Original Contribution

Association of Hormone-Related Characteristics and Breast Cancer Risk by Estrogen Receptor/Progesterone Receptor Status in the Shanghai Breast Cancer Study

Ping-Ping Bao, Xiao Ou Shu*, Yu-Tang Gao, Ying Zheng, Hui Cai, Sandra L. Deming, Zhi-Xian Ruan, Yinghao Su, Kai Gu, Wei Lu, and Wei Zheng

* Correspondence to Dr. Xiao Ou Shu, Vanderbilt Epidemiology Center, Institute of Medicine and Public Health, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37203-1738 (e-mail: xiao-ou.shu@vanderbilt.edu).

Initially submitted August 20, 2010; accepted for publication April 8, 2011.

Etiologic differences between subtypes of breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status are not well understood. The authors evaluated associations of hormone-related factors with breast cancer subtypes in a population-based case-control study involving 1,409 ER-positive (ER+) /PR-positive (PR+) cases, 712 ER-negative (ER-/PR-) cases, 301 ER+/PR+/C0 cases, 254 ER-/PR+/C0 cases, and 3,474 controls aged 20–70 years in Shanghai, China (phase I, 1996–1998; phase II, 2002–2005). Polytomous logistic regression and Wald tests for heterogeneity across subtypes were conducted. Breast cancer risks associated with age at menarche, age at menopause, breastfeeding, age at first livebirth, waist-to-hip ratio, and oral contraceptive use did not differ by hormone receptor status. Among postmenopausal women, higher parity (>2 children vs. 1) was associated with reduced risk (odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.52, 0.91) and higher body mass index (BMI; weight (kg)/height (m)2) with increased risk (highest quartile: OR = 2.40, 95% CI: 1.65, 3.47) of the ER+/PR+ subtype but was unrelated to the ER-/PR- subtype (for parity, P heterogeneity = 0.02; for BMI, P heterogeneity < 0.01). Hormone replacement therapy (OR = 2.25, 95% CI: 1.40, 3.62) and alcohol consumption (OR = 1.59, 95% CI: 1.01, 2.51) appeared to be preferentially associated with the ER+/PR- subtype. These findings indicate that BMI, parity, hormone replacement therapy, and alcohol consumption may play different roles in subtypes of breast cancer. More research is needed to better understand the etiology of 2 relatively rare subtypes, ER+/PR-/ tumors and ER-/PR+ tumors.

breast neoplasms; China; hormones; receptors, estrogen; receptors, progesterone; risk factors; women

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HRT, hormone replacement therapy; OR, odds ratio; PR, progesterone receptor; WHR, waist-to-hip ratio.

Epidemiologic and biologic evidence suggests a pivotal role for estrogen and progesterone in the development of breast cancer. The effects of these hormones are mediated by their respective receptors, estrogen receptor (ER) and progesterone receptor (PR). ER and PR status are biologic markers considered to be a crucial factor in treatment recommendations (1). Furthermore, it has been hypothesized that hormone-related risk factors that reflect exposure to estrogen and progesterone may be predominantly associated with breast tumors that express ER and PR but not with tumors that are hormone receptor-negative (2–4). Given the evidence for differential associations, it is important to take into account the ER/PR status of breast tumors with respect to risk and prognosis prediction and therapeutic decision-making.

In a systematic review of publications on the etiology of hormone receptor-defined breast cancer, Althuis et al. (5) concluded in 2004 that nulliparity, later age at first livebirth, and early age at menarche were associated with increased risk of ER-positive (ER+) tumors but not ER-negative (ER-) tumors. Althuis et al. also reported that postmenopausal obesity was more consistently associated with an
increased risk of ER+/PR-positive (PR+) tumors compared with ER-/PR-negative (PR-) tumors. Another meta-analysis published in 2006 (6) suggested that each birth reduced the risk of ER+/PR+ cancer by 11% (relative risk = 0.89, 95% confidence interval (CI): 0.84, 0.94) and that women who were older at the time of their first birth had a greater risk of ER+/PR+ cancer than women whose first livebirth occurred at a younger age (relative risk = 1.27, 95% CI: 1.07, 1.50). Neither parity nor age at first birth was associated with the risk of ER-/PR—cancer (6). The protective effects of longer duration of breastfeeding and later age at menarche did not differ by ER/PR status (6). Recent studies have also found that the associations of some hormone-related factors with breast cancer risk, such as parity, age at first livebirth, age at menarche, and obesity, differed by ER/PR status (3, 7–9). However, inconsistent results have also been reported (10, 11). Although most previous studies have included a large number of ER+ breast cancer patients, only a few have included a sizable number (n = 500) of ER-/PR—patients. Sample sizes for patients with ER+/PR+ and ER-/PR—cancer are even smaller, yielding limited evidence for these 2 subtypes of breast cancer.

Results on breast cancer risk factors among subgroups defined by ER/PR status have been predominantly derived from studies of Western populations, and few studies have been conducted among other racial or ethnic groups. It has been suggested that ER/PR status varies significantly across racial/ethnic groups, and Chinese women are more often diagnosed with hormone receptor-negative tumors than Caucasian women (12, 13). However, few studies have investigated etiologic differences for subtypes of breast cancer among Chinese women (14, 15). In this study, we conducted a comprehensive evaluation of hormone-related breast cancer risk factors among breast cancer subgroups defined by ER/PR status, using data from the Shanghai Breast Cancer Study.

MATERIALS AND METHODS

Study population

The Shanghai Breast Cancer Study is a large, population-based case-control study of 3,443 cases and 3,474 controls being conducted in Shanghai, China. The study had 2 phases of recruitment, phase I (August 1996–March 1998) and phase II (April 2002–February 2005). The study design has been described in detail elsewhere (16). Briefly, eligible breast cancer patients were identified through a rapid case ascertainment system based on the population-based Shanghai Cancer Registry. All participants were permanent residents of urban Shanghai, were between 20 and 70 years of age, and had no prior history of cancer. Controls were randomly selected from the general female population using the Shanghai Resident Registry and were frequency-matched to cases on age distribution in 5-year groups. In phase I of the study, 1,455 (90.8%) cases and 1,556 (90.3%) controls were recruited, and in phase II, 1,988 (83.2%) cases and 1,918 (70.4%) controls were recruited. All participants in the study provided written informed consent, and the study protocol was approved by the institutional review boards of all participating study institutions.

Data collection

In-person interviews were conducted by trained interviewers using a structured questionnaire to collect information on demographic characteristics, family history of cancer, detailed menstrual and reproductive history, use of oral contraceptives, use of hormone replacement therapy (HRT), behavioral and dietary habits, and regular physical exercise during the 10 years preceding the interview. Current weight, waist and hip circumferences, and sitting and standing heights were measured. Body mass index (BMI; weight (kg)/height (m)$^2$) and waist-to-hip ratio (WHR) were computed from these measurements.

We reviewed medical and pathology records from the hospital where patients were originally diagnosed to obtain information on the ER and PR status of cases, which was primarily measured by the immunohistochemical method. Among patients whose ER/PR status could not be obtained from medical charts, tumor slides were available for 299. For these 299 patients, ER and PR status was evaluated by the Vanderbilt Molecular Epidemiology Laboratory using a double immunohistochemical staining method. Of the total of 3,443 cases, data on ER status were available for 2,700 (78.4%) cases, PR status for 2,679 (77.8%) cases, and joint ER/PR status for 2,676 (77.7%) cases.

Data analysis

Patients were grouped into the following joint categories: ER+/PR+ (receptor-positive), ER-/PR— (receptor-negative), ER+/PR—, and ER-/PR+. Analysis of variance and Pearson $\chi^2$ tests were used to compare differences in continuous and categorical variables in the frequency distributions between cases and controls and across case subgroups. Multiple polytomous unconditional logistic regression analysis was used to calculate odds ratios and corresponding 95% confidence intervals for hormone-related factors in association with breast cancer case subtypes (ER+/PR+, ER-/PR—, ER+/PR—, and ER-/PR+). Included in the models were the following variables: age at diagnosis for cases and age at interview for controls (years; continuous variable), educational level (college or above, senior high school, junior high school, or elementary school or below), first-degree family history of breast cancer (yes, no), height (m)2) and waist-to-hip ratio (WHR) were computed from these measurements.

In-person interviews were conducted by trained interviewers using a structured questionnaire to collect information on demographic characteristics, family history of cancer, detailed menstrual and reproductive history, use of oral contraceptives, use of hormone replacement therapy (HRT), behavioral and dietary habits, and regular physical exercise during the 10 years preceding the interview. Current weight, waist and hip circumferences, and sitting and standing heights were measured. Body mass index (BMI; weight (kg)/height (m)$^2$) and waist-to-hip ratio (WHR) were computed from these measurements.

We reviewed medical and pathology records from the hospital where patients were originally diagnosed to obtain information on the ER and PR status of cases, which was primarily measured by the immunohistochemical method. Among patients whose ER/PR status could not be obtained from medical charts, tumor slides were available for 299. For these 299 patients, ER and PR status was evaluated by the Vanderbilt Molecular Epidemiology Laboratory using a double immunohistochemical staining method. Of the total of 3,443 cases, data on ER status were available for 2,700 (78.4%) cases, PR status for 2,679 (77.8%) cases, and joint ER/PR status for 2,676 (77.7%) cases.

Multiple polytomous unconditional logistic regression analysis was used to calculate odds ratios and corresponding 95% confidence intervals for hormone-related factors in association with breast cancer case subtypes (ER+/PR+, ER-/PR—, ER+/PR—, and ER-/PR+). Included in the models were the following variables: age at diagnosis for cases and age at interview for controls (years; continuous variable), educational level (college or above, senior high school, junior high school, or elementary school or below), first-degree family history of breast cancer (yes, no), height (m)2) and waist-to-hip ratio (WHR) were computed from these measurements.

In-person interviews were conducted by trained interviewers using a structured questionnaire to collect information on demographic characteristics, family history of cancer, detailed menstrual and reproductive history, use of oral contraceptives, use of hormone replacement therapy (HRT), behavioral and dietary habits, and regular physical exercise during the 10 years preceding the interview. Current weight, waist and hip circumferences, and sitting and standing heights were measured. Body mass index (BMI; weight (kg)/height (m)$^2$) and waist-to-hip ratio (WHR) were computed from these measurements.

We reviewed medical and pathology records from the hospital where patients were originally diagnosed to obtain information on the ER and PR status of cases, which was primarily measured by the immunohistochemical method. Among patients whose ER/PR status could not be obtained from medical charts, tumor slides were available for 299. For these 299 patients, ER and PR status was evaluated by the Vanderbilt Molecular Epidemiology Laboratory using a double immunohistochemical staining method. Of the total of 3,443 cases, data on ER status were available for 2,700 (78.4%) cases, PR status for 2,679 (77.8%) cases, and joint ER/PR status for 2,676 (77.7%) cases.
Wald tests to evaluate the heterogeneity of the associations across breast cancer subtypes. All statistical tests were based on 2-sided probability with a significance level of 0.05 and were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

**RESULTS**

Table 1 shows the frequency distributions of sociodemographic and study variables for cases by joint ER/PR status and for controls. Controls tended to have a lower educational level, later age at menarche, younger age at first livebirth, a greater percentage of breastfeeding, lower BMI, less HRT use, more regular exercise, and less frequent family history of breast cancer than cases and were less likely to have a personal history of breast fibroadenoma than cases. Among cases with known receptor status, 1,409 (52.7%) were ER+/PR+, 712 (26.6%) were ER-/PR-, 301 (11.2%) were ER+/PR-, and 254 (9.5%) were ER-/PR+. Age at breast cancer diagnosis ($F$: test: $P < 0.01$), menopausal status ($\chi^2$ test: $P < 0.01$), duration of oral contraceptive use ($F$: test: $P = 0.03$), and HRT use ($\chi^2$ test: $P_{\chi^2} < 0.01$) differed across the 4 case groups with known ER/PR information. Overall, we had information on joint ER/PR status for 2,676 (77.7%) breast cancer cases. Cases with missing data on ER/PR status were similar to those with known ER/PR status with respect to most known breast cancer risk factors, with a few exceptions. Cases with known ER/PR status appeared to have a slightly lower percentage of livebirths (93.22% vs. 95.44%) and lower BMI (23.33 vs. 23.74) and WHR (0.817 vs. 0.824) than those with unknown ER/PR status (see Web Table 1, which appears on the *Journal*’s Web site (http://aje.oxfordjournals.org/)). We adjusted for these variables throughout subsequent analyses.

Table 2 presents associations between menstrual factors and breast cancer by joint ER/PR status. No differences in risk were found across the 4 ER/PR breast cancer subtypes for age at menarche, age at menopause, or years of menstruation. Later age at menarche was inversely associated with risk for the ER+/PR+ and ER-/PR- subtypes of breast cancer ($P$-trend $< 0.01$ for both). Compared with women who were younger at menarche (age $\leq$13 years), there was a 34% reduction (odds ratio (OR) = 0.66, 95% CI: 0.53, 0.82) in risk of ER+/PR+ and a 38% reduction (OR = 0.62, 95% CI: 0.46, 0.83) in risk of ER-/PR- cancer for women who were older at menarche (age $\geq$17 years). Later age at menarche was associated with a statistically nonsignificantly reduced risk of ER+/PR- and ER-/PR+ cancers. Women in the highest quartile of years of menstruation had increased risk of all 4 subtypes of breast cancer, although trend tests were significant only for the ER+/PR+ and ER-/PR- subtypes. However, the association with menopausal status differed between subtypes defined by ER/PR status (heterogeneity test: $P < 0.01$), with menopausal status being associated with a reduced risk of ER+/PR+ and ER-/PR+ breast cancer.

Associations of breast cancer risk with never having a livebirth were confined to women with ER+ breast cancer, although the tests for heterogeneity across subtypes of breast cancer were not significant (Table 3). Later age at first livebirth was associated with both ER+/PR+ and ER-/PR+ breast cancer. Having multiple children was significantly related to a reduced risk of ER+/PR+ breast cancer ($P$-trend $= 0.02$). Longer duration of breastfeeding was significantly and inversely related to the ER+/PR+ subtype ($P$-trend $= 0.01$). However, the test for heterogeneity was not significant for any of these factors.

As shown in Table 4, we found no association between oral contraceptive use (ever use or duration of use) and breast cancer for any subtype defined by ER and PR status. Risk was higher for women with ER+/PR- tumors who had used HRT (OR = 2.25, 95% CI: 1.40, 3.62), and associations differed statistically across the 4 subtypes (heterogeneity test: $P = 0.01$), mainly between the ER+/PR- and ER-/PR+ subgroups.

Alcohol intake was not associated with risk of the ER+/PR+, ER-/PR-, or ER-/PR+ subtypes of breast cancer but was related to increased risk of ER+/PR- breast cancer (OR = 1.59, 95% CI: 1.01, 2.51) (Table 4). However, the heterogeneity test did not reach statistical significance ($P = 0.12$). The percentage of alcohol intake (5.09%) was low in our study population.

BMI was associated with a significantly increased risk of ER+/PR+ breast cancer ($P$-trend $< 0.01$), and the test for heterogeneity across the 4 subtypes of breast cancer was statistically significant ($P = 0.01$) (Table 5). Increasing WHR substantially increased the risk of all 4 tumor subtypes. Compared with women in the lowest quartile of WHR, women in the highest quartile ($\geq$0.843) had more than double the risk of breast cancer for all subtypes (OR range = 2.20–2.72).

We further analyzed associations of hormone-related factors with ER+/PR+ and ER-/PR- breast cancer by menopausal status. Results for WHR and other factors that had significant heterogeneity are presented in Table 6. Because the numbers of patients with ER+/PR- and ER-/PR+ tumors were too small to provide stable estimates, we did not include them in the stratified analyses. We found that parity was significantly and inversely associated with both ER+/PR+ and ER-/PR- tumors among premenopausal women (heterogeneity test: $P = 0.56$). Among postmenopausal women, the heterogeneity test for parity between ER+/PR+ and ER-/PR- was significant ($P = 0.02$). Compared with women who had 1 livebirth, having 2 or more livebirths was associated with a substantially lower risk of ER+/PR+ breast cancer in postmenopausal women (OR = 0.69, 95% CI: 0.52, 0.91). The inverse association of breastfeeding with ER+/PR+ and ER-/PR- breast cancer was mainly confined to postmenopausal women. BMI was positively associated with ER+/PR+ breast cancer in postmenopausal women ($P$-trend $< 0.01$), and the odds ratio for the highest quartile was 2.40 (95% CI: 1.65, 3.47). Statistically significant differences for ER+/PR+ and ER-/PR- subtypes were found for BMI in postmenopausal women (heterogeneity test: $P < 0.01$). WHR was positively associated with ER+/PR+ and ER-/PR- tumors in both pre- and postmenopausal women. There were no statistically significant ER+/PR+ and ER-/PR- subgroup differences for age at menarche, age at first livebirth, oral contraceptive use, or alcohol.
Table 1. Characteristics of Cases and Controls by Estrogen Receptor and Progesterone Receptor Status, Shanghai Breast Cancer Studies I (1996–1998) and II (2002–2005), Shanghai, China

| Characteristics                        | Controls (n = 3,474) | ER+/PR+ (n = 1,409) | ER−/PR− (n = 712) | ER+/PR− (n = 301) | ER−/PR+ (n = 254) | Unknown (n = 767) | P Valuea | P Valueb |
|----------------------------------------|----------------------|----------------------|-------------------|-------------------|-------------------|-------------------|----------|----------|
| Age, years                             | 49.90 (8.76)         | 49.77 (8.12)         | 50.01 (8.51)      | 51.18 (8.21)      | 48.09 (7.65)      | 49.33 (8.43)      | 0.37     | <0.01    |
| Educational level                      |                      |                      |                   |                   |                   |                   |          |          |
| Elementary school or below             | 12.58 7.31 8.99      | 7.31                 | 37.87 38.98 39.37 | 14.33 (1.59)      | 14.54 (1.67)      | <0.01 0.80       |          |          |
| Junior high school                     | 41.02 39.46 39.47    | 37.64                 | 38.58 36.25       |                   |                   |                   |          |          |
| Senior high school                     | 35.29 37.26 37.64    | 15.97                 | 18.27 15.75       |                   |                   |                   |          |          |
| College or above                       | 11.11 15.97 13.90    | 13.90                 | 17.04 13.04       |                   |                   |                   |          |          |
| Age at menarche, years                 | 14.66 (1.74)         | 14.38 (1.62)         | 14.39 (1.62)      | 14.43 (1.59)      | 14.33 (1.76)      | 14.54 (1.67)      | <0.01 0.01|          |
| Postmenopausal                         | 43.49 37.26 42.42    | 49.83                 | 29.53 41.07       |                   |                   |                   | <0.01 0.01|          |
| Age at menopause (postmenopausal women)| 47.92 (4.71)         | 48.39 (4.29)         | 48.40 (4.53)      | 48.40 (4.48)      | 48.40 (4.64)      | 48.29 (4.49)      | 0.01 1.00|          |
| Ever had a livebirth                   | 96.20 95.03 96.63    | 94.68                 | 95.28 93.22       |                   |                   |                   | 0.01 0.35|          |
| No. of livebirths                      | 1.47 (0.82) 1.35 (0.70) 1.39 (0.75) 1.42 (0.76) 1.29 (0.60) 1.49 (0.85) | <0.01 0.11 |       |                   |                   |                   |          |          |
| Age at first livebirth, years          | 26.35 (3.82) 27.03 (3.73) 26.75 (3.86) 26.77 (3.75) 27.28 (3.72) 26.81 (4.05) | <0.01 0.17 |       |                   |                   |                   |          |          |
| Ever breastfed                         | 79.44 75.80 77.33    | 81.05                 | 76.03 78.18       |                   |                   |                   | 0.02 0.28|          |
| Body mass index*                       | 23.31 (3.30) 23.85 (3.31) 23.51 (3.36) 23.70 (3.12) 23.77 (3.48) 23.33 (3.32) | <0.01 0.18 |       |                   |                   |                   |          |          |
| Waist-to-hip ratio                     | 0.81 (0.06) 0.82 (0.05) 0.82 (0.06) 0.83 (0.06) 0.82 (0.06) 0.82 (0.06) | <0.01 0.25 |       |                   |                   |                   |          |          |
| Ever consumed alcohol                  | 5.50 4.47 4.63       | 7.64                  | 4.33 4.04         |                   |                   |                   | 0.13 0.13|          |
| Ever used oral contraceptives          | 20.03 18.45 19.24    | 24.25                 | 15.35 20.60       |                   |                   |                   | 0.50 0.05|          |
| Duration of oral contraceptive use     | 42.74 (58.49) 38.53 (59.04) 55.83 (76.55) 34.25 (48.43) 54.36 (70.11) 45.31 (57.86) | 0.67 0.03 |       |                   |                   |                   |          |          |
| (among users, months)                  |                      |                      |                   |                   |                   |                   |          |          |
| Ever used hormone replacement therapy  | 3.02 3.55 4.07       | 7.97                  | 1.57 3.66         |                   |                   |                   | 0.04 0.01|          |
| Regular exercise*                      | 30.20 25.20 26.12    | 26.25                 | 22.05 23.21       |                   |                   |                   | <0.01 0.61|          |
| History of breast fibroadenoma         | 5.47 10.31 7.62      | 8.64                  | 10.63 10.99       |                   |                   |                   | <0.01 0.20|          |
| First-degree family history of breast  | 2.76 4.40 4.63       | 6.64                  | 5.12 4.30         |                   |                   |                   | <0.01 0.42|          |
| cancer                                 |                      |                      |                   |                   |                   |                   |          |          |

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation.

a P for cases versus controls from a $\chi^2$ test (categorical variables) or analysis of variance (continuous variables).
b P for comparison across the 4 known hormone receptor status groups for cases.
c Weight (kg)/height (m)$^2$.
d At least twice a week (yes, no).
| Age at menarche, years | No. of Controls | ER+/PR+ |   | ER-/PR− |   | ER+/PR− |   | ER-/PR+ |   | P Value
|-----------------------|----------------|--------|---|--------|---|--------|---|--------|---|---------|
| ≤13                   | 981            | 479    | 1.0<sup>d</sup> | 240   | 1.0<sup>d</sup> | 95    | 1.0<sup>d</sup> | 89    | 1.0<sup>d</sup>  
| 14                    | 743            | 292    | 0.84       | 0.70   | 1.01       | 0.87 | 0.70       | 1.09  | 0.92       | 0.66       | 1.29       | 0.81       | 0.57       | 1.17       |
| 15–16                 | 1,244          | 493    | 0.88       | 0.76   | 1.03       | 0.83 | 0.68       | 1.01  | 0.99       | 0.74       | 1.33       | 0.80       | 0.58       | 1.10       |
| ≥17                   | 495            | 140    | 0.66       | 0.53   | 0.82       | 0.62 | 0.46       | 0.83  | 0.79       | 0.52       | 1.20       | 0.77       | 0.49       | 1.20       |
|                       |                |        |            |        |            |      |            |      |            |            |            |            |            |            |
| Menopausal<sup>e</sup> |               |        |            |        |            |      |            |      |            |            |            |            |            |            |
| No                    | 1,957          | 882    | 1.0<sup>d</sup> | 409   | 1.0<sup>d</sup> | 151  | 1.0<sup>d</sup> | 178  | 1.0<sup>d</sup>  
| Yes                   | 1,508          | 522    | 0.58       | 0.47   | 0.71       | 0.89 | 0.69       | 1.15  | 1.05       | 0.73       | 1.51       | 0.54       | 0.35       | 0.82       | <0.01      |
| Age at menopause (among women with natural menopause), years<sup>e</sup> | | | | | | | | | |
| ≤46                   | 303            | 77     | 1.0<sup>d</sup> | 50    | 1.0<sup>d</sup> | 17    | 1.0<sup>d</sup> | 12    | 1.0<sup>d</sup>  
| 47–49                 | 412            | 146    | 1.32       | 0.95   | 1.83       | 0.96 | 0.64       | 1.43  | 1.60       | 0.87       | 2.94       | 1.35       | 0.63       | 2.92       |
| 50–51                 | 319            | 112    | 1.25       | 0.88   | 1.77       | 1.24 | 0.82       | 1.87  | 2.07       | 1.12       | 3.85       | 1.47       | 0.67       | 3.28       |
| ≥52                   | 276            | 102    | 1.23       | 0.85   | 1.76       | 1.33 | 0.87       | 2.04  | 1.89       | 0.97       | 3.67       | 1.61       | 0.70       | 3.68       |
|                       |                |        |            |        |            |      |            |      |            |            |            |            |            |            |
| Years of menstruation (interval between age at menarche and age at menopause/current age) | | | | | | | | | |
| ≤27                   | 841            | 257    | 1.0<sup>d</sup> | 142   | 1.0<sup>d</sup> | 55    | 1.0<sup>d</sup> | 60    | 1.0<sup>d</sup>  
| 28–31                 | 863            | 365    | 1.40       | 1.14   | 1.72       | 1.12 | 0.86       | 1.46  | 0.99       | 0.67       | 1.47       | 1.40       | 0.94       | 2.09       |
| 32–34                 | 805            | 323    | 1.38       | 1.10   | 1.73       | 1.26 | 0.94       | 1.67  | 1.03       | 0.67       | 1.57       | 1.25       | 0.78       | 2.02       |
| ≥35                   | 951            | 458    | 1.66       | 1.30   | 2.11       | 1.38 | 1.01       | 1.87  | 1.31       | 1.85       | 2.02       | 1.71       | 1.03       | 2.86       |
|                       |                |        |            |        |            |      |            |      |            |            |            |            |            |            |

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

<sup>a</sup> Results were adjusted for age, education, history of breast fibroadenoma, first-degree family history of breast cancer, regular exercise (yes/no), body mass index, waist-to-hip ratio, history of livebirth, parity, and study phase (I or II). Missing values (<0.6%) were excluded from the model.

<sup>b</sup> Test for heterogeneity of \( P_{\text{trend}} \) values between the 4 hormone receptor groups, calculated using multivariable polytomous logistic regression.

<sup>c</sup> Also adjusted for menopausal status (yes/no).

<sup>d</sup> Reference category.

<sup>e</sup> Also adjusted for age at menarche.
Table 3. Odds Ratios for Breast Cancer According to Reproductive Factors, by Estrogen Receptor and Progesterone Receptor Status ($n = 6,150$), Shanghai Breast Cancer Studies I (1996–1998) and II (2002–2005), Shanghai, China$^a$

| History of livebirth | ER+/PR+ | | ER-/PR− | | ER+/PR− | | ER-/PR− | | P Value$^b$ |
|---------------------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|
|                     | No. of | No. of | No. of | No. of | No. of | No. of |         |           |
|                     | Controls | Cases | OR 95% CI | Cases | OR 95% CI | Cases | OR 95% CI | Cases | OR 95% CI |
| History of livebirth |         |       |           |       |           |       |           |       |           |
| Ever                | 3,330   | 1,333 | 1.0$^c$  | 684   | 1.0$^c$  | 284   | 1.0$^c$  | 241   | 1.0$^c$  |
| Never               | 130     | 70    | 1.40 1.03, 1.90 | 24    | 0.90 0.57, 1.41 | 16    | 1.53 0.89, 2.63 | 11    | 1.07 0.56, 2.04 | 0.25 |
| Parity (among parous women) |       |       |           |       |           |       |           |       |           |
| 1                   | 2,279   | 1,009 | 1.0$^c$  | 495   | 1.0$^c$  | 200   | 1.0$^c$  | 186   | 1.0$^c$  |
| 2                   | 693     | 220   | 0.71 0.58, 0.88 | 142   | 0.90 0.70, 1.17 | 58    | 0.75 0.51, 1.10 | 44    | 1.05 0.69, 1.61 |
| ≥3                  | 358     | 104   | 0.80 0.58, 1.12 | 47    | 0.61 0.40, 0.95 | 26    | 0.76 0.42, 1.37 | 11    | 0.66 0.31, 1.51 |
| P_trend             | 0.02    | 0.06  |         | 0.22  |         | 0.61  |         | 0.96  |         |
| Age at first livebirth (among parous women), years |       |       |           |       |           |       |           |       |           |
| ≤24                 | 959     | 311   | 1.0$^c$  | 182   | 1.0$^c$  | 65    | 1.0$^c$  | 50    | 1.0$^c$  |
| 25–26               | 859     | 300   | 0.89 0.72, 1.10 | 164   | 0.85 0.65, 1.10 | 79    | 1.29 0.88, 1.89 | 50    | 0.88 0.56, 1.37 |
| 27–28               | 745     | 335   | 1.14 0.92, 1.41 | 157   | 0.92 0.70, 1.20 | 63    | 1.20 0.79, 1.82 | 66    | 1.36 0.88, 2.10 |
| ≥29                 | 758     | 386   | 1.24 1.00, 1.54 | 178   | 0.98 0.74, 1.28 | 76    | 1.32 0.87, 1.99 | 74    | 1.49 0.96, 2.33 |
| P_trend             | <0.01   | 0.84  |         | 0.31  |         | 0.01  |         | 0.13  |         |
| Lifetime duration of breastfeeding (among parous women), months |       |       |           |       |           |       |           |       |           |
| Never breastfed     | 685     | 324   | 1.0$^c$  | 155   | 1.0$^c$  | 54    | 1.0$^c$  | 58    | 1.0$^c$  |
| <9                  | 839     | 381   | 0.96 0.80, 1.15 | 186   | 0.98 0.77, 1.25 | 85    | 1.29 0.90, 1.84 | 70    | 0.98 0.68, 1.41 |
| 9–17                | 1,044   | 407   | 0.79 0.66, 0.94 | 222   | 0.91 0.72, 1.15 | 95    | 1.05 0.74, 1.50 | 73    | 0.85 0.59, 1.23 |
| ≥18                 | 762     | 221   | 0.71 0.53, 0.95 | 121   | 0.76 0.52, 1.11 | 50    | 0.65 0.38, 1.12 | 40    | 1.23 0.65, 2.34 |
| P_trend             | 0.01    | 0.18  |         | 0.30  |         | 0.72  |         | 0.59  |         |

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

$^a$ Results were adjusted for age, education, history of breast fibroadenoma, first-degree family history of breast cancer, regular exercise (yes/no), years of menstruation, body mass index, waist-to-hip ratio, parity, and study phase (I or II). Missing values (<0.6%) were excluded from the model.

$^b$ Test for heterogeneity of $P_{trend}$ values between the 4 hormone receptor groups, calculated using multivariable polytomous logistic regression.

$^c$ Reference category.
consumption among pre- or postmenopausal women (data not shown).

**DISCUSSION**

In this large study of 2,676 breast cancer cases with hormone receptor information and 3,474 controls from the Shanghai Breast Cancer Study, we found that parity and BMI were differently associated with ER+ breast cancers but not ER− breast cancers among postmenopausal Chinese women (heterogeneity test: \( P < 0.05\)) and that HRT and alcohol consumption were associated only with ER+ breast cancer. There were no differences in associations between the 4 breast cancer subtypes and parity. The associations of other reproductive factors did not appear to differ by the ER/PR status of the tumor. Consistent with previous reviews (5, 6), we found that the inverse association with long-duration breastfeeding did not vary according to the receptor status of the tumor. This finding supports the notion that, in addition to hormonal mechanisms, breastfeeding may act through other, nonhormonal mechanisms—such as differentiation of breast epithelial cells induced by lactation—to reduce the risk of breast cancer (19).

Evidence has shown that the association between obesity and breast cancer risk may vary by menopausal status (20) and hormone receptor status (3, 5). Multiple studies have found that excess endogenous estrogen due to obesity contributes to an increased risk of ER+/PR+ breast cancer in postmenopausal women (8, 9, 21). In a recent meta-analysis that included 9 cohort studies and 22 case-control studies, Suzuki et al. (9) concluded that excessive BMI was associated with differences in risk of developing ER+/PR+ tumors according to menopausal status, with a 10% (95% CI: −18, −1) reduction in risk for every 5-unit increase in BMI among premenopausal women and a 33% (95% CI: 20, 48) increase in risk for every 5-unit increase in BMI among postmenopausal women. Consistent with these results, we found that BMI was more strongly associated with receptor-positive tumors among postmenopausal women. However,
BMI was unrelated to either ER+/PR+ or ER−/PR− breast cancer among premenopausal women. We observed no heterogeneity across tumor subtypes for associations with WHR in analyses with and without stratification by menopausal status. Our findings are supported by 2 (10, 22) of 3 other published studies on WHR (10, 22, 23) that took into account joint ER/PR status.

Our finding that higher BMI was differentially associated with the risk of ER+/PR+ and ER−/PR− breast tumors among postmenopausal women while the WHR associations were observed across subtypes of breast cancer suggests that different biologic mechanisms may be involved. It has been suggested that higher BMI increases levels of circulating steroids (21, 24) and reduces levels of sex hormone-binding globulin among postmenopausal women (25, 26). This may increase the overall level of bioavailable estrogen, which binds estrogen receptors to promote the development of hormone receptor-positive breast cancer. In addition to being inversely correlated with sex hormone-binding globulin (26), WHR is also associated with increased insulin levels and insulin-like growth factors (27), which may stimulate the growth of breast cancer cells, an effect that does not depend on ER/PR status.

Data have accumulated linking use of HRT solely to ER+/PR+ tumors (8, 18, 28–31), although null findings have also been observed (17, 23, 32, 33). Slanger et al. (30) suggested that associations between HRT use and histologic type could potentially be attributed to ER/PR status. In our study, interestingly, the increased risk for HRT use was associated with ER+/PR− tumors. This finding is consistent with the French E3N cohort study (34), which found that the use of some HRT was more markedly associated with the risk of ER+/PR− tumors than with ER+/PR+ tumors and suggested that progestogens might have increased the potency of growth factors and hence preferentially affected the risk of ER+/PR− tumors. Potter et al. (32) also suggested that there were differences in risk associated with HRT for ER+/PR− tumors as compared with the other 3 ER/PR categories in the Iowa Women’s Health Study.

There is increasing evidence that ER+/PR− tumors may be a distinct subgroup of breast cancers that occur more frequently than ER+/PR+ tumors in older patients and patients with a higher frequency of overexpression of human epidermal growth factor receptors 1 and 2 (35). Our finding that alcohol consumption increased the risk of ER+/PR− breast cancer supports the notion that the ER+/PR− subtype may be etiologically distinct. However, all previous studies, including the current study, have had relatively small sample sizes for a comprehensive evaluation of the etiology of ER+/PR− breast cancer tumors. The same applies to ER−/PR+ breast cancer. Further studies with larger sample sizes are needed to confirm our findings and to further elucidate the risk profiles of the 2 mixed ER/PR subgroups and the potential mechanisms underlying them.

Several potential limitations of this study should be noted. Hormone receptor information for patients was collected primarily from medical records. Hence, misclassification of hormone receptor status was unavoidable. The percentage of ER+/PR− positivity previously reported in Chinese populations has varied. The percentage of ER− breast cancer in our

### Table 5. Odds Ratios for Breast Cancer According to Measures of Obesity, by Estrogen Receptor and Progesterone Receptor Status (n = 6,150), Shanghai Breast Cancer Studies I (1996–1998) and II (2002–2005), Shanghai, China

| WHR Category | No. of Controls | ER+/PR+ | 95% CI | ER−/PR− | 95% CI | ER+/PR− | 95% CI | ER−/PR− | 95% CI | P Value |
|--------------|----------------|---------|--------|---------|--------|---------|--------|---------|--------|---------|
| <20.10       | 864            | 266     | 1.0d   | 159     | 1.0d   | 53      | 1.0d   | 55      | 1.0d   |         |
| 20.10–23.02  | 865            | 319     | 1.09   | 0.90, 1.32 | 183 | 1.00 | 0.78, 1.27 | 77    | 1.24 | 0.85, 1.80 | 60 | 1.03 | 0.70, 1.53 |
| 23.03–25.15  | 866            | 385     | 1.25   | 1.03, 1.52 | 177 | 0.89 | 0.69, 1.14 | 85    | 1.23 | 0.84, 1.80 | 56 | 0.93 | 0.62, 1.40 |
| ≥25.16       | 865            | 433     | 1.37   | 1.12, 1.68 | 189 | 0.89 | 0.68, 1.15 | 85    | 1.14 | 0.76, 1.69 | 81 | 1.31 | 0.87, 1.96 |
| P<0.01       | 0.25           | 0.66    | 0.24   | 0.01 |

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

**a** Results were adjusted for age, education, history of breast fibroadenoma, first-degree family history of breast cancer, regular exercise (yes/no), years of menstruation, history of livebirth, parity, and study phase (I or II); results were also mutually adjusted for body mass index and waist-to-hip ratio. Missing values (<0.6%) were excluded from the model.

**b** Test for heterogeneity of P<0.01 values between the 4 hormone receptor groups, calculated using multivariable polynomial logistic regression.

**c** Weight (kg)/height (m)².

**d** Reference category.

### References

1. (10, 22) published studies on WHR (10, 22, 23) that took into account joint ER/PR status.

2. Our study, interestingly, the increased risk for HRT use was associated with ER+/PR− tumors. This finding is consistent with the French E3N cohort study (34), which found that the use of some HRT was more markedly associated with the risk of ER+/PR− tumors than with ER+/PR+ tumors and suggested that progestogens might have increased the potency of growth factors and hence preferentially affected the risk of ER+/PR− tumors. Potter et al. (32) also suggested that there were differences in risk associated with HRT for ER+/PR− tumors as compared with the other 3 ER/PR categories in the Iowa Women’s Health Study.

3. There is increasing evidence that ER+/PR− tumors may be a distinct subgroup of breast cancers that occur more frequently than ER+/PR+ tumors in older patients and patients with a higher frequency of overexpression of human epidermal growth factor receptors 1 and 2 (35). Our finding that alcohol consumption increased the risk of ER+/PR− breast cancer supports the notion that the ER+/PR− subtype may be etiologically distinct. However, all previous studies, including the current study, have had relatively small sample sizes for a comprehensive evaluation of the etiology of ER+/PR− breast cancer tumors. The same applies to ER−/PR+ breast cancer. Further studies with larger sample sizes are needed to confirm our findings and to further elucidate the risk profiles of the 2 mixed ER/PR subgroups and the potential mechanisms underlying them.

4. Several potential limitations of this study should be noted. Hormone receptor information for patients was collected primarily from medical records. Hence, misclassification of hormone receptor status was unavoidable. The percentage of ER+/PR− positivity previously reported in Chinese populations has varied. The percentage of ER− breast cancer in our
### Table 6. Odds Ratios for Breast Cancer According to Selected Hormone-Related Factors and Menopausal Status (n = 5,593), Shanghai Breast Cancer Studies I (1996–1998) and II (2002–2005), Shanghai, China

| Parity (among parous women) | Premenopausal Women | Postmenopausal Women |
|-----------------------------|---------------------|-----------------------|
|                             | No. of Controls     | No. of Cases | OR | 95% CI | P Value | No. of Controls | No. of Cases | OR | 95% CI | P Value |
| 1                           | 1,723               | 786          | 1.0 | c          | 370 | 1.0 | c          | 556 | 223 | 1.0 | c          | 125 | 1.0 | c          |
| ≥2                          | 162                 | 55           | 0.70 | 0.49, 0.99 | 25 | 0.60 | 0.37, 0.96 | 889 | 269 | 0.69 | 0.52, 0.91 | 164 | 1.12 | 0.79, 1.58 | 0.02 |

**Lifetime duration of breastfeeding (among parous women), months**

| Lifetime duration | Premenopausal Women | Postmenopausal Women |
|-------------------|---------------------|-----------------------|
|                   | No. of Controls     | No. of Cases | OR | 95% CI | P Value | No. of Controls | No. of Cases | OR | 95% CI | P Value |
| Never breastfed   | 506                 | 244          | 1.0 | c          | 101 | 1.0 | c          | 179 | 80 | 1.0 | c          | 54 | 1.0 | c          |
| <9                | 608                 | 293          | 1.01 | 0.82, 1.26 | 134 | 1.12 | 0.84, 1.50 | 231 | 88 | 0.82 | 0.56, 1.19 | 52 | 0.73 | 0.47, 1.14 | 0.04 |
| 9–17              | 679                 | 269          | 0.78 | 0.63, 0.97 | 144 | 1.05 | 0.79, 1.39 | 365 | 138 | 0.76 | 0.54, 1.08 | 78 | 0.65 | 0.43, 0.97 | 0.09 |
| ≥18               | 92                  | 35           | 1.02 | 0.56, 1.84 | 16 | 1.11 | 0.49, 2.49 | 670 | 186 | 0.66 | 0.44, 0.99 | 105 | 0.48 | 0.30, 0.77 | 0.04 |

**P trend**

| Quartile of body mass index | Premenopausal Women | Postmenopausal Women |
|-----------------------------|---------------------|-----------------------|
| <21.00                      | 586                 | 212 | 1.0 | c          | 113 | 1.0 | c          | 278 | 54 | 1.0 | c          | 46 | 1.0 | c          |
| 21.00–23.02                 | 537                 | 219 | 0.96 | 0.76, 1.21 | 116 | 0.98 | 0.73, 1.31 | 328 | 100 | 1.15 | 0.90, 1.45 | 67 | 1.10 | 0.72, 1.68 | 0.45 |
| 23.03–25.15                 | 455                 | 233 | 1.09 | 0.86, 1.39 | 90 | 0.81 | 0.59, 1.11 | 411 | 152 | 1.93 | 1.34, 2.79 | 87 | 1.06 | 0.70, 1.60 | 0.08 |
| ≥25.16                      | 378                 | 218 | 1.07 | 0.82, 1.39 | 90 | 0.84 | 0.59, 1.19 | 487 | 215 | 2.40 | 1.65, 3.47 | 99 | 1.00 | 0.66, 1.53 | 0.07 |

**P trend**

| Quartile of waist-to-hip ratio | Premenopausal Women | Postmenopausal Women |
|-------------------------------|---------------------|-----------------------|
| <0.772                       | 621                 | 169 | 1.0 | c          | 89 | 1.0 | c          | 250 | 60 | 1.0 | c          | 25 | 1.0 | c          |
| 0.772–0.805                  | 513                 | 217 | 1.49 | 1.17, 1.89 | 107 | 1.46 | 1.07, 2.00 | 341 | 93 | 0.96 | 0.66, 1.40 | 56 | 1.53 | 0.91, 2.57 | 0.05 |
| 0.806–0.842                  | 474                 | 242 | 1.76 | 1.37, 2.25 | 106 | 1.62 | 1.17, 2.24 | 408 | 118 | 1.06 | 0.74, 1.54 | 80 | 2.02 | 1.22, 3.34 | 0.06 |
| ≥0.843                       | 348                 | 254 | 2.41 | 1.84, 3.14 | 107 | 2.31 | 1.62, 3.28 | 505 | 249 | 1.73 | 1.21, 2.48 | 141 | 2.92 | 1.78, 4.79 | 0.06 |

**Abbreviations:** CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

*Results were adjusted for age, education, history of breast fibroadenoma, first-degree family history of breast cancer, regular exercise (yes/no), years of menstruation, body mass index, waist-to-hip ratio, history of livebirth, parity, and study phase (I or II). Missing values (<0.6%) were excluded from the model.*

*Test for heterogeneity of P trend values between the 2 hormone receptor groups, calculated using multivariable polytomous logistic regression.*

*Reference category.*

*Weight (kg)/height (m)^2.*
study was similar to that reported for the largest hospital-based study conducted in China (63.8% vs. 64.1%), while the percentage of PR+ breast cancer was lower (62.1% vs. 70.2%) (36). However, these rates were higher than rates reported from a hospital-based study conducted in China (49.3% for ER+ and 46.1% for PR+) (37) and a study conducted in Hong Kong (54.1% for ER+ and 47.4% PR+) (13). The ER/PR distribution of our patients, however, more closely resembled that of Chinese women in the United States (52.7% vs. 60.6% for ER+/PR+ tumors and 26.6% vs. 22.6% for ER−/PR− tumors), according to a Surveillance, Epidemiology, and End Results report (38). To further evaluate the possible bias introduced by misclassification of ER/PR status, we compared ER/PR status distributions between cases diagnosed by teaching hospitals or municipal hospitals (third-tier hospitals, the highest quality) and those diagnosed by district hospitals (second-tier hospitals) and found no major differences (Web Table 2). We also analyzed associations for hormone-related factors and breast cancer subgroups by including ER/PR information on cases from only the teaching or municipal hospitals and observed similar association patterns (Web Table 3). Another limitation was missing data on ER/PR status for 22% of our cases. Although the differences between cases with and without known data on receptor status were small (Web Table 1), potential bias could not be completely ruled out. Last, statistical power was limited for our ER+/PR− and ER−/PR+ analyses. However, compared with previous published reports, our study had the largest number of cases for these 2 subgroups.

Our study is one of the largest to date with the capacity to conduct an in-depth investigation of the association between hormonal risk factors and breast cancer risk characterized by ER/PR status. The comprehensively collected exposure information also allowed for adjustment for multiple potential confounders during the analysis. The high response rate minimized selection bias. Additionally, over 98% of Chinese women living in Shanghai belong to a single ethnic group (Han Chinese), thus greatly reducing potential confounding by unknown and/or unmeasured factors related to ethnic differences in culture, heritage, lifestyle, etc.

In summary, our study found that associations of BMI, parity, HRT use, and alcohol consumption with breast cancer risk differed by ER/PR status and by menopausal status. However, the association of other hormone-related factors with breast cancer did not vary by ER/PR status. More research is needed to better understand the etiologic differences and underlying mechanisms for subtypes of breast cancer, particularly the rarely rare subtypes, ER+/PR− and ER−/PR+.

ACKNOWLEDGMENTS

Author affiliations: Shanghai Municipal Center for Disease Control and Prevention, Shanghai, People’s Republic of China (Ping-Ping Bao, Yingzheng, Kai Gu, Wei Lu); Division of Epidemiology, Department of Medicine; Vanderbilt University Medical Center; and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Xiao Ou Shu, Hui Cai, Sandra L. Deming, Yinghao Su, Wei Zheng); and Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People’s Republic of China (Yu-Tang Gao, Zhixian Ruan).

This research was supported by US National Cancer Institute grant R01 CA064277. Dr. Ping-Ping Bao was supported by grant D43 TW00831-01 from the Fogarty International Center.

The authors thank Dr. Jin Fan for her contribution to the data collection, the research staff of the Shanghai Breast Cancer Study for their support, and Bethanie Rammer and Rodney Jones for their assistance in the preparation of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. Anderson E. The role of oestrogen and progesterone receptors in human mammary development and tumorigenesis. Breast Cancer Res. 2002;4(5):197–201.
2. Ma H, Bernstein L, Ross RK, et al. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res. 2006;8(4):R39. (doi: 10.1186/bcr1514).
3. Chen WY, Colditz GA. Risk factors and hormone-receptor status: epidemiology, risk-prediction models and treatment implications for breast cancer. Nat Clin Pract Oncol. 2007;4(7):415–423.
4. Osborne CK, Schiff R. Estrogen-receptor biology: continuing progress and therapeutic implications. J Clin Oncol. 2005;23(8):1616–1622.
5. Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone-receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004;13(10):1558–1568.
6. Ma H, Bernstein L, Pike MC, et al. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res. 2006;8(4):R43. (doi: 10.1186/bcr1525).
7. Lord SJ, Bernstein L, Johnson KA, et al. Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: a case-control study. Cancer Epidemiol Biomarkers Prev. 2008;17(7):1723–1730.
8. Setiawan VW, Monroe KR, Wilkens LR, et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: the Multiethnic Cohort Study. Am J Epidemiol. 2009;169(10):1251–1259.
9. Suzuki R, Orsini N, Saji S, et al. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis. Int J Cancer. 2009;124(3):698–712.
10. Pinheiro RL, Sarian LO, Pinto-Neto AM, et al. Relationship between body mass index, waist circumference and waist to hip ratio and the steroid hormone receptor status in breast carcinoma of pre- and postmenopausal women. Breast. 2009;18(1):8–12.
11. Colditz GA, Rosner BA, Chen WY, et al. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst. 2004;96(3):218–228.
12. Chu KC, Anderson WF. Rates for breast cancer characteristics by estrogen and progesterone receptor status in the major

Am J Epidemiol. 2011;174(6):661–671
rational, and ethnic groups. *Breast Cancer Res Treat*. 2002;74(3):199–211.
13. Chow LW, Ho P. Hormonal receptor determination of 1,052 Chinese breast cancers. *J Surg Oncol*. 2000;75(3):172–175.
14. Zhang C, Ho SC, Lin F, et al. Soy product and isoflavone intake and breast cancer risk defined by hormone receptor status. *Cancer Sci*. 2010;101(2):501–507.
15. Adams SA, Matthews CE, Hebert JR, et al. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1170–1178.
16. Gao YT, Shu XO, Dai Q, et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. *Int J Cancer*. 2000;87(2):295–300.
17. Cotterchio M, Kreiger N, Theis B, et al. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiol Biomarkers Prev*. 2003;12(10):1053–1060.
18. Rosenberg LU, Einarsdottir K, Friman EI, et al. Risk factors for hormone receptor-defined breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2482–2488.
19. Lipworth L, Bailey LR, Trichopoulos D. History of breastfeeding in relation to breast cancer risk: a review of the epidemiologic literature. *J Natl Cancer Inst*. 2000;92(4):302–312.
20. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000;152(6):514–527.
21. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: a prospective cohort study. *Int J Cancer*. 2006;119(7):1683–1689.
22. Britton JA, Gammon MD, Schoenberg JB, et al. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20–44 years of age. *Am J Epidemiol*. 2002;156(6):507–516.
23. Huang WY, Newman B, Millikan RC, et al. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol*. 2000;151(7):703–714.
24. Iwasaki M, Otani T, Inoue M, et al. Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. *Ann Epidemiol*. 2007;17(4):304–312.
25. Seidell JC, Cigolini M, Deurenberg P, et al. Fat distribution, androgens, and metabolism in nonobese women. *Am J Clin Nutr*. 1989;50(2):269–273.
26. Wei S, Schmidt MD, Dwyer T, et al. Obesity and menstrual irregularity: associations with ShBG, testosterone, and insulin. *Obesity (Silver Spring)*. 2009;17(5):1070–1076.
27. Bruning PF, Bonfrer JM, van Noord PA, et al. Insulin resistance and breast-cancer risk. *Int J Cancer*. 1992;52(4):511–516.
28. Chen WY, Hankinson SE, Schnitt SJ, et al. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer*. 2004;101(7):1490–1500.
29. Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA*. 2003;289(24):3254–3263.
30. Slanger TE, Chang-Claude JC, Obi N, et al. Menopausal hormone therapy and risk of clinical breast cancer subtypes. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1188–1196.
31. Brinton LA, Richesson D, Leitzmann MF, et al. Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study cohort. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11):3150–3160.
32. Potter JD, Cerhan JR, Sellers TA, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women’s Health Study: how many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev*. 1995;4(4):319–326.
33. Borgquist S, Anagnostaki L, Jirström K, et al. Breast tumours following combined hormone replacement therapy express favourable prognostic factors. *Int J Cancer*. 2007;120(10):2202–2207.
34. Fournier A, Fabre A, Mesrine S, et al. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol*. 2008;26(8):1260–1268.
35. Arpino G, Weiss H, Lee AV, et al. Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. *J Natl Cancer Inst*. 2005;97(17):1254–1261.
36. Gao JD, Wang J, Feng XL, et al. Characterization of hormone receptor status in 5758 Chinese females with breast cancer [in Chinese]. *Zhonghua Zhong Liu Za Zhi*. 2009;31(9):683–686.
37. Fan L, Zheng Y, Yu KD, et al. Breast cancer in a transitional society over 18 years: trends and present status in Shanghai, China. *Breast Cancer Res Treat*. 2009;117(2):409–416.
38. Chu KC, Anderson WF, Fritz A, et al. Frequency distributions of breast cancer characteristics classified by estrogen receptor and progesterone receptor status for eight racial/ethnic groups. *Cancer*. 2001;92(1):37–45.