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Diet, Serum Markers and Breast Cancer Mortality in China

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This county-based correlation study examined associations of breast cancer mortality with dietary habits and certain serum biochemical markers, utilizing data collected from an ecological survey in 65 Chinese rural counties. Univariate correlation and multivariate regression analysis showed that consumption of animal foods, including eggs, fish and meat, was positively linked to county-wide mortality rates of breast cancer in Chinese women. No clear associations between breast cancer mortality rates and consumption of green vegetables, carrots and fruits were observed in this study. A modest inverse correlation between serum vitamin C levels and breast cancer mortality was observed, while selenium levels were positively related to the mortality rates. Positive correlations for serum ferritin and hemoglobin were found, in agreement with recent reports of an elevated cancer risk with increased body iron stores. Limitations of these ecological data preclude causal inferences, but the findings provide clues to breast cancer risk and protective factors in a low incidence area of the world.

Key words: Breast cancer mortality — Diet — Serum marker — China

Breast cancer incidence is relatively low in China compared with western countries.[1)] Within China, however, considerable geographic variation in mortality rates has been observed, with cumulative rates ranging from less than 1 to 8 per thousand women aged less than 65.[2)] The causes of breast cancer are not fully understood, but hormonal factors associated with early menarche, late age at first birth, low parity, and late age at menopause have been documented as risk factors.[3,4)] In addition, dietary and life-style factors, including alcohol drinking, have been linked to breast cancer.[5-9)] With few exceptions,[10)] most of the earlier investigations concerning dietary intake have been conducted in western countries.[9)] To provide clues to the role of dietary and hormonal factors in the geographic variation of breast cancer within China, we correlated breast cancer mortality rates with data from an ecological survey of diet, life-style and biochemical markers in 65 Chinese rural counties.[11)]

MATERIALS AND METHODS

Methods for data collection have been presented in detail elsewhere.[11,12)] Briefly, breast cancer mortality rates obtained during the 1973–75 nationwide survey in China were correlated with ecological data on diet, life-style and biochemical markers collected in a survey in 65 rural counties in 1983. Within each county, 100 adult residents, with approximately equal numbers of men and women in each of the age groups of 35–44, 45–54, and 55–64 years, were randomly recruited from two communes. Ten milliliters of fasting blood were drawn from each study participant and divided into aliquots. The aliquots for each individual were combined into age- and sex-specific pools for each commune. The assumption that pooled samples reflect the average values for individual samples was verified for a number of assays in laboratories in both Beijing, China and at Cornell University in the United States, with good agreement between pooled values and averages of individual values. All assays were then conducted on the pooled blood specimens except for hemoglobin, for which individual samples were used. Only females were included for this correlation study.

At blood collection, a structured questionnaire was administered to obtain information on demographic characteristics, dietary habits, smoking, alcohol drinking and other reproductive variables. Mean responses (for continuous variables such as meat intake, alcohol drinking, and serum vitamin C) and percentage of positive answers (for dichotomous variables such as ever smoked and ever drunk alcohol) were calculated by sex for each county, and treated as independent variables for this correlation study.

The cumulative (to age 64) breast cancer mortality rate was treated as the dependent variable. Pearson correlation coefficients (r)[13)] were calculated as a measure of the relationship between breast cancer mortality and the interview and biochemical variables. In addition, stepwise regression analysis[13)] was performed including all variables significantly correlated with breast cancer mortality, plus factors previously linked with breast cancer. Because of the high correlation between diet and serum markers, analyses were performed separately for dietary variables and serum biochemical markers. Two final models were developed by including variables selected from stepwise regression and those based on *a priori* hypotheses. Log-transformed values for certain variables with skewed distributions were used in the regression. One county with an outlying value for breast cancer mortality was excluded from the analysis. Any county with an outlying value for a study variable was also excluded when the variable was analyzed.

RESULTS

Table I shows the Pearson correlations between the breast cancer mortality rates and geographic, socioeconomic and demographic characteristics. Breast cancer mortality was high in areas with a high percentage of the population employed in industry, and inversely related to county birth rates. No significant association was detected with education, per capita commercial output, and geographic variables (longitude, latitude and heat zone) (Fig. 1).

In univariate analyses (Table II), all animal foods were positively correlated with breast cancer mortality, with the highest correlation coefficient observed for egg consumption. Since the correlation coefficients for each individual animal food were in the same direction and of similar magnitude, these were combined to form an index of animal foods, which was significantly correlated with breast cancer mortality (r=0.27, P<0.05). Furthermore, the average breast cancer mortality rate increased in each tertile of counties with increasing animal food consumption (Table III). The associations between breast cancer mortality and green vegetables, carrots, sweet potatoes, and fruit consumption were not statistically significant. Although intakes were low throughout the counties, total alcohol consumption was moderately associated with elevated risk of breast cancer, while no appreciable correlations were observed for beer, wine and liquor separately.

Among serum nutrients, vitamin C levels were inversely correlated with breast cancer (r=−0.26, P< 0.05). In contrast, a positive association was observed for α-tocopherol. No significant correlations were found for retinol, β-carotene, or selenium levels.

Among other serum markers, levels of hemoglobin (r=0.28, P<0.05) and ferritin (r=0.30, P<0.05) were associated with elevated breast cancer mortality. In addition, a positive correlation between breast cancer mortality and testosterone concentration (r=0.31, P<0.05) was seen, although no significant associations were found for estradiol, sex hormone binding globulin and prolactin. Total cholesterol levels showed a non-significant positive correlation.

A strong inverse association between the mortality rate of breast cancer and age at menarche (r=−0.37, P<0.01) was observed, while no clear associations were found for age at first birth and total numbers of pregnancies (although as noted earlier, the breast cancer rates were correlated with the county birth rates). No associations were seen for the Quetelet index (weight in kg/height in m^2) and average daily consumption of tobacco.

The multiple regression coefficients for the dietary factors are shown in Table IV. After adjusting for county birth rate, a significant positive association was found for consumption of animal foods (r=0.28, P<0.03). No

Table I. Pearson Correlation Coefficients of Female Breast Cancer Mortality Rates with Geographic and Socioeconomic Status, Chinese Rural Counties[a)]

Factor	Correlation coefficient
Heat zone (zones 1–10, increasing order)	−0.137
Latitude (degrees north)	0.078
Longitude (degrees E)	0.181
Per capita commercial output (yuan)	0.210
% with junior/middle school education in 1982	−0.011
Birth rate (1/1000)	−0.291[b)]
% Population employed in industry[c)]	0.389[d)]

a) One of the 65 participating counties was omitted due to an outlying value of mortality.
b) P<0.05.
c) One county was omitted due to an outlying value of the indicated variable.
d) P<0.01.

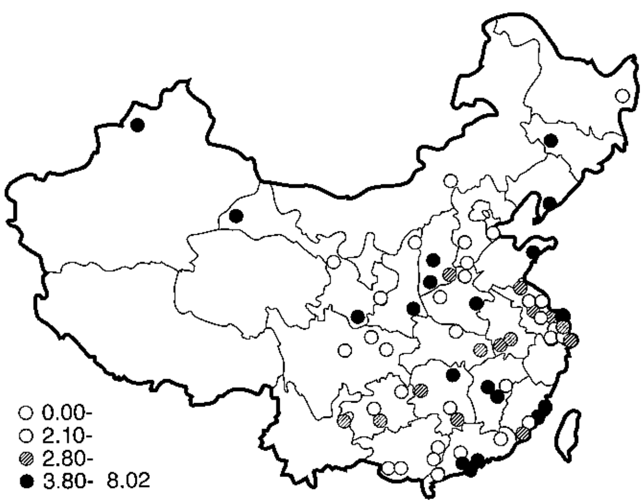

Fig. 1. Geographic distribution of female breast cancer mortality rates in 65 survey counties. (Cumulative rate, 0–64)/ 1000.

Table II. Pearson Correlation Coefficients of Female Breast Cancer Mortality Rates with Selected Blood Elements and Dietary Factors, Chinese Rural Counties[a)]

Study factor	Correlation coefficient	Median
Dietary factors		
Animal foods (times/year)[b)]	0.270[c)]	86.7
Meat[b)]	0.187	35.9
Fish	0.210[d)]	11.5
Egg	0.247[c)]	23.4
Fresh fruits and vegetables (times/year)		
Green vegetables	0.033	192.3
Carrots	−0.047	3.9
Sweet potato	−0.110	24.6
Fruit	0.225	11.5
Alcoholic beverages		
Ever drink (%)		
Beer	0.075	0.0
Wine	0.139	0.0
Liquor	−0.099	3.8
Total alcohol (g/person/day)	0.227[d)]	0.9
Blood elements		
Micronutrients		
Vitamin C (mg/dl)	−0.256[c)]	1.2
Retinol (μg/dl)	0.150	41.4
β-Carotene (μg/dl)	−0.038	10.7
α-Tocopherol (μg/dl)	0.241[d)]	722.5
Selenium (μg/dl)	0.168	8.1
Others		
Total cholesterol (mg/dl)	0.173	125.5
Hemoglobin (g/dl)	0.278[c)]	12.9
Ferritin (μg/dl)	0.298[c)]	45.0
Estradiol (pg/ml)[b)]	0.065	60.8
Sex hormone binding globulin (nmol/liter)	−0.184	72.6
Prolactin (ng/ml)[b)]	−0.171	6.0
Testosterone (ng/dl)[b)]	0.310[c)]	30.0
Others		
Age at menarche (years)[b, e)]	−0.365[f)]	17.0
Age at first birth (years)	−0.125	21.9
Total numbers of pregnancies	0.042	5.3
Quetlet index (weight/height^2)	0.062	20.5
Daily consumption of tobacco[b, g)]	0.021	0.4

a) One of the 65 participating counties was omitted due to an outlying value of mortality.
b) One county was omitted due to an outlying value of the indicated variable.
c) $P<0.05$.
d) $P<0.10$.
e) Data were transformed logarithmically.
f) $P<0.01$.
g) 80% of current consumption of manufactured cigarettes plus total current daily consumption of other tobacco.

significant association was obtained for consumption of green vegetables, carrots/sweet potato, or fruits. A positive, although not statistically significant, association was also observed for alcohol intake (Table III).

Table III. Average Female Breast Cancer Mortality Rates by per Capita Consumption Levels of Animal Foods in Rural Counties of China[a)]

Animal foods[b)] Median (times/year) (Tertile)	Average cumulative breast cancer mortality rate per 1000
41.1	2.44
86.7	2.91
185.7	3.48

a) One of the 65 participating counties was omitted due to an outlying value of mortality.
b) One county was omitted due to an outlying value of animal food intake.

In the multivariate analysis of serum nutrients (Table V), a mild inverse association was observed for vitamin C, whereas the positive association with selenium was strengthened (r=0.31, P=0.01). Ferritin concentration remained a strong positive correlate (r=0.31, P=0.02) of breast cancer in the multivariate model. No significant correlation was found for total cholesterol levels and other antioxidants (α-tocopherol, β-carotene) or retinol with breast cancer mortality.

DISCUSSION

Several dietary factors and serum nutrient markers were linked to breast cancer mortality in this county-based correlation study. Notably, animal foods, including meat, fish and eggs, were significantly correlated with breast cancer mortality. A strong association between breast cancer and increased meat, fat, and protein intake has been noted in international comparisons,[14)] but limited variation has often precluded assessment of correlations within countries. We did not have information on the average percent of calories derived from fat in each county, but intake of animal foods was so low (median consumption of 1.7 times/week) that the counties generally had levels of less than 20% fat. Hence it is noteworthy that, even in this limited range, there was a gradient in risk of breast cancer mortality. Though consistent with a role of fat, findings on fat as a risk factor arising from analytic studies have been mixed,[14–16)] and variation with consumption of animal foods in rural China may reflect other factors, including a generally better standard of living in counties that consumed greater amounts of animal foods. It should be pointed out, however, that adjustment for percentage of population employed in industry, used as an indicator for standard of living, did not substantially alter the association with animal foods.

The relative uniformity in the consumption of fresh vegetables, and the low intake of fruits in rural China,

Table IV. Multiple Regression Coefficients of Female Breast Cancer Mortality Rates with Selected Dietary Factors in Chinese Rural Counties[a]

Dietary factor	RC[b]	SRC[c]	P-value
Animal foods[d, e]	0.003	0.275	0.03
Green vegetables[d]	−0.001	−0.049	0.70
Carrots/sweet potato[d]	−0.001	−0.037	0.77
Fruits[d]	0.012	0.148	0.24
Total alcohol (g/person/day)	0.086	0.177	0.15
Birth rate (1/1000)	−0.072	−0.279	0.02

a) One of the 65 participating counties was omitted due to an outlying value of mortality.
b) Regression coefficients.
c) Standardized regression coefficients.
d) Times/year.
e) One county was omitted due to an outlying value of the indicated variable.

Table V. Multiple Regression Coefficients of Female Breast Cancer Mortality Rates with Selected Blood Nutrients in Chinese Rural Counties[a]

Blood nutrient	RC[b]	SRC[c]	P-value
α-Tocopherol (μg/dl)	0.000	0.001	0.99
Retinol (μg/dl)	0.014	0.080	0.55
β-Carotene (μg/dl)	0.008	0.033	0.80
Vitamin C (mg/dl)	−0.501	−0.201	0.10
Selenium (μg/dl)	0.153	0.308	0.01
Total cholesterol (mg/dl)	0.011	0.134	0.27
Ferritin (ng/ml)	0.025	0.308	0.02
Birth rate (1/1000)	−0.088	−0.344	<0.01

a) One of the 65 participating counties was omitted due to an outlying value of mortality.
b) Regression coefficients.
c) Standardized regression coefficients.

may limit our ability to detect an expected association between their intake and breast cancer.[17] Green vegetables and sweet potatoes are common food items consumed almost daily, while fruits are cash crops and therefore rarely consumed by the local rural population. In our data, the average per capita fruit consumption among the counties was <12 times per year. Although there was an absence of an association with fresh vegetables and fruits, rich sources of vitamin C, serum ascorbic acid levels were inversely linked to breast cancer mortality. Serum vitamin C level has been shown to be a good indicator of dietary vitamin C intake,[18] of importance because our limited questionnaire data are not sufficiently diverse to distinguish dietary intake levels among the counties. Vitamin C has antioxidant and other antitumor effects and has been associated with lower risk of several cancers, especially stomach cancer.[19] The evidence is more limited for breast cancer, but vitamin C has been found to be protective against breast cancer in some epidemiologic studies as well as in animal models.[9, 20]

Because of its antioxidant effect, selenium has been suggested to play a protective role against cancer.[21, 22] Our finding of a significant positive correlation of breast cancer mortality with serum selenium, therefore, is difficult to interpret, although selenium has been linked to increased risks of breast and other cancers in some studies.[23, 24] Chance should not be ruled out as a possible explanation for this association in view of the multiple comparisons in the analyses.

Another finding of interest is the significant positive correlation with serum ferritin concentration. High body iron stores, as measured by indices such as transferrin saturation and serum ferritin, have been linked to cancer in a number of studies.[25–27] It has been suggested that iron can catalyze the production of oxygen radicals[28] and be a limiting nutrient for the growth and development of cancer cells.[29] It has also been shown that iron supply and distribution in breast cancer cells are controlled differently than in normal cells.[30] Our finding adds to the limited evidence of a possible role of body iron stores in cancer risk.

We also found a significant inverse relationship of breast cancer mortality with age at menarche, and a positive correlation with serum testosterone levels. Earlier age at menarche may be related to hormonal factors, but also, in part may be due to an improved and richer diet. Other factors, such as average age at first birth, ranging from 19 to 25 years of age, perhaps have too small a variation to allow detection of a significant effect on breast cancer mortality. Results from the one-time measurement of serum hormones may be difficult to interpret because of the large fluctuation of hormonal levels in a woman's lifecycle. We found no significant associations for most female hormones, but rates rose in proportion to testosterone, an intriguing finding in view of prior reports linking this hormone to obesity,[31] a risk factor for breast cancer, and increased breast cancer risk.[32]

The limitations of this study should be considered when interpreting the results. First, the findings were based on average exposure values and on countywide mortality rates, not on individual data, and thus causal inferences cannot be drawn from these data. Second, mortality rates were obtained from the 1973–1975 survey, but exposure data were from 1983, so the potential cause and effect sequence is out of order. Because of the relative stability in lifestyles of rural Chinese counties, however, the relative values of both the dietary and other exposure variables and the breast cancer mortality rates probably have not changed greatly over time. Finally, we analyzed the associations between breast cancer mortality and a large number of variables, so that some of the apparently significant findings may arise by chance alone. Nevertheless, the inverse association with vitamin C and the positive correlation with animal foods and concentrations of serum ferritin and hemoglobin are biologically plausible and consistent with earlier investigations.

Despite the limitations, our findings from this nationwide, systematic investigation of breast cancer in China indicate that risk factors for this malignancy in the low-risk Chinese rural population may be similar to those in western societies, where breast cancer is a common malignancy. Analytical epidemiologic studies in urban as well as rural areas of China should help to delineate the effect of dietary components on breast cancer risk.

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