# Consumption of Animal Foods, Cooking Methods, and Risk of Breast Cancer[1]

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## Abstract

**Cumulative evidence suggests a possible interaction of cooking methods with diet in the pathogenesis of breast cancer. Studies, however, are few and inconsistent. We evaluated the association of animal food intake and degree of browning by deep-frying with breast cancer risk in a population-based case-control study conducted during 1996–1998 among Chinese women in Shanghai, a population with a traditionally low risk of breast cancer. Included in the study were 1459 cases and 1556 age-frequency-matched controls with response rates of 91.1 and 90.3%, respectively. A validated food frequency questionnaire was used to obtain information on usual intake of animal foods and cooking oils and usual cooking methods. Increasing intake of red meat and freshwater fish was related to a moderately elevated risk of breast cancer risk. Stratified analyses showed that the positive association with red meat intake was primarily restricted to those who used deep-frying cooking method, particularly among those who deep-fried foods to well-done (odds ratio, 1.92; 95% confidence interval, 1.30–2.83 for the highest *versus* the lowest quintile; *P* for trend, 0.002). On the other hand, high intake of nonhydrogenated soybean cooking oil was related to a reduced risk of breast cancer among women who never deep-fried animal foods (odds ratio, 0.48; 95% confidence interval, 0.28–0.82 for the highest *versus* the lowest quintile; *P* for trend, 0.02). The positive association of breast cancer risk with red meat intake, especially well-done red meat, was more pronounced among women with a high body mass index than those without this risk factor, and the test for multiplicative interaction was statistically significant. This study suggests that high intake of deep-fried, well-done red meat may be associated with an increased risk of breast cancer, and the positive association may be modified by body weight. This study also suggests that nonhydrogenated soybean oil, if not used in high-temperature cooking, may be associated with a reduced risk of breast cancer.**

## Introduction

Although ecological studies have suggested a positive correlation between intake of meat and dietary fat and the risk of breast cancer (1, 2), results from analytic studies have been inconsistent (3). Several epidemiological studies have revealed an increased risk of breast cancer associated with high meat intake (4–7). A very recent pooled analysis of nine cohort studies conducted among the Western societies, however, did not find an association (8). Part of the inconsistency may be explained by the fact that the potential modifying effect of cooking methods and doneness level were not evaluated in most of these previous studies (8). Evidence from some animal and recent epidemiological studies has suggested that intake of well-done meat and concomitant mammary carcinogens may be associated with a substantially elevated risk of breast cancer (5, 9–12). The results, however, have not been consistent (13–15), and all previous studies were conducted in Western societies. Fish intake has been suggested to be related to a reduced risk of breast cancer in some (9, 15–17) but not all previous (18) studies. No other study has evaluated the association of breast cancer with fish intake by cooking method. Of the six cohort studies conducted in Western Countries, five suggest no or an inverse association between milk consumption and breast cancer (6, 19–22), and one showed a positive association (7). A recent pooled analysis found no significant association between dairy products and breast cancer risk (8).

Similar to grilling and pan-frying, deep-frying, although rarely studied previously, is a high temperature (typically 240–270°C) cooking method and may also result in the production of many chemicals, including heterocyclic amines and polycyclic aromatic hydrocarbons (23). In addition to volatile mutagenic compounds, nonvolatile detrimental products, such as hydroperoxides, *trans* fatty acids, and aldehydes can be detected in deep-fried soybean oil (24, 25). Deep-frying cooking is one of the most common cooking methods in China and many other countries. However, the association between deep-frying cooking and breast cancer risk has not been studied adequately. Furthermore, very few studies have evaluated the association of breast cancer with the intake of plant seed cooking oils other than olive oil (26–30).

The preponderance of evidence from animal and human studies has substantiated a causal relationship between postmenopausal estrogen levels and the risk of breast cancer (31–33). Mammary carcinogenesis has been demonstrated as a "cell proliferation" model in which hormones, such as estrogens, both induce and promote mammary tumors by increasing mammary cell division (34). It is plausible that cells during division are more susceptible to carcinogenic stimulus, or hormones trigger the progression of the tumor cells initiated by carcino-

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gens. After menopause, adipose tissue is the major site for estrogen synthesis, and women with a high BMI[3] have an elevated level of endogenous estrogens (35). Therefore, it is possible that estrogens and estrogen-related factors, such as BMI, may modify the association between intake of carcinogens from foods cooked at high temperature and breast cancer risk.

Using data from the Shanghai Breast Cancer Study, we evaluated the associations of breast cancer risk with consumption of animal foods and soybean cooking oils according to cooking methods and BMI in a population with a traditionally low risk of breast cancer.

## Materials and Methods

The Shanghai Breast Cancer Study is a population-based case-control study conducted among Chinese women in Shanghai. Eligible cases included all women 25–64 years of age who were newly diagnosed with breast cancer from August 1996 to March 1998. Through a rapid case-ascertainment system, supplemented by the population-based Shanghai Tumor Registry, 1602 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 1459 (91.1%). The major reasons for nonparticipation were refusal (109 cases, 6.8%), death prior to interview (17 cases, 1.1%), and inability to locate (17 cases, 1.1%). Two senior pathologists reviewed all slides to confirm all cancer diagnoses.

The Shanghai Resident Registry, which keeps records for all permanent residents in urban Shanghai, was used to randomly select controls from female residents, and frequency-matched to cases by age (5-year interval). The number of controls in each age-specific stratum was determined in advance according to the age distribution of the incident breast cancer cases reported to the Shanghai Cancer Registry from 1990 to 1993. Only women who lived at the registered address during the study period were considered to be eligible for the study. In-person interviews were completed for 1556 (90.3%) of the 1724 eligible controls. Reasons for nonparticipation included refusal (166 controls, 9.6%) and death (2 controls, 0.1%).

All study participants were interviewed in person by trained interviewers and measured for weight, circumferences of waist and hip, and sitting and standing heights. A structured questionnaire was used to elicit detailed information related to demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight, and family history of cancer. Usual dietary habits over the past 5 years were assessed through in-person interviews using a validated quantitative FFQ that was designed to capture >85% of foods consumed by residents in Shanghai. The FFQ listed 76 food items, including 18 animal foods that were grouped into the following seven food groups in data analyses: red meats, organ meats, white meats, freshwater fish, marine fish, eggs, and milk. Red meat included pork, beef, and lamb meats, and white meat included poultry meats. Information on intake level of soybean, rapeseed, peanut, and lard oils, the four major cooking oils consumed in Shanghai, was also obtained. In a recently completed validation study of about 200 Shanghai women with 24 days (twice a month) of 24-h dietary recalls, we found that the intake level of red meat, fish, and eggs from the FFQ was correlated well with those derived from 24-h dietary survey, and log-transformed correlation coefficients were 0.52, 0.50, and 0.58 ($P < 0.001$) for red meat, total fish, and eggs, respectively.

During the interview, each study participant was first asked how frequently she consumed a specific food or group of foods (per day, week, month, year, or never), followed by a question on how many liangs (1 liang = 50 g) she usually ate per unit of time in the majority of the time over the previous 5-year period, ignoring any recent changes. The participant was also asked whether she used deep-fried and/or stir-fried methods, the two most common cooking methods in Shanghai, to prepare meats, eggs, and fish, and how frequently she used each cooking method in cooking these foods. Furthermore, because deep-frying is regarded as a high temperature cooking method, the participant was asked to report whether she usually deep-fried meat and fish to the level that: level 1, the entire surface is brown with a slightly burnt flavor; level 2, the majority of the surface is brown; level 3, a small portion of surface is brown; level 4, virtually no surface is brown; or level 5, the bone still has bloody color. Levels 1 and 2 described above were considered as well-done in data analyses.

Student's *t* test was used for the comparison of continuous variables between cases and controls, and the $\chi^2$ test was used for categorical variables. Unconditional logistic regression models were used to obtain maximum likelihood estimates of the ORs and their 95% CIs, after adjusting for potential confounding variables (36). Age was included as a continuous variable throughout, and categorical variables were treated as dummy variables in the model. Testing for a linear trend was performed by entering categorical variables as numeric variables in the logistic models. For each dietary variable, subjects were classified into five groups based on the quintile distribution of the variable among controls. Stratified analyses were performed to further define exposure status by cooking methods and to evaluate potential modifying effects. Further analyses for selected food groups by cooking methods were stratified by menopausal status, BMI, and WHR. The 75th percentile of BMI and WHR among controls was used as a cutpoint in these stratified analyses, because Chinese women are, in general, thinner than Caucasian women. All statistical tests were based on two-sided probability.

## Results

Table 1 shows comparisons of cases and controls on demographic factors, known risk factors of breast cancer, and total energy and fat intakes. Compared with controls, cases were slightly younger at menarche and older at the interview, at menopause, and at first live birth. Cases were more likely to have a higher education, a family history of breast cancer among first-degree relatives, a history of breast fibroadenoma, a higher BMI or WHR, and were less likely to exercise. All of these variables were considered as potential confounders and adjusted for in subsequent analyses. No statistically significant differences between cases and controls were observed for parity, months of breastfeeding, alcohol consumption, hormone replacement therapy, and usual intakes of total energy and fat.

Presented in Table 2 are comparisons of the median consumption of animal foods between cases and controls. The median intakes of red meat and freshwater fish were significantly higher in cases than controls. No other significant difference was observed. The associations of intakes of animal foods with the risk of breast cancer are presented in Table 3. After adjusting for total energy and other potential confounders, the risk of breast cancer increased with intake of total meat (*P*

[3] The abbreviations used are: BMI, body mass index; FFQ, food frequency questionnaire; OR, odds ratio; CI, confidence interval; WHR, waist:hip ratio.

*Table 1* Comparison of cases and controls on demographics and selected breast cancer risk factors, Shanghai Breast Cancer Study, 1996–1998

| | Cases[a] ($n$ = 1459) | Controls[a] ($n$ = 1556) | $P$ |
|---|---|---|---|
| Age (yr) | 47.8 ± 8.0 | 47.2 ± 8.8 | 0.03 |
| Education (%) | | | |
| No formal education | 3.6 | 5.5 | |
| Elementary school | 8.5 | 8.4 | |
| Middle and high school | 74.3 | 75.4 | |
| Professional, college, and above | 13.6 | 10.7 | 0.01 |
| Breast cancer in first-degree relatives (%) | 3.7 | 2.4 | 0.05 |
| Ever had breast fibroadenoma (%) | 9.6 | 5.0 | <0.01 |
| Regular alcohol drinking (%) | 4.0 | 4.1 | 0.99 |
| Ever used oral contraceptives (%) | 21.9 | 20.9 | 0.51 |
| Ever used hormone replacement therapy (%)[c] | 2.9 | 2.7 | 0.76 |
| Ever exercised (%) | 18.8 | 25.2 | <0.01 |
| BMI (kg/m$^2$) | 23.5 ± 3.4 | 23.1 ± 3.4 | <0.01 |
| WHR | 0.81 ± 0.06 | 0.80 ± 0.06 | <0.01 |
| Nulliparous (%) | 5.1 | 3.9 | 0.13 |
| Number of live births[b] | 1.5 ± 0.85 | 1.5 ± 0.86 | 0.54 |
| Age at first live birth[b] (yr) | 26.8 ± 4.2 | 26.2 ± 3.9 | <0.01 |
| Age at menarche (yr) | 14.5 ± 1.6 | 14.7 ± 1.7 | <0.01 |
| Postmenopausal (%) | 34.8 | 36.4 | 0.35 |
| Age at menopause[c] (yr) | 48.1 ± 4.6 | 47.5 ± 4.9 | 0.02 |
| Energy intake (kcal/day) | 1871.0 ± 464.5 | 1845.1 ± 463.6 | 0.13 |
| Total fat intake (g/day) | 36.1 ± 17.4 | 35.3 ± 16.2 | 0.08 |

[a] Unless otherwise specified, mean ± SD are presented. Subjects with missing values were excluded from the analysis.
[b] Among women who had live births.
[c] Among postmenopausal women.

*Table 2* Comparison of animal foods consumed by cases and controls, Shanghai Breast Cancer Study, 1996–1998

| Type of animal foods | Median (25th, 75th percentile), g/day | | % difference[a] | $P$[b] |
|---|---|---|---|---|
| | Cases ($n$ = 1459) | Controls ($n$ = 1556) | | |
| Total meat | 74.8 (47.4, 116.7) | 69.1 (45.6, 102.1) | 8.2% | <0.0001 |
| Red meat | 57.6 (36.5, 90.3) | 53.1 (33.1, 78.2) | 8.5% | <0.0001 |
| Organ meat | 0.7 (0, 3.3) | 0.7 (0, 3.3) | 0.0% | 0.97 |
| White meat | 11.0 (4.4, 22.0) | 10.4 (4.5, 22.0) | 5.8% | 0.35 |
| Fish | 27.4 (15.0, 47.3) | 24.8 (12.9, 45.7) | 10.5% | <0.0001 |
| Freshwater fish | 12.4 (4.8, 20.7) | 9.7 (3.9, 20.7) | 27.8% | <0.0001 |
| Marine fish | 10.0 (3.5, 25.0) | 10.3 (3.5, 25.0) | −2.9% | 0.68 |
| Eggs | 25.1 (12.6, 44.0) | 25.1 (12.6, 44.0) | 0.0% | 0.05 |
| Milk | 13.7 (0, 200.0) | 28.6 (0, 200.0) | −52.1% | 0.59 |

[a] Expressed as ($median_{cases}$ − $median_{controls}$)/$median_{controls}$.
[b] $P$s (two-sided) were from the Wilcoxon rank-sum test.

for trend, 0.002), with an OR of 1.58 (95% CI, 1.22–2.04) for the highest *versus* the lowest quintile of intake. Analyses by meat type showed that the positive association was confined to red meat intake. The risk of breast cancer also increased with intake of fish ($P$ for trend, <0.0001), with a 60% elevated risk (95% CI, 1.31–2.11) associated with the highest intake quintile compared with the lowest intake quintile. This increased risk, however, was attributed to the intake of freshwater fish. A high intake of eggs was associated with a slightly reduced risk of breast cancer, but the ORs were not statistically significant. No association was found for milk intake with breast cancer risk.

The associations of intake of meat and fish with the risk of breast cancer were further analyzed, stratified by the use of deep-fried cooking method (Table 4). The positive association between red meat intake with breast cancer was primarily confined to those who ever used the deep-frying method in cooking red meat ($P$ for trend, 0.005), particularly those who usually deep-fried red meat until well-done ($P$ for trend, 0.002). White meat consumption was not related to risk, whereas freshwater fish intake was positively related to risk in all three strata defined by use of the deep-frying method. Similar patterns of the above associations were observed in both pre- and postmenopausal women (data not shown in tables). For example, among women who usually deep-fried red meat until well done, the ORs across quintile with increasing red meat intake were 1.00, 1.05, 1.69, 149, and 1.89 ($P$ for trend, <0.01) for premenopausal women and 1.00, 1.96, 1.70, 1.44, and 2.04 ($P$ for trend, 0.17) for postmenopausal women.

To evaluate potential modifying effects of WHR and BMI on the associations of intake of red meat and freshwater fish with the risk of breast cancer risk by cooking method, additional stratified analyses were performed (Table 5). The risks were substantially elevated with increasing intake of red meats, particularly deep-fried, well-done red meat, among those who had a high BMI (25 or greater), whereas the dose-response relation was less apparent among thinner women. The tests for

*Table 3* Association between consumption of animal foods and cooking oils and the risk of breast cancer, Shanghai Breast Cancer Study, 1996–1998[a]

| Food items | Intake quintile | | | | | |
|---|---|---|---|---|---|---|
| | Q1 (low) | Q2 | Q3 | Q4 | Q5 | *P* for trend |
| Total meat | 1.0 | 1.05 (0.83–1.33) | 0.98 (0.77–1.26) | 1.03 (0.80–1.31) | 1.58 (1.22–2.04) | 0.002 |
| Red meat | 1.0 | 1.00 (0.79–1.28) | 1.26 (0.98–1.59) | 1.00 (0.78–1.29) | 1.53 (1.19–1.96) | 0.003 |
| Organ meat | 1.0 | 1.30 (0.90–1.89) | 1.00 (0.81–1.23) | 1.14 (0.94–1.39) | 0.93 (0.75–1.15) | 0.98 |
| White meat | 1.0 | 0.94 (0.74–1.19) | 0.85 (0.67–1.07) | 0.90 (0.71–1.13) | 1.03 (0.82–1.31) | 0.95 |
| Fish | 1.0 | 1.24 (0.97–1.58) | 1.28 (1.02–1.62) | 1.30 (1.03–1.65) | 1.66 (1.31–2.11) | <0.0001 |
| Freshwater fish | 1.0 | 1.08 (0.86–1.36) | 1.23 (0.96–1.57) | 1.41 (1.12–1.76) | 1.48 (1.16–1.89) | 0.0001 |
| Marine fish | 1.0 | 0.80 (0.63–1.02) | 0.90 (0.73–1.11) | 0.87 (0.69–1.08) | 1.14 (0.90–1.45) | 0.53 |
| Eggs | 1.0 | 0.94 (0.75–1.19) | 0.87 (0.69–1.09) | 0.79 (0.65–0.97) | 0.88 (0.67–1.16) | 0.04 |
| Milk | 1.0 | 0.82 (0.66–1.02) | 0.92 (0.77–1.10) | 1.09 (0.84–1.41) | | 0.61 |

[a] All ORs are adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, WHR, age at menarche, physical activity, ever had live birth, age at first live birth, menopausal status, age at menopause, and total energy.

*Table 4* Association between consumption of meat, fish, and cooking oils and the risk of breast cancer stratified by use of deep-frying cooking method and doneness level, the Shanghai Breast Cancer Study, 1996–1998[a]

| Food items (g/day) | Use of deep-fried cooking method | | | | | |
|---|---|---|---|---|---|---|
| | Never | | Ever | | Well-done | |
| | Cases/Controls | OR (95% CI) | Cases/Controls | OR (95% CI) | Cases/Controls | OR (95% CI) |
| Red meat | | | | | | |
| ≤28.6 | 153/172 | 1.00 | 95/140 | 1.00 | 81/126 | 1.00 |
| ≤44.6 | 118/150 | 0.90 (0.64–1.26) | 135/161 | 1.20 (0.84–1.71) | 122/142 | 1.31 (0.89–1.91) |
| ≤62.2 | 129/143 | 1.01 (0.72–1.41) | 184/168 | 1.63 (1.15–2.30) | 164/154 | 1.71 (1.18–2.48) |
| ≤87.1 | 110/135 | 0.84 (0.59–1.20) | 148/176 | 1.25 (0.88–1.78) | 133/147 | 1.44 (0.98–2.11) |
| >87.1 | 165/115 | 1.49 (1.04–2.15) | 222/195 | 1.78 (1.24–2.55) | 200/166 | 1.92 (1.30–2.83) |
| Trend test | $P = 0.11$ | | $P = 0.005$ | | $P = 0.002$ | |
| White meat | | | | | | |
| ≤3.8 | 190/204 | 1.00 | 120/122 | 1.00 | 111/112 | 1.00 |
| ≤6.9 | 110/111 | 1.03 (0.73–1.46) | 159/187 | 0.87 (0.62–1.22) | 149/173 | 0.88 (0.62–1.24) |
| ≤12.8 | 94/119 | 0.78 (0.55–1.10) | 174/199 | 0.88 (0.63–1.22) | 168/187 | 0.89 (0.63–1.25) |
| ≤23.6 | 91/115 | 0.75 (0.52–1.07) | 197/190 | 0.99 (0.71–1.39) | 184/174 | 1.02 (0.73–1.44) |
| >23.6 | 111/110 | 0.96 (0.67–1.37) | 217/201 | 1.06 (0.76–1.48) | 207/209 | 1.05 (0.74–1.48) |
| Trend test | $P = 0.30$ | | $P = 0.37$ | | $P = 0.38$ | |
| Freshwater fish | | | | | | |
| ≤2.9 | 132/201 | 1.00 | 139/157 | 1.00 | 124/133 | 1.00 |
| ≤8.3 | 123/180 | 1.10 (0.79–1.53) | 171/182 | 1.05 (0.77–1.45) | 156/161 | 1.05 (0.74–1.47) |
| ≤12.4 | 115/134 | 1.33 (0.94–1.88) | 126/127 | 1.12 (0.79–1.58) | 109/116 | 1.02 (0.70–1.47) |
| ≤20.7 | 172/156 | 1.62 (1.17–2.23) | 193/169 | 1.23 (0.89–1.69) | 176/150 | 1.21 (0.86–1.70) |
| >20.7 | 142/135 | 1.46 (1.03–2.07) | 146/114 | 1.50 (1.05–2.13) | 132/94 | 1.52 (1.05–2.22) |
| Trend test | $P = 0.003$ | | $P = 0.02$ | | $P = 0.02$ | |
| Marine fish | | | | | | |
| ≤3.5 | 241/249 | 1.00 | 146/140 | 1.00 | 132/119 | 1.00 |
| ≤5.8 | 86/112 | 0.74 (0.53–1.05) | 107/121 | 0.79 (0.55–1.12) | 96/99 | 0.84 (0.57–1.24) |
| ≤15.0 | 152/195 | 0.82 (0.62–1.10) | 195/198 | 0.93 (0.68–1.27) | 178/188 | 0.86 (0.62–1.19) |
| ≤25.0 | 105/141 | 0.80 (0.58–1.10) | 175/176 | 0.89 (0.65–1.24) | 154/154 | 0.87 (0.61–1.23) |
| >25.0 | 100/109 | 0.94 (0.67–1.33) | 152/114 | 1.29 (0.91–1.84) | 137/95 | 1.32 (0.91–1.93) |
| Trend test | $P = 0.43$ | | $P = 0.17$ | | $P = 0.25$ | |

[a] All ORs are adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, WHR, age at menarche, physical activity, ever had live birth, age at first live birth, menopausal status, age at menopause, and total energy.

multiplicative interaction between red meat intake and BMI were statistically significant. After further stratifying analysis by menopausal status, the potential interaction of well-done red meat intake with BMI only appeared among postmenopausal women (data not shown in the table). For example, the ORs were 1.00, 3.37, 3.20, 2.42, and 3.83 (*P* for trend, 0.12) with increasing intake of red meat (deep-fried until well done) among women with a BMI ≥25. On the other hand, the corresponding ORs were 1.00, 1.38, 1.33, 1.13, and 1.37 among thin women (BMI <25). Similarly, the association of red meat intake with breast cancer risk appeared stronger among women with a high WHR than those with low WHR, although the test for interaction was not statistically significant (Table 5). The potential modifying effect of WHR, however, was observed in both pre- and postmenopausal women (data not shown in the table). The associations between freshwater fish and breast cancer risk did not vary appreciably by the level of BMI and WHR (data not shown).

We also analyzed the association between cooking oil consumption and breast cancer risk by cooking method (data not shown in tables). Soybean oil accounts for ~94% of cooking oils used in Shanghai. Intake of soybean oil was related to a reduced risk of breast cancer among women who never used the deep-frying method in preparing animal foods (*P* for trend,

*Table 5* Association of intake of red meat or deep-fried well-done red meats with breast cancer risk stratified by BMI and WHR, Shanghai Breast Cancer Study, 1996–1998

| | Adjusted ORs by intake quintile[a] | | | | | |
|---|---|---|---|---|---|---|
| | Q1[b] (low) | Q2[b] | Q3[b] | Q4[b] | Q5[b] | *P* for trend |
| Red meat, never deep-fried | | | | | | |
| BMI <25 | | | | | | |
| Cases/controls | 107/121 | 82/109 | 100/103 | 76/107 | 111/78 | |
| OR | 1.00 | 0.80 (0.53–1.19) | 1.01 (0.68–1.51) | 0.71 (0.47–1.08) | 1.35 (0.86–2.11) | 0.46 |
| BMI ≥25 | | | | | | |
| Cases/controls | 46/51 | 36/41 | 29/40 | 34/28 | 54/37 | |
| OR | 1.00 | 1.10 (0.58–2.07) | 0.88 (0.46–1.68) | 1.29 (0.65–2.57) | 1.81 (0.94–3.49) | 0.08 |
| BMI ≥27 | | | | | | |
| Cases/controls | 23/32 | 18/26 | 14/20 | 12/15 | 31/17 | |
| OR | 1.00 | 1.18 (0.49–2.85) | 1.09 (0.42–2.82) | 1.15 (0.42–3.19) | 3.34 (1.33–8.42) | 0.02 |
| | | | Test for interaction, $P = 0.01$[c] | | | |
| WHR <0.835 | | | | | | |
| Cases/controls | 112/123 | 86/108 | 92/107 | 68/100 | 111/82 | |
| OR | 1.00 | 0.89 (0.60–1.33) | 0.93 (0.63–1.39) | 0.69 (0.46–1.05) | 1.49 (0.96–2.31) | 0.39 |
| WHR ≥0.835 | | | | | | |
| Cases/controls | 41/49 | 32/42 | 37/36 | 42/35 | 54/33 | |
| OR | 1.00 | 0.97 (0.50–1.88) | 1.49 (0.76–2.92) | 1.37 (0.68–2.75) | 1.76 (0.88–3.52) | 0.07 |
| WHR ≥0.85 | | | | | | |
| Cases/controls | 29/33 | 27/28 | 29/22 | 36/25 | 40/22 | |
| OR | 1.00 | 1.29 (0.59–2.83) | 1.97 (0.88–4.42) | 1.82 (0.80–4.13) | 2.19 (0.95–5.02) | 0.04 |
| | | | Test for interaction, $P = 0.61$[c] | | | |
| Red meat, deep-fried to well-done | | | | | | |
| BMI <25 | | | | | | |
| Cases/controls | 58/92 | 82/113 | 113/118 | 95/109 | 134/127 | |
| OR | 1.00 | 1.09 (0.70–1.71) | 1.63 (1.06–2.52) | 1.48 (0.94–2.32) | 1.75 (1.11–2.77) | 0.007 |
| BMI ≥25 | | | | | | |
| Cases/controls | 23/34 | 40/29 | 51/36 | 38/38 | 66/39 | |
| OR | 1.00 | 2.16 (1.02–4.58) | 1.98 (0.97–4.03) | 1.39 (0.67–2.88) | 2.45 (1.16–5.18) | 0.14 |
| BMI ≥27 | | | | | | |
| Cases/controls | 10/14 | 14/15 | 17/20 | 20/14 | 34/14 | |
| OR | 1.00 | 1.58 (0.48–5.15) | 1.50 (0.49–4.62) | 2.04 (0.65–6.41) | 4.27 (1.31–13.94) | 0.01 |
| | | | Test for interaction, $P = 0.03$[c] | | | |
| WHR <0.835 | | | | | | |
| Cases/controls | 64/99 | 85/103 | 113/116 | 101/119 | 131/126 | |
| OR | 1.00 | 1.26 (0.81–1.95) | 1.57 (1.03–2.40) | 1.36 (0.88–2.10) | 1.69 (1.07–2.65) | 0.04 |
| WHR ≥0.835 | | | | | | |
| Cases/controls | 16/33 | 40/38 | 48/34 | 33/29 | 69/38 | |
| OR | 1.00 | 1.85 (0.83–4.16) | 2.81 (1.27–6.23) | 2.13 (0.90–5.03) | 3.45 (1.51–7.88) | 0.007 |
| WHR ≥0.85 | | | | | | |
| Cases/controls | 14/20 | 26/22 | 29/22 | 23/21 | 50/26 | |
| OR | 1.00 | 2.50 (0.93–6.70) | 3.08 (1.15–8.21) | 2.07 (0.76–5.63) | 4.31 (1.62–11.45) | 0.02 |
| | | | Test for interaction, $P = 0.27$[c] | | | |

[a] All ORs are adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, WHR, age at menarche, physical activity, ever had live birth, age at first live birth, menopausal status, age at menopause, and total energy.
[b] The same quintile cutpoints were used as those in Table 3.
[c] *P*s were derived from logistic regressions by treating dietary variables (red meat) and modifying variables (WHR or BMI) as continuous variables.



0.02), with an OR of 0.48 (95% CI, 0.28–0.82) observed for the highest *versus* lowest intake quintile.

## Discussion

In this large population-based case-control study, we found that intake of red meat was associated with an elevated risk of breast cancer, particularly among women who usually deep-fried red meat to well done. This positive association was more pronounced among women with a high BMI than those without this risk factor, particularly among postmenopausal women. Intake of freshwater fish was related to an increased risk of breast cancer, whereas intake of marine fish was not related to the risk. Consumption of soybean oil was linked to a reduced risk of breast cancer, particularly among women who never used the deep-fried cooking method. These findings are intriguing and consistent with evidence from previous studies implicating important roles of dietary factors in the etiology of breast cancer.

High intake of red meat has been shown to be associated with an elevated risk of breast cancer in some, but not all, previous epidemiological studies (4–7). Some of the inconsistencies may be explained by the fact that most previous studies did not evaluate the association between red meat intake and breast cancer risk by cooking method (4–7). Meats cooked at high temperature may contain mammary carcinogens, such as heterocyclic amines and polycyclic aromatic hydrocarbons. In Western societies, the most commonly used high-temperature cooking methods include grilling, baking, broiling, and pan-frying. Several recent epidemiological studies have shown that intake of well-done meat may be associated with an increased risk of breast cancer (5, 9–12). This association, however, was not observed in other studies (13–15). Variation in cooking methods across study populations or discrepant dietary assessment (including cooking methods) across these studies may have contributed to the inconsistent findings. The association between using a deep-frying cooking method, the most commonly used high-temperature cooking method in Chinese and some other ethnic populations, and the risk of breast cancer has been rarely studied. One previous case-control study conducted in Uruguay found a stronger positive association of breast cancer risk with fried meat than with broiled meat (5). Oil temperature is normally at approximately 240–270°C when used for deep-fried cooking. It has been reported that deep-fried cooking oil not only produces fumes containing mutagenic compounds, such as 1,3-butadiene, benzene, acrolein, and formaldehyde (37), but also generates nonvolatile hazardous compounds, such as hydroperoxides, *trans* fatty acids, and aldehydes (24, 25). Both hydroperoxides and aldehydes are endogenous reactive chemicals and have mutagenic and carcinogenic potential (38–40). Thus, the positive association of breast cancer risk with well-done deep-fried red meat observed in this study may be attributable to those mutagens or carcinogens that originate from burnt meats and heated cooking oils.

We found that the positive association between red meat intake and breast cancer risk may be modified by BMI and WHR, particularly among postmenopausal women. After menopause, adipose tissue is the major site for estrogen synthesis, and women with a high BMI have an elevated level of endogenous estrogens (35). Central obesity (measured by WHR) and body weight (measured by BMI) have also been associated with insulin resistance (41). Consistent with results from studies conducted in Western societies, in this Chinese study population, BMI was only related to the risk of breast cancer in postmenopausal women, whereas WHR was with risk in both pre- and postmenopausal women (42). Other factors related to insulin resistance, such as high insulin, C-peptide, and insulin-like growth factor-1, and low physical activity have also been shown to be associated with an increased risk of breast cancer our studies (43–45) as well as studies conducted in other populations (46, 47). It is plausible that high levels of insulin and estrogens may stimulate the transformation of breast cancer cells initiated by carcinogens from well-done meats and heated cooking oils (47) and, therefore, promote the development of breast cancer.

Soybean oil, accounting for ~94% of the cooking oil in Shanghai, was found to be associated with a reduced risk of breast cancer among women who never deep-fried animal foods. Soybean oil contains a very high level of vitamin E and phytosterols, a group of phytochemicals that has been shown to inhibit the growth and metastasis of breast cancer in cell culture and animal experiments (48, 49). In addition, soybean oil contains high concentrations of essential fatty acids, such as linoleic and linolenic acid (mostly $\alpha$-linolenic). Epidemiological studies investigating the association between linoleic and linolenic acid and breast cancer risk have thus far generated conflicting results, with both inverse and positive associations reported (30, 50, 51). In Western countries, hydrogenated oils (including soybean oil) have been commonly used for cooking or salad dressing for decades. Hydrogenated cooking oils are one of the major sources of *trans* fatty acids. Several recent epidemiological studies have suggested that *trans* fatty acids may be a risk factor for breast cancer (52). Therefore, the inconsistent results from previous studies were possibly attributable to a lack of distinction between hydrogenated and nonhydrogenated soybean oils (27–29). Hydrogenated cooking oils are seldom manufactured in China. Although some *trans* polyunsaturated fatty acids may also be formed during heating of vegetable oil, such as deep-frying (24), it has been reported that the plasma level of C18:1 *trans* fatty acid isomers was almost 10 times lower in Shanghai residents than the United States population (53). Therefore, the Shanghai Breast Cancer Study provides a unique opportunity to evaluate the association between nonhydrogenated soybean oil and breast cancer risk by cooking method.

The finding for a positive association with freshwater fish was somewhat unexpected. Virtually all previous studies on the association of breast cancer risk with fish did not analyze marine and freshwater fish separately. Both animal and epidemiological studies suggest that long chain omega-3 fatty acids may have protective effects against breast cancer (16, 29, 54). Humans ingest eicosapentaenoic acid and docosahexaenoic acid mainly through intake of fish, especially deep-ocean fish. Cultured freshwater fish and meat, however, are high in omega-6 but low in omega-3 fatty acids (55, 56). In addition, freshwater fish raised in industrial areas, such as Shanghai, may have a high level of methylmercury (57), polychlorinated dibenzo-*p*-dioxins, and dibenzofurans (58), organochlorine residues, and other chemicals, and some of them have been shown to be mutagens or animal carcinogens. For example, one study in China found that 41% of freshwater fish had a methylmercury content exceeding the National Tolerance Limit (57). Another study found that residents living in the Ya-Er Lake area had a higher daily intake of polychlorinated dibenzo-*p*-dioxin/F, which is highly lipophilic and bioaccumulated by fish, than the tolerable level recommended by the World Health Organization (58). These chemicals have high toxicity and carcinogenic potency, and a few epidemiological studies suggested that pesticides and some of these chemicals may be related to breast cancer risk (59–61).

Similar to any other retrospective studies, a concern for the study is the potential for misclassification, both differential and nondifferential, in exposure assessment. The diets of cases may have changed as a result of cancer diagnosis and treatment (62), and current diet may influence the recall of usual diet (62). Through a rapid case-reporting system, we were able to complete an in-person interview for nearly half of the cases before they received any cancer treatment. We performed additional analyses by restricting cases to those who were interviewed before any treatment. The results from this subset were similar to those from all subjects combined. In fact, the positive association with well-done meat intake was stronger in this subset than those presented in the tables, suggesting that potential differential recall bias by treatment may be small in this study (63). Our study is population based; this, coupled with a very high response rate, has minimized potential selection bias. The sample size is large, providing adequate statistical power to investigate potential interactions.

In summary, we found that red meat, especially well-done red meat, was associated with breast cancer risk, and this association may be modified by BMI, particularly among postmenopausal women. On the other hand, high consumption of soybean cooking oil was associated with a reduced risk of breast cancer among those who do did not use the deep-fried cooking method. Freshwater fish, but not marine fish, may be related to an elevated risk of breast cancer. These findings suggest that dietary factors and their interaction with body weight may play an important role in the etiology of breast cancer.

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