account (26.6/100 000).

DISCUSSION

Schatzkin *et al.* [4], arguing that the international coincidence of fat intake and breast cancer risk represents serious evidence, have cited two strengths of ecological data. The first is that ecological analysis captures greater exposure variance than would be found in a single, within-region study. In this study of 65 counties in China, the mean county fat intake ranges from approximately 12 to 186 g/day: a difference of 1500%. As a 186 g/day lipid intake is extraordinary and could be seen as an aberrancy, we repeated the analysis excluding the county with that 186 g/day lipid intake: the results were essentially the same. The quintile means range from approximately 25 to 73 g/day: a difference of 300%. The mean per cent of calories from fat ranges from a county low of 5.9 to a high of 44.8, or a difference of over 700%. The quintile means, ranging from a low of 9 to a high of 24, reveal a nearly 3-fold difference. These compare well with international variation: in the ecological analysis reported by Prentice *et al.* [1], the highest county fat intake was about twice that of the lowest. There is substantial variation in these 65 counties in the rate of breast cancer mortality among women age 55+. The average rate in the upper quintile of counties is approximately 34.7/100 000, that in the lowest quintile approximately 6.6/100 000. The ratio of these rates, 5.3, is higher even than the corresponding ratio in the international comparison published by Prentice *et al.* [1]. There is, in these counties,

substantial variation in both lipid exposure and in breast cancer risk.

Schatzkin *et al.* [4] have recognised that ecological data are subject to confounding; and these results may well be confounded. In these results, for example, higher parity is associated with higher risk and a higher age at first birth with lower risk, these (statistically insignificant) findings contradict nearly all individual-based studies.

Variation in the extent of industrialisation is a possible confounder. However, this study was conducted within relatively rural counties that are relatively homogeneous with respect to industrialisation. The mean county literacy rate is 68%, with most counties between 50 and 90%. The mean county percentage with a middle or junior school education is 17%, with most counties between 9 and 25% [16].

Possible confounding of these data is also reflected in their extrapolation to the USA: absence of confounding would imply that the extrapolation should approximate actual USA experience. In the extrapolations based on fat intake alone, the data generate predicted upper quintile breast cancer mortality rates for the USA that are only about one-half the actual overall rate. Additional variables pertinent to the aetiology of breast cancer are probably partly responsible for the differences between the USA and China. A possible clue to confounding lies in the strong association of age at menarche with breast cancer risk in these data. With age at menarche taken into account, the extrapolation of these findings to USA women comes much closer to approximating their actual risk experience. It is possible that a dietary effect partly reflected in age at menarche could be especially pertinent to breast cancer risk. It is possible that, if premenarcheal diet could be measured, the association of that diet with risk could be stronger than the association observed between population diet and breast cancer risk. Even taking age at menarche into account, however, the analysis suggests that risk is altered to a non-trivial degree by dietary lipid intake.

Several investigators [25] have criticised the focussing of concern upon the consumption of single nutrients, even upon fat intake. It is clearly possible that, though fat intake may be linked to risk, it may be only one of a set of correlated nutrients which contribute to risk. Fat intake may simply indicate a more general dietary pattern which increases risk; it may be the pattern, rather than any single constituent, which increases risk. It may be significant, though, that the association of fat intake with risk does not appear to be a result of confounding by total caloric intake. If both lipids and total calories as risk predictors are evaluated simultaneously as in Table 4, lipid intake clearly emerges as more important. If the ratio of lipid to total calories is juxtaposed to calories as a predictor of risk, that ratio is a significant predictor of risk and calories is insignificant; the higher the ratio of fat to total calories, the higher the risk. If the procedure proposed by Howe *et al.* [7, 10] for distinguishing fat derived from other calories is used, with risk predicted by calories from fats as opposed to calories from protein and carbohydrate, calories from fats is clearly the most important factor: t statistic of fat calorie coefficient = 3.00; t statistic of other calorie coefficient = 0.92; $r^2 = 0.13$. In these data, lipid intake dominates calorie intake as a predictor of breast cancer risk.

As diet in these counties was assessed several years after cancer, interpretations of the association of diet and breast cancer assume that both diet and breast cancer mortality are relatively stable; that diet as reported in 1983 is an indicator of long-term diet, and that breast cancer mortality in 1973–1975 is a good indicator of long-term breast cancer mortality. Over 90% of subjects on average still live in the county of their birth, and dietary practices are largely dependent upon locally grown foods in a food distribution system which has changed little in the past several decades; these support the assumption. Piazza [26] has shown that the proportions of total food energy contributed by grains and other crops, as opposed to animal products, respectively, declined in China between 1950 and 1980. The decline, however, was only from 96 to 94%. Similarly, the proportions of protein contributed by grains and other crops declined from 94 to 91%, while the proportion of fat contributed by grains and other crops has declined from 75 to 62%. In light of the low intakes of protein and especially fat in the Chinese diet, these data can be seen as indicating relative consistency in the composition of that diet. Whether the consistency would have been uniform across each of the 65 counties is difficult to assess; our uncertainty regarding this aspect of the measurement of dietary practices must be regarded as a limitation of these findings.

Although extensive efforts were expended in attempting to provide complete and consistent ascertainment of cancer mortality in each county, some breast cancer mortality in some countries may have been missed or falsely recorded. Such errors, if independent of lipid intake, could cause attenuation of the true association of breast cancer mortality and lipid status [20]. Any association of such errors with lipid status could bias the results. With breast cancer mortality a product of incidence and case fatality, the most desirable indicator of breast cancer risk for this study would be breast cancer incidence. These results could be distorted by associations of case fatality with lipid intake, independent of incidence. Although we have little reason to suspect that this bias is large, it could be, and it could be in any direction.

Whether these results, which apply most directly to postmenopausal breast cancer, generalise to premenopausal breast cancer can be debated. Howe *et al.*'s recent meta analysis [7] suggests that fat intake is related to post-, but not to premenopausal breast cancer. On the other hand, Howe *et al.*'s [10] results revealed a stronger effect in a group of women that included pre, peri and postmenopausal women than in one that included only postmenopausal women. Although the extent to which the findings can be generalised to non-Chinese women can also be debated, there is not a great deal of reason to suspect that patterns observed among the Chinese would not apply to other women.

Most of the lipid–breast cancer associations in these data are positive, although not all are statistically significant. Our best estimate is that relative risk in the upper two fat intake quintiles of China is about 1.1 to 1.4 times that of the lowest quintiles. Such an effect is not trivial. However, with true relative risks in upper fat-intake quintiles of 1.2, it is possible that some individual-based epidemiological studies would fail to uncover a pattern of relative risk enhancement among those with increased lipid intake, especially with dietary measurement error as profound as has been estimated [13].

Schatzkin *et al.* [4] have observed that ecological aggregates typified by high fat consumption can be clearly differentiated from those with low fat consumption. An ecological study is critically limited by the extent to which ecological units reflect homogeneity within those units, and heterogeneity among them. In the ecologic analyses which appear most strongly to evidence the association of fat intake and breast cancer [1], food disappearance data are used to represent each country's lipid intake. The

degree to which such data effectively describe homogeneity within countries and heterogeneity among them is not easily evaluated. Willett and Stampfer [15] have described such data as "unworthy of sophisticated statistical analysis". In this study of 65 counties in China, lipid status measurement was based upon physiological indicators and eating patterns among subjects carefully sampled within the counties studied. It is difficult to imagine that lipid status in this study is not far more adequately assessed than any attempt based on food disappearance data.

The strongest correlation of lipid indicators with breast cancer mortality in this study is about 0.35, with the 95% confidence interval around that correlation encompassing the range (0.13, 0.57). This interval is well beneath the point estimate of the international correlation cited by Schatzkin *et al.* and Prentice *et al.* as strong evidence that dietary fat intake increases breast cancer risk. The correlation in this or any study may be attenuated by error in the measurement of diet and of breast cancer risk. The inability to characterise counties by biological markers reflects their heterogeneity. This within-county as opposed to among-county heterogeneity amounts to a form of measurement error, and measurement error is known to diminish estimates of associations and effects. It is well known that the association of a variable with another cannot exceed the validity of either variable's measurement. The correlation of fat intake and breast cancer risk reported by Prentice *et al.* [1] is approximately 0.76; the highest one observed in this study, that between risk and lipid intake as measured by diet survey, is 0.35. In all likelihood, measurement of lipid status in this study is better than in studies based on food-disappearance data. If the association reported by Prentice represents a valid result, and if this study were to involve better exposure measurement, then the observed correlation in this study should be higher than 0.76, rather than lower.

The alpha reliability coefficients for the indices in these analyses range from about 0.2 to nearly 0.9. The reliability among these counties of an index as well characterised among individuals as cholesterol is only 0.77. The reliability among counties of such readily measured attributes as height and weight, the Quetelet index, and age at menarche range around 0.8 to 0.9. It is difficult to imagine that indices of lipid and total caloric intake would be a great deal more reliable. The intake data were based on household amount-based 3-day food records for 30 households in each county. Although the total number of person days used to typify each county was fairly large, the data are, nonetheless, a mere 3-day snapshot of each study subject's actual dietary pattern. There clearly could be some attenuation of risk in estimates based on such data. However, it is difficult to imagine that food disappearance data could possibly be more accurate than those data.

The dependent variable in this study, breast cancer mortality, represents a relatively uncommon event, and the 55+ female population base of some counties was under 100000. Thus, the number of breast cancer deaths observed in some counties was small and subject to significant random variation. For six counties, the number of breast cancer deaths recorded was ≤ 5. We repeated all lipid, calorie and lipid ratio analyses excluding county observations based on fewer than 10 deaths; the results changed very little. Nevertheless, it is possible that, if the number of person years were larger, thus lessening the impact of random variation, the correlations observed could increase substantially. The relatively small numbers of breast cancer deaths in even the larger counties provide, at best, a flawed indicator of the true breast cancer mortality risk for those counties.

Thus, attenuation due to mismeasurement of lipid exposure and of breast cancer risk could be partly responsible for the divergence of these findings from some others based upon ecological analysis [14]. The standard formula for correcting correlations for measurement attenuation suggests that, if the observed correlation of lipid status and breast cancer risk were 0.35, and the average reliability of both indicators less than 0.5, the true association could exceed 0.7 [18]. It is possible, though not likely, that lipid and mortality reliabilities in these data are that poor.

It must be emphasised that these analyses are based mainly on the use of the data in natural units. The associations were also estimated with logarithmic transformation of breast cancer and each indicator. Use of transformed data would minimise possible distortion by outliers in either breast cancer or the exposure indicators, and would also address modest curvilinearity in the relationship of these factors with breast cancer. We were particularly concerned over the possibility of a 'threshold effect', with risk increasing to a certain point, then levelling off. It has been proposed that all Western countries are at elevated risk, that risk differences can be seen only among societies with substantially lower overall lipid intake. Although these transformations changed some of the lipid coefficients and some of the control variables, the change was modest, and it was difficult to discern any consistent pattern in the results of these transformations. Lipid and total caloric intake reported for one county are extraordinarily high; elimination of that county, however, has a negligible impact on the results. Although we believe the analysis is most sound if based on all the data, the findings in a sample of as few as 65 counties are vulnerable to small numbers of outlying observations.

Thus, these findings provide modest support to the hypothesis linking lipid intake to breast cancer risk. They provide only weak ecological evidence of a positive association, indicating that, in aggregates typified by higher lipid intake, the risk of breast cancer mortality is higher. Stronger evidence emerges from lipid intake data than from data based on biological markers of lipid status. In the end, evaluation of the pertinence of lipid intake, at various points in the life cycle, to breast cancer risk will require consideration of evidence from a variety of epidemiological study designs: case-control and prospective studies, as well as ecological pattern analyses.

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ABEP as Primary Chemotherapy for Hodgkin's Disease

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20 untreated Hodgkin's disease patients and 1 patient relapsing after radiotherapy (17 stage IIB–IV and 4 stage I–IIA) were given doxorubucin, bleomycin, etoposide and prednisone on a 21-day cycle. The response rate was 95% and 16 patients (76%) achieved complete remission. 4 patients have relapsed 2, 5, 22 and 50 months after treatment. Survival was 100% at a median follow-up of 35 months. However, due to dyspnoea on exertion in 2 patients, bleomycin will be abandoned, and the occurrence of two second malignancies questions the role of etoposide as a leukaemogenic agent.

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INTRODUCTION

DRAMATIC IMPROVEMENT in the management of Hodgkin's disease (HD) has been made over the past 20 years with the use of mechloretamine, vincristine, procarbazine and prednisone (MOPP) and similar chemotherapy regimens [1, 2]. However, long term results show an increase in the occurrence of second malignancies [3]. Such toxicity has so far not been the case with ABVD and this regimen has become a valid alternative to MOPP [4]. Furthermore, ABVD is apparently non-cross-resistant to MOPP despite the close relationship between vincristine and vinblastine, and procarbazine and dacarbazine.

The latest chemotherapeutical advance in the past few years comes with the use of etoposide which has emerged as a very active drug for HD, either as single agent [5] or in combination with other agents [6–8].

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In order to develop a new combination containing active drugs with different mechanism of cytotoxicity, we have built the ABEP regimen with doxorubicin, bleomycin, etoposide and prednisone.

PATIENTS AND METHODS

From January 1984 until December 1990, 21 patients requiring chemotherapy for Hodgkin's disease were treated at our institution. 20 patients were previously untreated and 1 was relapsing from radiotherapy. 12 patients were males and the median age was 37 years (range 18–64 years). Investigations included clinical examination, full blood count and erythrocyte sedimentation rate, biochemistry and liver function tests, chest X-ray and computed tomography (CT) scan, abdominal ultrasound or CT scan, bone marrow trephine and aspirate, and appropriate biopsy for histological diagnosis.

15 patients had nodular sclerosis, 3 had mixed cellularity, 2 had lymphocytic predominance and one remained undefined. The majority of patients had advanced disease, 3 with stage IVB, 4 with stage IIIB, 6 with stage IIIA, 4 with stage IIB, 3 with stage IIA and 1 with stage IA.