Aspirin Use and Risk of Breast Cancer: Systematic Review and Meta-analysis of Observational Studies

Shanliang Zhong1, Lin Chen2, Xiaohui Zhang1, Dandan Yu3, Jinhai Tang3, and Jianhua Zhao1

Abstract

Previous studies concerning the association between aspirin use and breast cancer risk yielded inconsistent results. We aimed to investigate the association by meta-analysis. PubMed and EMBASE were searched for relevant studies. We calculated the summary relative risks (RR) and 95% confidence intervals (CI) using random-effects models. Seventeen cohort studies and 15 case–control studies were included. The overall result showed that aspirin use decreased risk of breast cancer (RR, 0.90; 95% CI, 0.85–0.95). However, there was evidence of publication bias and heterogeneity and the association disappeared after correction using the trim-and-fill method. When stratified by study design, a significant benefit for aspirin users was only found in population-based and hospital-based case–control studies but not in cohort or nested case–control studies. Further subgroup analyses showed that aspirin use could decrease risk of in situ breast tumors or hormone receptor–positive tumors and reduce risk of breast cancer in postmenopausal women. Aspirin use may not affect overall risk of breast cancer, but decrease risk of in situ breast tumors or hormone receptor–positive tumors and reduce risk of breast cancer in postmenopausal women. Considering between-study significant heterogeneity and publication bias, confirmation in future studies is also essential. Cancer Epidemiol Biomarkers Prev; 24(11): 1–11. ©2015 AACR.

Introduction

Breast cancer, one of the most frequently diagnosed cancers among women of all racial and ethnic groups, leads to the second most common cancer-associated death among U.S. women (1). Despite many efforts, few modifiable risk factors for breast cancer have been identified. Recently, the potential anticancer properties of aspirin, commonly known as pain reliever, have attracted more interest (2). Aspirin display anticancer activity by inhibiting cyclooxygenase (COX; ref. 3), thus decreasing the formation of downstream tissue-specific signaling lipids known as prostanoids. Prostanoids play an important role in carcinogenesis by affecting cellular proliferation, apoptosis, and angiogenesis (4). Although protection of aspirin against cancer has been shown, the protective effects are seen mainly in colorectal, esophageal, gastric, and endometrial cancers (3, 5). Previously, we have investigated the effect of aspirin intake on the mortality in breast cancer, but only found that aspirin use has a small effect on the survival of breast cancer patients (6).

A number of observational studies have investigated the effect of aspirin use on the risk of breast cancer in the past three decades, but their results are conflicting rather than conclusive. A meta-analysis (7) including 33 studies has evaluated the association and found that a decreased risk of breast cancer for aspirin users was found in the pooled analysis of all studies [odds ratio (OR) = 0.86; 95% confidence interval (CI) = 0.81–0.92] but not in a randomized controlled trial (OR, 0.98; 95% CI, 0.87–1.09). The investigators concluded that regular use of aspirin may be associated with reduced risk of breast cancer. However, the subjects of two included articles (8, 9) were overlapped in another two included articles (10, 11). The duplicated data could bias the results. We also noted that two studies (12, 13) examining the association between aspirin use and mortality in breast cancer patients but not between aspirin use and breast cancer risk were also included in that meta-analysis. In addition, previous meta-analysis has not performed a subgroup analysis according to hormone receptor status, menopausal status, or cancer stage. Since the meta-analysis, seven large observational studies have published. Therefore, we performed a meta-analysis with all available studies to explore the association between aspirin use and risk of breast cancer. Besides, we also performed a dose–response analysis to further evaluate the potential dose–response relations.

Materials and Methods

Literature search

We searched PubMed (from 1980 to present) and Embase (from 1977 to present) using the following terms: “aspirin” or...
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"acetylsalicylic acid" or "non-steroidal anti-inflammatory drug" or "non-steroidal anti-inflammatory drugs," and "breast cancer" and "risk" or "incidence". The latest date of this search was April 2015. All cohort or case–control studies evaluating the relationship between aspirin use and risk of breast cancer were eligible, without language restriction. Reference lists from relevant articles were examined manually to further identify potentially relevant studies. All searches were conducted independently by two reviewers; differences were checked by the two and resolved by discussion. When two or more studies presented possible overlap, we included the one with largest populations.

Inclusion criteria
All the studies were included in this meta-analysis if they met the following criteria: (i) the exposure of interest was aspirin use; (ii) the outcome of interest was breast cancer; (iii) the study design was case–control or cohort; and (iv) risk estimates and 95% CIs were reported (or information to calculate them).

Data extraction
Two independent investigators extracted data from the eligible articles. The extracted data included the last name of first author, year of publication, origin of the study, follow-up period, study design, sample size, aspirin use, risk estimates, and corresponding 95% CIs, and covariates adjusted for in the multivariable analysis. For studies provided more than one risk estimate, we extracted the one that was adjusted for the greatest number of confounding factors. Discrepancies were resolved by consensus, involving a third investigator.

Study quality assessment
Two investigators assessed the methodological quality of included studies independently using the nine-star Newcastle Ottawa scale (NOS; ref. 14). Each study was evaluated based on eight items, categorized into three broad perspectives, including selection, comparability, and outcome, for cohort studies or exposure for case–control studies. We considered studies with a score of 7 or greater as high quality. Discrepancies were resolved by discussion or through consultation with a third investigator.

Statistical analysis
Because outcomes were relatively rare, the ORs and HRs were considered approximations of relative risks (RR). Summary estimates of RRs and 95% CIs were obtained using a random-effects model where the restricted maximum likelihood estimator was used to evaluate the interstudy heterogeneity (15, 16). We calculated prediction interval (PI) of summary estimate for the random effects model to depict the uncertainty around the estimate (17). If studies did not report a summary risk estimate for aspirin use, a summary risk estimate was calculated using risk estimates for each of the aspirin use categories (18–33). Interstudy heterogeneity was estimated using a $\chi^2$-based Q test (34), with a P value of $<0.10$ considered statistically significant (35). We also calculated the I² quantity (34), which lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity. Metaregression was conducted to further explore the sources of heterogeneity. Sensitivity analyses were performed to reflect the influence of individual data on summary HRs. Finally, the potential for publication bias was examined using Begg and Egger regression test (36). Where publication bias was found, the trim-and-fill method was used to estimate the potential influence of this bias on pooled summary estimates (37).

A two-stage random-effects dose–response meta-analysis was performed to compute the trend from the correlated log RR estimates across levels of aspirin use into account the between-study heterogeneity (38). A potential nonlinear relation between aspirin use and risk of death was investigated using restricted cubic splines with three knots at the 25th, 50th, and 75th percentiles of the exposure distribution. Then, the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (39). A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. For each study, we calculated the median level of aspirin use for each category by assigning the midpoint of upper and lower boundaries in each category as the average aspirin use level. When the highest category was open-ended, we assigned the lower end value of the category multiplied by 1.5. Studies were not eligible if the required data were not reported or could not be estimated. All of the statistical analyses were done with R software, version 3.1.1, using the packages metafor (40) and dosresmeta (41). All statistical tests were two-sided.

Results
Characteristics of the studies
Figure 1 presents the process of study selection. Two thousand six hundred and ten abstracts and titles were identified and assessed, and 45 studies were evaluated in detail with regard to their fulfillment of the inclusion criteria. Four articles were excluded as the exposure of interest was not aspirin use, or no usable data were reported (42–45). Nine studies were excluded because their

![Flow chart of the selection of publications included in the meta-analysis.](cebp.aacrjournals.org)
Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Follow-up period</th>
<th>Study design</th>
<th>Sample size</th>
<th>Aspirin use</th>
<th>RR (95% CI)</th>
<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brasky</td>
<td>2014</td>
<td>USA</td>
<td>1993–2010</td>
<td>Cohort</td>
<td>126,689</td>
<td>Nonuser</td>
<td>HR 1.00</td>
<td>Age, observational study enrollment, hormone therapy trial enrollment, diet modification trial enrollment, calcium/vitamin D trial enrollment, U.S. region, education, ethnicity, height, BMI, physical activity, alcohol consumption, pack-years of smoking, fruit and vegetable consumption, red meat consumption, family histories of: breast cancer, cervical cancer, endometrial cancer, and colorectal cancer; screening for: breast cancer, colon cancer, and cervical cancer; age at menarche, age at menopause, gravidity, age at first birth, duration of estrogen therapy, duration of combined postmenopausal hormone therapy, hysterectomy status, multivitamin use, use of antihypertensive medication, history of coronary heart disease, use of cholesterol-lowering medication, history of arthritis, history of migraine, history of ulcer, and other NSAID use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inconsistent use</td>
<td>0.99 (0.91–1.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consistent use</td>
<td>1.11 (1.00–1.24)</td>
<td></td>
</tr>
<tr>
<td>Cui</td>
<td>2014</td>
<td>USA</td>
<td>2001–2011</td>
<td>PCC</td>
<td>5,078</td>
<td>Nonusers</td>
<td>OR 1.00</td>
<td>Personal history of benign breast disease, first-degree family history of breast cancer, menopausal status, history of live birth, age at first live birth, use of hormone replacement therapy, regular exercise, alcohol consumption, and cigarette smoking status.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Everusers</td>
<td>0.82 (0.69–0.99)</td>
<td></td>
</tr>
<tr>
<td>Hollestein</td>
<td>2014</td>
<td>The Netherlands</td>
<td>1998–2010</td>
<td>Cohort</td>
<td>55,597</td>
<td>Nonusers</td>
<td>HR 1.00</td>
<td>Age, sex, unique number of dispensings and unique number of hospitalizations in the year prior to start of follow-up. Urbanization, income, diabetes mellitus, metformin usage, statin usage, estrogen usage, and progesterone usage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median 9.7 years</td>
<td></td>
<td></td>
<td>Users</td>
<td>1.02 (0.97–1.08)</td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>2012</td>
<td>China</td>
<td>2002–2008</td>
<td>PCC</td>
<td>67,388</td>
<td>0–27 cDDD</td>
<td>OR 1.00</td>
<td>Age, sex, age at menarche, height, BMI at age 18 years, weight change since age 18 years, parity and age at first birth, history of breast cancer in parent or sibling, history of benign breast disease, alcohol consumption, physical activity, and postmenopausal hormone use.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>28–364 cDDD</td>
<td></td>
<td></td>
<td>≥365 cDDD</td>
<td>0.92 (0.87–0.99)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.79–0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang</td>
<td>2012</td>
<td>USA</td>
<td>1980–2008</td>
<td>Cohort</td>
<td>84,602</td>
<td>Nonuser</td>
<td>RR 1.00</td>
<td>Age, sex, age at menarche, height, BMI at age 18 years, weight change since age 18 years, parity and age at first birth, history of breast cancer in parent or sibling, history of benign breast disease, alcohol consumption, physical activity, and postmenopausal hormone use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28 years</td>
<td></td>
<td></td>
<td>Past</td>
<td>0.97 (0.88–1.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current</td>
<td>0.96 (0.87–1.05)</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
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<th>RR (95% CI)</th>
<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardia</td>
<td>2011</td>
<td>USA</td>
<td>1986-2005 13 years</td>
<td>Cohort</td>
<td>26,580</td>
<td>Never</td>
<td>RR 1.00</td>
<td>0.80 (0.71-0.90)</td>
</tr>
<tr>
<td>Bosco</td>
<td>2011</td>
<td>USA</td>
<td>1995-2007</td>
<td>Cohort</td>
<td>59,000</td>
<td>Nonuse</td>
<td>RR 1.0</td>
<td>1.15 (0.95-1.38)</td>
</tr>
<tr>
<td>Brasky</td>
<td>2010</td>
<td>USA</td>
<td>1996-2001</td>
<td>PCC</td>
<td>3,285</td>
<td>Nonusers</td>
<td>OR 1.00</td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>Cronin-Fenton</td>
<td>2010</td>
<td>Denmark</td>
<td>1991-2006</td>
<td>NCC</td>
<td>90,145</td>
<td>Never</td>
<td>OR 1.00</td>
<td>0.98 (0.90-1.07)</td>
</tr>
<tr>
<td>Eliassen</td>
<td>2009</td>
<td>USA</td>
<td>1989-2003 14 years</td>
<td>Cohort</td>
<td>112,292</td>
<td>Nonusers</td>
<td>RR 1.00</td>
<td>1.21 (1.03-1.41)</td>
</tr>
<tr>
<td>Friis</td>
<td>2008</td>
<td>Denmark</td>
<td>1993-2003 Average 7.5 years (Range 0.1-10.1)</td>
<td>Cohort</td>
<td>28,695</td>
<td>Nonusers</td>
<td>RR 1.00</td>
<td>1.31 (1.12-1.53)</td>
</tr>
<tr>
<td>Gierach</td>
<td>2008</td>
<td>USA</td>
<td>1995-2003 Average 3.43 years for cases (range, 1 day to 7.13 years); 6.75 years for noncases (range, 1 day to 7.17 years)</td>
<td>Cohort</td>
<td>126,124</td>
<td>Never</td>
<td>RR 1.00</td>
<td>0.95 (0.89-1.03)</td>
</tr>
<tr>
<td>Ready</td>
<td>2008</td>
<td>USA</td>
<td>2000-2004</td>
<td>Cohort</td>
<td>35,323</td>
<td>None</td>
<td>HR 1.00</td>
<td>0.99 (0.80-1.23)</td>
</tr>
</tbody>
</table>

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<th>RR (95% CI)</th>
<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallicchio</td>
<td>2007</td>
<td>USA</td>
<td>1989–2006</td>
<td>Cohort</td>
<td>15,651</td>
<td>Nonusers</td>
<td>RR 1.00</td>
<td>Age</td>
</tr>
<tr>
<td>Gill</td>
<td>2007</td>
<td>USA</td>
<td>1993–2002</td>
<td>Cohort</td>
<td>98,920</td>
<td>Users</td>
<td>0.90 (0.70–1.16)</td>
<td>Age, ethnicity, BMI, family history of breast cancer, education, mammography screening, alcohol intake, age at menarche, age at first livebirth, number of children, menopausal status, age at menopause, hormone replacement therapy, and all pain medication use.</td>
</tr>
<tr>
<td>Jacobs</td>
<td>2007</td>
<td>USA</td>
<td>1992–2003</td>
<td>Cohort</td>
<td>76,303</td>
<td>Nonusers</td>
<td>HR 1.00</td>
<td>Age, race, education, smoking, BMI, physical activity level, use of hormone replacement therapy, history of mammography, history of colorectal endoscopy, use of nonaspirin NSAIDs, and history of heart attack, diabetes, and hypertension.</td>
</tr>
<tr>
<td>Slattery</td>
<td>2007</td>
<td>USA</td>
<td>1999–2004</td>
<td>PCC</td>
<td>4,850</td>
<td>No Users</td>
<td>0.75 (0.64–0.88)</td>
<td>Age, study center, referent year BMI, lifetime physical activity score, parity, and percentage Native American ancestry.</td>
</tr>
<tr>
<td>Harris</td>
<td>2006</td>
<td>USA</td>
<td>2003–2004</td>
<td>HCC</td>
<td>770</td>
<td>Nonusers</td>
<td>OR 1.00</td>
<td>Age, body mass, parity, menopausal status, family history, smoking, and alcohol intake.</td>
</tr>
<tr>
<td>Marshall</td>
<td>2005</td>
<td>USA</td>
<td>1995–2001</td>
<td>Cohort</td>
<td>114,460</td>
<td>Regular use</td>
<td>RR 1.00</td>
<td>Race, BMI, first-degree family history of breast cancer, menopausal and hormone therapy use status, smoking, alcohol intake, physical activity, mammography history, breast biopsy history, parity status before age 30, and neighborhood socioeconomic status.</td>
</tr>
<tr>
<td>Rahme</td>
<td>2005</td>
<td>Canada</td>
<td>1998–2002</td>
<td>NCC</td>
<td>46,080</td>
<td>Not exposed</td>
<td>OR 1.00</td>
<td>Age, mammography in years 2 or 3 prior to index date, breast procedure in the prior 3 years, benign neoplasm of the breast in the prior 3 years, other breast disease in the prior 3 years, estrogen replacement therapy in the prior year, and visit to a gynecologist in the prior year.</td>
</tr>
<tr>
<td>Swede</td>
<td>2005</td>
<td>USA</td>
<td>1982–1998</td>
<td>HCC</td>
<td>4,861</td>
<td>Never</td>
<td>OR 1.00</td>
<td>Age at menarche, age at 1st birth, BMI, history of 1st-degree relative with breast cancer, and history of benign breast disease.</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>Zhang</td>
<td>2005</td>
<td>USA</td>
<td>1976–2002</td>
<td>HCC</td>
<td>3,960</td>
<td>Never used</td>
<td>OR 1.00</td>
<td>Age, year of interview, study center, race, years of education, benign breast disease, number of physician visits 2 years before hospitalization, duration of female hormone supplement use, duration of oral contraceptive use, age at menarche, age at menopause, age at first birth, parity, alcohol consumption, family history of breast cancer, practice of breast self-examination, and BMI.</td>
</tr>
<tr>
<td>Garcia Rodriguez</td>
<td>2004</td>
<td>UK</td>
<td>1995–2001</td>
<td>NCC</td>
<td>23,708</td>
<td>No use</td>
<td>OR 1.00</td>
<td>Age, calendar year, BMI, smoking, alcohol, prior benign breast disease, NSAIDs, paracetamol, steroid and HRT use.</td>
</tr>
<tr>
<td>Terry</td>
<td>2004</td>
<td>USA</td>
<td>1996–1997</td>
<td>PCC</td>
<td>2,862</td>
<td>Nonusers</td>
<td>OR 1.00</td>
<td>Age at diagnosis, migraine headache, BMI, and simultaneously adjusted for the other type of medication use.</td>
</tr>
<tr>
<td>Harris</td>
<td>2003</td>
<td>USA</td>
<td>From 1992 Average 43 months</td>
<td>Cohort</td>
<td>80,741</td>
<td>0–11 months</td>
<td>0.90 (0.72–1.13)</td>
<td>Age.</td>
</tr>
<tr>
<td>Harris</td>
<td>1999</td>
<td>USA</td>
<td>1991–1996 Average 4.7 years</td>
<td>Cohort</td>
<td>32,505</td>
<td>0, &lt;1 pill/week</td>
<td>RR 1.00</td>
<td>Age.</td>
</tr>
<tr>
<td>Harris</td>
<td>1996</td>
<td>USA</td>
<td>Not state</td>
<td>PCC</td>
<td>2,045</td>
<td>Nonusers</td>
<td>OR 1.00</td>
<td>Age, parity, menopausal status, and family history.</td>
</tr>
<tr>
<td>Schreinemachers</td>
<td>1994</td>
<td>USA</td>
<td>1971–1987 Average 12.4 years</td>
<td>Cohort</td>
<td>7,029</td>
<td>Nonusers</td>
<td>RR 1.00</td>
<td>None.</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; cDDD, cumulative defined daily dose; CI, confidence interval; HCC, hospital-based case–control study; NCC, nest case–control study; NSAID, nonsteroidal anti-inflammatory drugs; PCC, population-based case–control study.
data duplicated or overlapped with other articles (8, 9, 46–52). Nevertheless, one of these studies (46) was included in the subgroup analysis by hormone receptor status, and another study (48) was included in dose-response analysis. Finally, 17 cohort studies (10, 18, 20–25, 29–31, 53–58) and 15 case-control studies (11, 19, 26–28, 32, 33, 39–66) involving 1350,913 participants were selected for meta-analysis. Table 1 shows the characteristics of the included studies. Supplementary Tables S1 and S2 summarize the methodological quality of all the included studies. The NOS results showed that the average score was 6.9 (range 4–9) for cohort studies and 6.3 (range 4–9) for case-control studies. There were 18 studies with a score of 7 or more.

**Evidence synthesis**

Figure 2 presents the pooled RR of the association between aspirin use and risk of breast cancer. When the association of aspirin use on breast cancer risk was analyzed as users versus nonusers, a RR of 0.90 (95% CI, 0.85–0.95, P < 0.01; 95% PI, 0.68–1.19) was found. In stratified by study design, a significant benefit for aspirin users was only found in population-based case-control (PCC) studies (RR, 0.80; 95% CI, 0.73–0.88, P < 0.01; 95% PI, 0.65–0.98) and hospital-based case-control (HCC) studies (RR, 0.82; 95% CI, 0.75–0.91, P < 0.01; 95% PI, 0.75–0.91; Fig. 2). In the subgroup analysis by estrogen receptor (ER) or/and progesterone receptor (PR) status, a decreased breast cancer risk was found for aspirin users with ER-positive tumors (RR, 0.90; 95% CI, 0.81–0.99, P = 0.04; 95% PI, 0.68–1.19), PR-positive tumors (RR, 0.87; 95% CI, 0.77–0.98, P = 0.02; 95% PI, 0.67–1.13), and ER- and PR-positive tumors (RR, 0.88; 95% CI, 0.79–0.99, P = 0.04; 95% PI, 0.68–1.14; Fig. 3). When stratifying by menopausal status, the results revealed that postmenopausal women who used aspirin had a RR of 0.86 (95% CI, 0.80–0.93, P < 0.01; 95% PI, 0.75–1.00) for breast cancer risk (Fig. 3). Further analysis by cancer stage showed that aspirin use was only associated with decreased risk of in situ breast cancer (RR, 0.79; 95% CI, 0.71–0.88, P < 0.01; 95% PI, 0.71–0.88; Fig. 3).

**Dose-response meta-analysis**

The dose-response effects of aspirin on breast cancer risk were assessed with 14 studies (10, 11, 18, 20, 22, 24, 27–29, 48, 54, 55, 60, 63). Among these studies, exposure to aspirin was expressed in duration of exposure (11, 18, 20, 24, 27–29, 55, 63) or frequency (e.g., pills/week; refs. 10, 22, 27, 48, 54, 55, 60, 63). If exposure to aspirin was expressed in a times/week (or days/week) scale (10, 22, 55), we assumed the scale equals to average score was 6.9 (range 4–9) for cohort studies and 6.3 (range 4–9) for case-control studies. There were 18 studies with a score of 7 or more.

**Sensitivity analysis and publication bias**

From the results of the leave-one-out sensitivity analysis, the summary RR was not materially altered (data not shown). We explored the source of heterogeneity by country (United States and others), study design (cohort, NCC, PCC, and HCC), publication year, methodological quality (continuous variables), and sample size (>8,000 and ≤8,000 subjects) with metaregression.

The results revealed that none of them contributed to the source of heterogeneity (data not shown).

The results of Begg (P < 0.05) and Egger tests (P = 0.01) have shown the evidence of publication bias. Then, trim-and-fill method was used to correct the result, and nine potential missing studies were required in the right side of the funnel plot in order to make the plot symmetric (Supplementary Fig. S1). However, the correction achieved a nonsignificant reduction of breast cancer risk for aspirin users (RR, 0.93; 95% CI, 0.88–1.02, P = 0.12; 95% PI, 0.65–1.38).

**Discussion**

The current meta-analysis investigated the relationship between aspirin use and risk of breast cancer involving 1350,913 participants. The summary results, as derived from 17 cohort studies and 15 case-control studies, indicated that the average effect of aspirin use was associated with decreased risk of breast cancer. However, there was evidence of publication bias and the association between aspirin use and breast cancer risk no longer existed after correction using the trim-and-fill method. We
Figure 3.
Subgroup analyses by hormone receptor status, menopausal status, and cancer stage for the association between aspirin use and risk of breast cancer. The squares and horizontal lines correspond to the study-specific relative risk and 95% CIs. The area of the square is proportional to the inverse of the sum of the between studies variance and the study-specific variance. The diamond represents the pooled multivariate relative risk and 95% CI.
Aspirin Use and Risk of Breast Cancer

The dose–response analysis with restricted cubic splines in a multivariate random-effects dose–response model for the relationships of duration of aspirin use and risk of breast cancer (A) and frequency of aspirin use and risk of breast cancer (B). The solid line and the short dash line represent the estimated relative risk and its 95% CI.

also noted significant heterogeneity between included studies. We explored the source of heterogeneity using meta-regression and subgroup analysis but failed to find convincing explanations for the significant heterogeneity. When stratified by study design, a significant benefit for aspirin users was only found in PCC and HCC studies but not in cohort and nest case–control (NCC) studies. PCC and HCC studies give a lower level of evidence than cohort and NCC studies and might provide spurious results because of selection bias and recall bias, which might have contributed to the different results. Considering above mentioned, we conclude that aspirin use may not be associated with decreased risk of breast cancer overall.

In subgroup analysis by ER or/and PR status, a benefit for aspirin use on breast cancer risk was only found in hormone receptor–positive tumors. Evidence suggested that endogenous estrogens are important risk factors for breast cancer (67). Postmenopausal women who are regular users of aspirin showed lower estrogen levels compared with nonusers, which could potentially lower the risk of breast cancer (68). As our result indicated, the effect for ever use of aspirin was beneficial among postmenopausal women but not premenopausal women. The different effect of aspirin may be due to postmenopausal women tend to have more hormone receptor–positive tumors (69). Further analysis by cancer stage showed that aspirin use was only associated with decreased risk of in situ breast cancer. Although COX2 overexpression has been observed in both invasive and in situ breast tumors, a higher frequency of COX2 expression was observed in in situ tumors suggesting that the potential therapeutic impact of COX2 inhibition may be more relevant for in situ breast cancer than invasive tumors (70).

We further explored the dose–response relationship between aspirin use and risk of breast cancer. Our results indicated a linear and borderline significant relationship between aspirin use and breast cancer risk. The risk of breast cancer was decreased by 2% for 1-year increment of aspirin use. There was a 4% breast cancer risk reduction for every 3 pills/week increment in aspirin use. Considering the small effect, long-term or high-frequency aspirin use is not recommended for prevention of breast cancer.

There is significant heterogeneity between included studies. However, we failed to find the source of heterogeneity. Several reasons may account for the heterogeneity. First, seven cohort studies reassessed exposure to aspirin during the course of follow-up, while ten cohort studies assessed the exposure only at baseline (Supplementary Table S1), which can lead to immortal time bias (71). Second, misclassification of aspirin use is likely to impact on the effect estimates of aspirin use. Most studies assessed the exposure to aspirin based on self-reported, while some studies obtained exposure data from prescription database or medical record. Self-reported data are not expected to be accurately recalled. Third, studies conducted among populations are varying in age and ethnicity. All of these may partly explain the significant heterogeneity between studies.

The potential limitations of our study should be considered when interpreting the results. First, there was evidence of publication bias and heterogeneity among included studies. Second, although included studies had adjusted for important risk factors, unmeasured factors related to aspirin use may also have influenced results of individual studies. Third, in the subgroup analyses, the limited study number with relatively small sample size in each subgroup may not have enough statistical power to explore the real association. Fourth, the included studies were major conducted in Western countries, and hence the results should be extrapolated to other populations with caution.

In conclusion, aspirin use may not affect overall risk of breast cancer, but decrease risk of in situ breast tumors or hormone receptor–positive tumors and reduce breast cancer risk in postmenopausal women. Considering the heterogeneity and publication bias, our results on the effect of aspirin use on risk of breast cancer overall or in the subgroups should be confirmed in future studies with well-controlled confounding factors, long enough follow-up time, and more accurate assessment of aspirin use, including quantity, frequency, and duration of use.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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