First-degree family history of prostate cancer is associated the risk of breast cancer and ovarian cancer

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Abstract

The evidence for associations between family history of prostate cancer and the risk of breast cancer and ovarian cancer is inconclusive. The first systematic review and meta-analysis of studies was conducted to assess the risk of breast cancer and ovarian cancer associated with a family history of prostate cancer.

A literature search was conducted using MEDLINE, Embase and Web of science databases up to January 31, 2019. Data were screened and extracted independently by 2 reviewers. The pooled risk ratio (RR) and its 95% confidence interval (CI) were calculated using random-effects models. The GRADE approach was used to assess the quality of evidence.

Nine observational studies including 8,011,625 individuals were included in the meta-analysis. The meta-analysis showed that family history of prostate cancer in first-degree relatives was associated with an increased risk of breast cancer (RR 1.12, 95%CI 1.09 to 1.14) with moderate quality evidence, subgroup analysis showed consistent results. Compared with no family history of prostate cancer, history of prostate cancer in first-degree relatives was associated with a slight risk of ovarian cancer (1.10, 95%CI 1.01 to 1.20) with moderate quality evidence. Family history of prostate cancer among sibling was associated with a 17% increased risk of ovarian cancer (95% CI 1.03 to 1.34), however, no significant association was found between family history of prostate cancer among parent and risk of ovarian cancer (RR 1.19, 95% CI 0.84 to 1.70).

This review demonstrates that women with a family history of prostate cancer in first-degree relatives was associated with an increased risk of breast cancer and ovarian cancer. These findings may aid in screening, earlier detection and treatment of women with a family history of prostate cancer in first-degree relatives.

Abbreviations: BRCA = breast cancer susceptibility gene, CI = confidence interval, HRs = hazard ratios, ORs = odds ratios, RR = risk ratio.

Keywords: breast cancer, family history, meta-analysis, ovarian cancer, prostate cancer

1. Introduction

Breast cancer is the most common cancer worldwide in women.11 Cancer epidemiological data showed that an estimated about 2,088,849 new breast cancer cases and almost 626,679 cancer deaths worldwide in 2018.12 Meanwhile, about 295,414 new ovarian cancer cases and almost 184,799 cancer deaths worldwide in 2018.2 Ovarian cancer is less common, but is associated with much high mortality.1,4 Family history is a well-established risk factor for both cancers.5,6 Compared to the women without a first-degree relative with breast cancer, those with a family history of breast cancer in first-degree relatives had a 2.1 times greater risk of developing breast cancer.77 Women with a family history of ovarian cancer in first-degree relatives had a 3.1 times greater risk of developing ovarian cancer.8

It is estimated that approximately 5% to 10% of all breast cancer cases and 10% to 15% of all ovarian cancers are thought to be hereditary.9–11 Hereditary breast and ovarian cancer syndrome have been considered to be associated with deleterious mutations in the breast cancer susceptibility gene (BRCA) genes.12,13 Previous studies have reported that individuals with mutations in BRCA1 and BRCA2 are at an increased risk of developing breast, ovarian, prostate and other cancers.13,14 The lifetime risk of breast cancer in BRCA1 and BRCA2 mutation carriers is 45–80% and for ovarian cancer, the lifetime risk is...
In addition, germline mutations in the BRCA2 gene confer an 8.6-fold increased risk of prostate cancer and BRCA1 mutation carriers have a 3.8-times increased risk of prostate cancer in men younger than 65 years. The BRCA gene alteration may be responsible for the clustering of breast, ovarian and prostate cancer.

Moreover, previous observational studies have reported family history of prostate cancer may be associated with risk of breast cancer and ovarian cancer. However, the results from these studies remain controversial. Therefore, to help clarify the evidence, we performed a systematic review and meta-analysis of all studies investigating the associations of family history of prostate cancer with breast cancer and ovarian cancer risk.

2. Methods

2.1. Search strategy and eligibility criteria
Medline, Embase and Web of Science databases were searched up to January 31, 2019. The terms used in the search included “prostate cancer OR prostate carcinoma OR prostate neoplasm,” “breast cancer OR breast carcinoma OR breast neoplasm,” “ovarian cancer OR ovarian carcinoma OR ovarian neoplasm” and “family history.” Other eligible articles were searched for via the reference lists of relevant studies. The study identification and selection process is shown in Figure 1. The eligible studies should meet the following inclusion criteria:

(1) articles with full text;
(2) studies that reported the association between the family history of prostate cancer and breast cancer and ovarian cancer risk;
(3) studies with odds ratios (ORs), risk ratio (RRs), standardized incidence ratios or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs);
(4) the published language was English.

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Data extraction and quality assessment

Two investigators extracted data independently using a standard data collection form. The data extracted from each study included first author, year of publication, study design, country of the population studied, sample size, follow-up duration, cancer site, source of family history, primary outcome reported, OR or RR or standardized incidence ratios or HR and 95% CIs with and without adjustment for potential confounders and potential confounders used for adjustment. The Newcastle-Ottawa Scale was used to assess the quality of the included studies by 2 independent investigators. "A" star rating system (maximum nine stars) was used to assess the quality of a study with 3 aspects including selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. Studies that scored 7 stars or greater were considered to be of medium quality, and studies that scored less than 7 stars were considered to be of low quality. Discrepancies in opinions were resolved by discussion and consensus.

2.3. Grading the quality of evidence

Two reviewers independently assessed the quality of evidence for outcomes using GRADEpro GDT (GRADEpro Guideline Development Tool, McMaster University, 2015, developed by Evidence Prime, Inc, Hamilton, Canada; https://gradepro.org/). Quality of evidence were based on risk of bias, inconsistency, indirectness, imprecision of the results, and publication bias. The quality of evidence for the main outcome was graded as very low, low, moderate, or high. Quality assessment of the evidence are given in Table 1.

2.4. Statistical analysis

Primary outcome was relative risks for breast cancer and ovarian incidence. Subgroup analyses of primary outcome were conducted according to study design, study region and source of family history. For each study, we computed the RR for breast cancer and ovarian cancer along with the 95% confidence interval. The pooled risk ratio was computed using random effect models. Chi-square-based Q test and the I² metric were used to assess heterogeneity between studies. The heterogeneity was considered significant when P < .10 and I² > 50%. The significance of the summary RR was determined by the Z-test and P < .05 was considered as statistically significant. Sensitivity analysis was performed by omitting 1 study each time to assess the stability of the results. Potential publication bias was assessed using Begg, Egger test and funnel plots. The statistical analysis was performed using STATA software version 12.0 (Stata Corporation, College Station, Texas).

3. Results

3.1. Studies retrieved and characteristics

The systematic search of articles published before January 31, 2019, 732 articles were identified in the initial search. 26 study reports assessed after screening titles and abstracts. After full text review, 9 published reports comprising 8,011,625 individuals met the inclusion criteria and were included in the analysis (Fig. 1). Overall, 3 studies were cohorts and 6 studies were case-controls studies, 4 of these studies based in America, 4 in Europe, and 1 in the Asia region. Breast cancer risk were reported in 7 studies, and ovarian cancer risk in 4 studies. Two studies report both breast cancer and ovarian cancer risk in the women with family history of prostate cancer. The articles were published between 1996 and 2016. The detailed characteristics of all the included studies are shown in Table 2. The quality of studies based on the Newcastle-Ottawa Scale score is presented in Table 3.

3.2. Associations between family history of prostate cancer and the risk of breast cancer incidence

Seven studies with 8,008,342 individuals in total evaluated the association between family history of prostate cancer and the risk of breast cancer incidence. The history of prostate cancer in first-degree relatives was significantly associated with breast cancer risk (RR = 1.12, 95% CI = 1.09–1.14, I² = 0.00%) (Fig. 2), with moderate quality evidence (Table 1). This increased risk with family history of prostate cancer persisted in subgroup analysis based on study design (cohort study: RR, 1.11; 95% CI, 1.09–1.14, I² = 0.00%, case-control study: RR, 1.12; 95% CI, 1.05–1.40, I² = 17.50%) and study region (Europe: RR, 1.11; 95% CI, 1.08–1.14, I² = 0.00%, America: RR, 1.16; 95% CI, 1.07–1.25, I² = 0.00%, Asia: RR, 1.70; 95% CI, 1.15–2.50) (Table 4).

### Table 1

| Association studied | No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Factors that can increase quality of evidence | Pooled effect estimate | Quality |
|---------------------|----------------|--------|--------------|---------------|--------------|-------------|---------------------------------------------|------------------------|---------|
| Family history of PCa in first degree relatives and risk of BCa | 7              | Observational study | Not serious   | Not serious   | Not serious   | All plausible confounding would reduce a demonstrated effect | 1.12 (1.09,1.14) | MODERATE |
| Family history of PCa in first degree relatives and risk of OCa | 4              | Observational study | Not serious   | Not serious   | Not serious   | All plausible confounding would reduce a demonstrated effect | 1.10 (1.01,1.20) | MODERATE |

BCa = breast cancer, OCa = ovarian cancer, PCa = prostate cancer.
3.3. Associations between family history of prostate cancer and the risk of ovarian cancer incidence

Four studies with 7,850,244 individuals in total evaluated the association between family history of prostate cancer and the risk of ovarian cancer incidence. The history of prostate cancer in first-degree relatives was slightly associated with ovarian cancer risk (RR = 1.10, 95% CI = 1.01–1.20, I² = 11.30%) (Fig. 3), with moderate quality evidence (Table 4). When we stratified our analysis by study design, there was no statistically significant increased association in the 2 pooled cohort studies (RR, 1.09;

| Author      | Year | Country | Study design | Follow up duration | Sample size | Cancer site | Exposure | Measure of effect | RR (95% CI) | Adjustment factors |
|-------------|------|---------|--------------|--------------------|-------------|-------------|----------|------------------|-------------|-------------------|
| Tutera      | 1996 | USA     | Cohort       | 1986-1992          | 41,837      | BCa         | Family history of PCa among first-degree relatives | RR       | 1.22 (0.98–1.50) | Age:          |
| Negri       | 1997 | Italy   | Case-control | —                  | Case:2,569  | BCa         | Family history of PCa among first-degree relatives | OR       | 1.05 (0.7–1.7)   | Age, area of residence, education, nulliparity/age at first birth and number of siblings. |
| Suzuki      | 2007 | Japan   | Case-control | —                  | Case:18,836 | BCa         | Family history of PCa among first-degree relatives | OR       | 1.7 (1.2–2.6)    | Smoking history, drinking, BMI, exercise habit, and referral pattern to our hospital. |
| Hemminki    | 2012 | Sweden  | Cohort       | 1958–2008          | 7,800,000   | BCa         | Family history of PCa among Parent | SIR      | 1.11 (1.08 1.14) | Sex and age. |
| Turati      | 2013 | Switzerland and Italy | Case-control | —                  | Case:12,000 | BCa         | Family history of PCa among first-degree relatives | OR       | 1.2 (1.0–1.8)    | Age, sex, center, year of interview, education, body mass index, alcohol drinking, tobacco smoking, and number of brothers and sisters. |
| Beebe-Dimmer| 2015 | USA     | Cohort       | 1993–2009          | 78,171      | BCa         | Family history of PCa among first-degree relatives | RR       | 1.14 (1.02–1.26) | Age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy. |
| Bethea      | 2016 | USA     | Case-control | —                  | Case:2,618  | BCa         | Family history of PCa among first-degree relatives | OR       | 1.16 (0.99–1.36) | Age, study, geographic region, questionnaire time period, and recency of mammogram. |
| Tung        | 2004 | USA     | Case-control | —                  | Case: 558   | OCa         | Family history of PCa among first-degree relatives | OR       | 1.64 0.97, 2.75  | Age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation. |
| Suzuki      | 2007 | Japan   | Case-control | —                  | Case:18,836 | OCa         | Family history of PCa among Parent | OR       | 0.6 (0.1–32.0)   | Smoking history, drinking, BMI, exercise habit, and referral pattern to our hospital. |
| Soegaard    | 2009 | UK      | Case-control | —                  | Case: 554   | OCa         | Family history of PCa among Parent | OR       | 1.0 (0.5,1.8)    | Age, pregnancy, number of additional pregnancies, duration of oral contraceptive use, and number of relevant relatives. |
| Hemminki    | 2012 | Sweden  | Cohort       | 1958–2008          | 7,800,000   | OCa         | Family history of PCa among Parent | SIR      | 1.05 0.97 1.14   | Age, calendar period, socioeconomic status, geographical region, number of children, and age at first birth. |

BCa = breast cancer, OCa = ovarian cancer, PCa = prostate cancer, SIR = standardized incidence ratio.

Table 2

| Author      | Year | Country | Study design | Follow up duration | Sample size | Cancer site | Exposure | Measure of effect | RR (prostate cancer risk) (95% CI) | Adjustment factors |
|-------------|------|---------|--------------|--------------------|-------------|-------------|----------|------------------|-------------------------------|-------------------|
| Tutera      | 1996 | USA     | Cohort       | 1986-1992          | 41,837      | BCa         | Family history of PCa among first-degree relatives | RR       | 1.22 (0.98–1.50) | Age:          |
| Negri       | 1997 | Italy   | Case-control | —                  | Case:2,569  | BCa         | Family history of PCa among first-degree relatives | OR       | 1.05 (0.7–1.7)   | Age, area of residence, education, nulliparity/age at first birth and number of siblings. |
| Suzuki      | 2007 | Japan   | Case-control | —                  | Case:18,836 | BCa         | Family history of PCa among first-degree relatives | OR       | 1.7 (1.2–2.6)    | Smoking history, drinking, BMI, exercise habit, and referral pattern to our hospital. |
| Hemminki    | 2012 | Sweden  | Cohort       | 1958–2008          | 7,800,000   | BCa         | Family history of PCa among Parent | SIR      | 1.11 (1.08 1.14) | Sex and age. |
| Turati      | 2013 | Switzerland and Italy | Case-control | —                  | Case:12,000 | BCa         | Family history of PCa among first-degree relatives | OR       | 1.2 (1.0–1.8)    | Age, sex, center, year of interview, education, body mass index, alcohol drinking, tobacco smoking, and number of brothers and sisters. |
| Beebe-Dimmer| 2015 | USA     | Cohort       | 1993–2009          | 78,171      | BCa         | Family history of PCa among first-degree relatives | RR       | 1.14 (1.02–1.26) | Age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy. |
| Bethea      | 2016 | USA     | Case-control | —                  | Case:2,618  | BCa         | Family history of PCa among first-degree relatives | OR       | 1.16 (0.99–1.36) | Age, study, geographic region, questionnaire time period, and recency of mammogram. |
| Tung        | 2004 | USA     | Case-control | —                  | Case: 558   | OCa         | Family history of PCa among first-degree relatives | OR       | 1.64 0.97, 2.75  | Age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation. |
| Suzuki      | 2007 | Japan   | Case-control | —                  | Case:18,836 | OCa         | Family history of PCa among Parent | OR       | 0.6 (0.1–32.0)   | Smoking history, drinking, BMI, exercise habit, and referral pattern to our hospital. |
| Soegaard    | 2009 | UK      | Case-control | —                  | Case: 554   | OCa         | Family history of PCa among Parent | OR       | 1.0 (0.5,1.8)    | Age, pregnancy, number of additional pregnancies, duration of oral contraceptive use, and number of relevant relatives. |
| Hemminki    | 2012 | Sweden  | Cohort       | 1958–2008          | 7,800,000   | OCa         | Family history of PCa among Parent | SIR      | 1.05 0.97 1.14   | Age, calendar period, socioeconomic status, geographical region, number of children, and age at first birth. |

3.3. Associations between family history of prostate cancer and the risk of ovarian cancer incidence

Four studies with 7,850,244 individuals in total evaluated the association between family history of prostate cancer and the risk of ovarian cancer incidence. The history of prostate cancer in first-degree relatives was slightly associated with ovarian cancer risk (RR = 1.10, 95% CI = 1.01–1.20, I² = 11.30%) (Fig. 3), with moderate quality evidence (Table 4). When we stratified our analysis by study design, there was no statistically significant increased association in the 2 pooled cohort studies (RR, 1.09;
### Table 4

Stratified analyses of family history of prostate cancer associated with breast cancer and ovarian cancer risk.

| Cancer site                   | No. of studies | Pooled RR (95% CI)     | $I^2$ statistics (%) | $P$-value for the heterogeneity Q test |
|-------------------------------|----------------|------------------------|----------------------|----------------------------------------|
| Breast cancer risk            | 8              | 1.12 (1.09,1.14)       | 0.00%                | 0.512                                  |
| Cohort                        | 4              | 1.11 (1.00,1.14)       | 0.00%                | 0.811                                  |
| Case-control                  | 4              | 1.22 (1.05,1.40)       | 17.50%               | 0.304                                  |
| European                      | 4              | 1.11 (1.08,1.14)       | 0.00%                | 0.923                                  |
| American                      | 3              | 1.16 (1.07,1.25)       | 0.00%                | 0.854                                  |
| Asian                         | 1              | 1.70 (1.15,2.50)       | —                    | —                                      |
| Ovarian cancer risk           | 5              | 1.10 (1.01,1.20)       | 11.30%               | 0.341                                  |
| Cohort                        | 2              | 1.09 (0.99,1.21)       | 46.40%               | 0.172                                  |
| Case-control                  | 3              | 1.33 (0.89,1.98)       | 0.00%                | 0.433                                  |
| European                      | 3              | 1.06 (1.01,1.18)       | 0.00%                | 0.383                                  |
| American                      | 1              | 1.64 (0.97,2.76)       | —                    | —                                      |
| Asian                         | 1              | 0.60 (0.03,10.73)      | —                    | —                                      |
| History of PCa among parent   | 3              | 1.19 (0.84,1.70)       | 50.60%               | 0.132                                  |
| History of PCa among sibling  | 2              | 1.17 (1.03,1.34)       | 0.00%                | 0.940                                  |

*BCa = breast cancer, OCa = ovarian cancer, PCa = prostate cancer.*

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**Figure 2.** Forest plot of studies reporting association between family history of prostate cancer in first-degree relatives and breast cancer risk.
95% CI, 0.99–1.21; $I^2=46.40\%$) and in the 2 pooled case-control studies (RR=1.33, 95% CI=0.89–1.98, $I^2=0.00\%$) (Table 4). Subgroup analyses based on study region showed that a slightly significant increased association between history of prostate cancer and ovarian cancer risk was observed in Europe (RR=1.08, 95% CI=1.01–1.16, $I^2=0.00\%$), but not in America (RR=1.64, 95% CI=0.97–2.76) and Asia region (RR=0.60, 95% CI=0.03–10.73) (Table 4). In addition, subgroup analyses based on source of history showed that family history of prostate cancer among sibling was associated with ovarian cancer risk (RR=1.17, 95% CI=1.03–1.34), however, no association was found between family history of prostate cancer among parent and ovarian cancer risk (RR=1.19, 95% CI=0.84–1.70) (Table 4).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was performed for breast cancer risk by removing individual studies, and the results showed the overall pooled RRs were not influenced by any individual study (Fig. 4), indicating the results of this meta-analysis are stable. No publication bias was observed based on visual inspection of funnel plots or according to Begg ($P=.108$) and Egger test ($P=.053$) for breast cancer risk (Fig. 5). We did not conduct sensitivity analysis and publication bias assessment for ovarian cancer risk due to the limited number of studies.

4. Discussion

Nine studies with a total of 8,011,625 participants met the inclusion criteria and were finally included into the meta-analysis. The findings of this meta-analysis suggest that the risk of breast cancer and ovarian cancer was increased in people with family history of prostate cancer in first-degree relatives. In addition, we also found that increased ovarian cancer risk in people with family history of prostate cancer among sibling, but not among parent. These findings may assist in targeting screening, earlier detection and treatment of breast cancer and ovarian cancer.

The cancer pathogenesis include both heritable and environmental causation.[27] Family history was one of the most significant risk factors for breast cancer and ovarian cancer.[7,8] A family history of prostate cancer has also been reported as a possible risk factor for breast cancer and ovarian cancer.[24] A cohort study conducted by Beebe-Dimmer et al. showed that a family history of prostate cancer was associated with a modest increase in breast cancer risk (HR 1.14; 95% CI, 1.02–1.26), and
women with familial prostate cancer had a 78% greater risk of breast cancer (HR, 1.78; 95% CI, 1.45–2.19). Similarly, a case-control study conducted by Suzuki et al. showed that women with familial prostate cancer had a 70% greater risk of breast cancer in Japanese population. However, several studies found no association between prostate cancer family history and breast cancer risk. Negri et al observed that a family history of prostate cancer was not associated with increased breast cancer risk (OR, 1.05; 95% CI, 0.7–1.7) in Italian. A cohort study and a case-control study also showed no association between risk of breast cancer and family history of prostate. In addition, 4 studies reported the association between family history of prostate cancer and ovarian cancer risk, of these, one cohort study and one case-control study showed the risk of breast cancer was associated with history of prostate cancer. The results are inconsistent with those of the other 2 studies. The most
likely explanation for this difference between studies is the difference in study design, sample size, nationalities or study regions.

In our analysis, we observed an increased risk of breast cancer and ovarian cancer in women with a family history of prostate cancer. Subgroup meta-analyses based on study design and study region showed the consistent results for breast cancer risk. However, no significant association was observed between family history of prostate cancer and ovarian cancer risk in the pooled cohort studies and the pooled case-control studies. Subgroup meta-analyses based on study region showed that a slightly significant increased association between history of prostate cancer and ovarian cancer risk was observed in Europe, but not in America and Asia region. In addition, subgroup analyses based on source of history showed that ovarian cancer risk was associated with family history of prostate cancer among sibling, but not among parent. It is considered that those negative associations for ovarian cancer risk were attributable to the relatively small number of studies included in the analysis, in addition, the disparity of data quality, the cultures and habits of different populations may also lead to differences in outcomes. Thus, more high quality studies are needed to assess the associations.

The underlying mechanisms of the associations are still unclear. A common gene alteration may be responsible for the clustering of prostate, breast cancer and ovarian cancer. The BRCA1 and BRCA2 genes mutation, confirmed to be linked with breast cancer, ovarian cancer and prostate cancer. The BRCA1 and BRCA2 genes mutation confer a 3.8-and 8.6-fold risk were attributable to the relatively small number of studies included in the analysis, in addition, the culture difference, the habits and different populations may also lead to differences in outcomes. Thus, more high quality studies are needed to assess the associations.

Further, previous study reported that 55% to 65% of women with a deleterious BRCA1 mutation and approximately 45% of women with a deleterious BRCA2 mutation will develop breast cancer by age 70 years. In addition, about 39% of women who inherit a harmful BRCA1 mutation and 11% to 17% of women who inherit a harmful BRCA2 mutation will develop ovarian cancer by age 70 years. These mutations could therefore be responsible for part of the identified associations between family history of prostate cancer and breast cancer and ovarian cancer risk. Further studies are needed to explore the mechanism of the association between family history of prostate cancer and risk of breast and ovarian cancer, and provide further data on the incidence and prognosis of breast and ovarian cancer in women with family history of prostate cancer.

To our knowledge, this is the first meta-analysis that evaluates the association between family history of prostate cancer and breast cancer and ovarian cancer risk. The sample size in our study is the large. There is no significant heterogeneity and publication bias in our meta-analysis. In addition, the quality of evidence for the main outcome was assessed rigorously using GRADE approach. However, some limitations of the present study should be considered. Firstly, there were too few studies to draw a solid conclusion for the risk of ovarian cancer in women with family history of prostate cancer, more prospective cohort studies are still needed to evaluate the risk of ovarian cancer in people with family history of prostate cancer. Second, we didn’t estimate the association between history of prostate cancer among parent or sibling and risk of breast cancer due to the lack of information available in the original studies. Thirdly, although no remarkable publication bias was observed based on the funnel plot, Begg test and Egger test, some publication bias may exist in the results because only studies published in English language were included.

5. Conclusion
In conclusion, results of this meta-analysis indicate that family history of prostate cancer in first relatives was associated with an increased risk of breast cancer and ovarian cancer. The findings may assist in targeting screening, earlier detection and treatment of breast cancer and ovarian cancer. However, further prospective cohort studies are needed to provide more conclusive evidence.

Author contributions
QFZ, ZJR, DLL and WRW participated in the design, data acquisition, manuscript writing, and have given final approval of the version to be published. QFZ, QLY, QZ, HBW performed data analysis, data interpretation. WRW and DLL revised the whole writing process. All authors read and approved the final manuscript.

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