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Aspirin might reduce the incidence of breast cancer

An updated meta-analysis of 38 observational studies

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Abstract

Background: Many epidemiologic studies were performed to clarify the protective effect of regular aspirin use on breast cancer risks, but the results remain inconsistent. Here, we conducted an updated meta-analysis of 38 studies to quantitatively assess the association of regular aspirin use with risk of breast cancer.

Method: We performed a bibliographic database search in PubMed, Embase, Web of Science, Cochrane library, Scopus, and Google Scholar from January 1939 to December 2019. Relative risk (RR) estimates were extracted from eligible case–control and cohort studies and pooled using a random effects model. Subgroup analysis was conducted based on study design, aspirin exposure assessment, hormone receptor status, menopausal status, cancer stage as well as aspirin use duration or frequency. Furthermore, sensitivity and publication bias analyses were performed.

Results: Thirty eight studies of 1,926,742 participants involving 97,099 breast cancer cases contributed to this meta-analysis. Compared with nonusers, the aspirin users had a reduced risk of breast cancer (RR = 0.91, 95% confidence interval [CI]: 0.87–0.95, *P* value of significance [P_{sig}] < .001) with heterogeneity (*P* value of heterogeneity [P_{het}] < .001, I^2 = 82.6%). Subgroup analysis revealed a reduced risk in case–control studies (RR = 0.83, 95% CI: 0.78–0.89, P_{sig} < .001), in hormone receptor positive tumors (RR = 0.91, 95% CI: 0.88–0.94, P_{sig} < .001), in situ breast tumors (RR = 0.79, 95% CI: 0.71–0.88, P_{sig} < .001), and in postmenopausal women (RR = 0.89, 95% CI: 0.83–0.96, P_{sig} = .002). Furthermore, participants who use aspirin for >4 times/wk (RR = 0.88, 95% CI: 0.82–0.96, P_{sig} = .003) or for >10 years (RR = 0.94, 95% CI: 0.89–0.99, P_{sig} = .025) appeared to benefit more from the reduction in breast cancer caused by aspirin.

Conclusions: Our study suggested that aspirin use might be associated with a reduced risk of breast cancer, particularly for reducing the risk of hormone receptor positive tumors or in situ breast tumors, and the risk of breast cancer in postmenopausal women.

Abbreviations: 95% CI = 95% confidence interval, OR = odds ratio, P_{het} = *P* value of heterogeneity, P_{sig} = *P* value of significance, RCT = randomized controlled trial, RR = relative risk.

Keywords: aspirin, breast cancer, chemoprevention, meta-analysis

1. Introduction

Breast cancer is the most frequent cancer and the leading cause of cancer death among women.[1] Therefore, effective breast cancer prevention strategies are urgently needed. Aspirin is commonly used to treat pain, fever, and inflammation. Based on its long-term safety and preliminary efficacy data, aspirin has been investigated extensively as a potential cancer chemopreventive agent, reducing incidence in oesophageal, colorectal, gastric, pancreatic, and prostate cancer.[2] Aspirin may inhibit tumor growth by modulating cellular proliferation and apoptosis, predominantly via suppression of endogenous production of prostaglandin from inhibition of cyclooxygenase (COX) enzyme activity, particularly COX-2. Convincing laboratory evidence has emerged to demonstrate that COX-2 was overexpressed in breast cancer, but not in normal breast issue, which made aspirin a potential chemopreventive agent of breast cancer.

Numerous epidemiologic studies have investigated the relationships between use of aspirin and risk of breast cancer. Some studies have suggested a modest reduction in breast cancer risk in relation to use of aspirin,[3–5] but a randomized clinical trial of long term use of aspirin and some of recent studies did not support a protective role.[6–8]

A meta-analysis[9] of 13 cohort studies recently published had found a borderline significant inverse association between aspirin

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use and breast cancer risk. The researchers had observed potential associations between aspirin intake frequency and breast cancer risk, and the duration of aspirin intake and breast cancer risk. However, results concluded only from cohort studies were less robust, as case–control studies tended to obtain more detailed data for aspirin use, which included the definition and updated assessment of aspirin exposure, appropriate adjustment in baseline characteristics. With the exception of that, estrogen receptor, progesterone receptor, and menopausal status as well as different stages of cancer were not evaluated in the study. Furthermore, 6 cohort studies[10–15] were leaved out in the meta-analysis, and the subjects of one included study[16] was overlapped with another one.[17] Both the missing and duplicated data could bias the results. Besides, 6 relevant studies were published recently.[3,4,6–8] So far, the effect of aspirin on the occurrence of breast cancer has remained uncertain.

The purpose of this meta-analysis was to investigate the association between aspirin use and breast cancer risk of all eligible studies by grouping type of study design, aspirin exposure assessment, hormone receptor status, menopausal status, cancer stage, frequency or duration of aspirin use.

2. Methods

2.1. Search strategy

We searched PubMed, Embase, Web of Science, Cochrane library, Scopus, and Google Scholar without language restriction from January 11, 1939 to October 19, 2019 with the following search terms: ("neoplasms" [Mesh] OR neoplas* OR "tumor" OR "tumour" OR "cancer" OR tumorigen* OR sarcoma* OR malignan* OR adenocarcinoma* OR "tumors"[tw] OR "tumours"[tw] OR "cancers"[tw]) AND ("aspirin"[Mesh] OR "anti-inflammatory agents, Non-Steroidal"[Mesh] OR "anti-inflammatory drugs, Non-Steroidal"[tw] OR "NSAIDs"[tw] OR "acetylsalicylic acid"[tw] OR salicyl* OR "Cyclooxygenase 2 Inhibitors"[tw] OR "cyclooxygenase inhibitors"[tw] OR "COX inhibitors"[tw]) AND ("breast"[Mesh] OR mamma*). The reference lists of previous systematic reviews on the same topic were reviewed to obtain additional eligible publications. We attempted to contact the authors if we required additional information. Two reviewers identified the publications independently and discussed to resolve the differences.

2.2. Study identification

Studies were included if they met the following criteria: evaluate the association between aspirin use and risk of breast cancer; use a randomized controlled trial (RCT) or case–control or cohort study design; provide the odds ratio (OR) or relative risk (RR) with confidence interval (CI) or data necessary to calculate them (raw data, *P* value, or variance estimate). When authors reported the same population in more than one publication, only the most recent report, or the most complete one, was included.[18] Whereas, studies controlling for aspirin use in statistical models without numerically reporting effect measures were excluded.[19] Reviewers resolved all the discrepancy by discussion during the study identification process.

2.3. Data extraction

Each eligible study was carefully reviewed by 2 independent investigators. The extracted data included the last name of first author, year of publication, location, study design, study time, setting, sample size, cancer cases, the number of people using aspirin, and nonuse, any matching factors and definition for aspirin user. For studies providing >1 risk estimate, we extracted the one that was adjusted for the greatest number of confounding factors.[20] We resolved discrepancies through discussion or the third investigator.

2.4. Statistical analysis

The analyses were conducted in 4 parts. First, we used meta-analysis to pool the estimates of RRs and 95% CIs. As low morbidity of breast cancer, we treated ORs as proxy measures of RRs.[19] Estimates of summary risks that were not represented in original articles were calculated based on each of aspirin use categories. Statistical inconsistency among included studies was tested by Cochran Q test at the $P < .05$ level of significance. We also calculated the quantity I^2 that describes the percentage variation across studies that is attributed to heterogeneity. When significant heterogeneity was found, the random-effects model was used for meta-analysis. Otherwise, the fixed-effects model was adopted.

Second, subgroup and sensitivity analyses were performed. We evaluated for potential source of heterogeneity stratified by the following rules: study design: cohort studies versus case–control studies; aspirin exposure ascertain: questionnaire versus interview versus automated databases; hormone receptor status: positive versus negative; menopausal status: premenopausal versus postmenopausal; cancer stage: in situ cancer versus invasive cancer; aspirin use frequency: ≤4 times/wk versus >4 times/wk; aspirin use duration: ≤10 years versus >10 years. To reflect the influence of individual study on summary RRs, a sensitivity analysis was performed.

Third, the potential for publication bias was investigated using Begg and Egger regression test. Egger test was performed to provide quantitative evidence, and $P < .05$ indicated the existed publication bias. Where publication bias was found, the trim-and-fill method was used to estimate the potential influence of this bias on pooled summary estimates. Stata 12.0 (Stata Corp, LLP, College Station, TX) was used for all analyses.

3. Results

3.1. Eligible studies

The overview of our search process was illustrated in Fig. 1. We identified 4186 articles through electronic databases research. After titles and abstracts review, there were 52 potentially eligible studies. We found an additional 11 papers after reviewing articles, reference lists, and other sources. Of the 63 publications, we reviewed in full-text and excluded 25 records according to the above inclusion criteria. The studies were excluded for no useable data reported[21–26] or as the exposure of interest was not aspirin use.[27–34] Eleven studies were excluded for overlapping with others.[16,17,35–43] As only a few studies reported subgroup results, we used data in duplicate studies if studies with the largest number of cancer cases didn't report those to allow studies to be as inclusive as possible.[16,35,37,38,42] At last, 38 studies met the predetermined criteria for inclusion, with 22 cohort studies[3,4,6,10–15,44–56] and 16 case–control studies.[5,8,57–70] Among the 1,926,742 participants of this meta-analysis, there were 97,099 incident breast cancers. The 38 studies were published

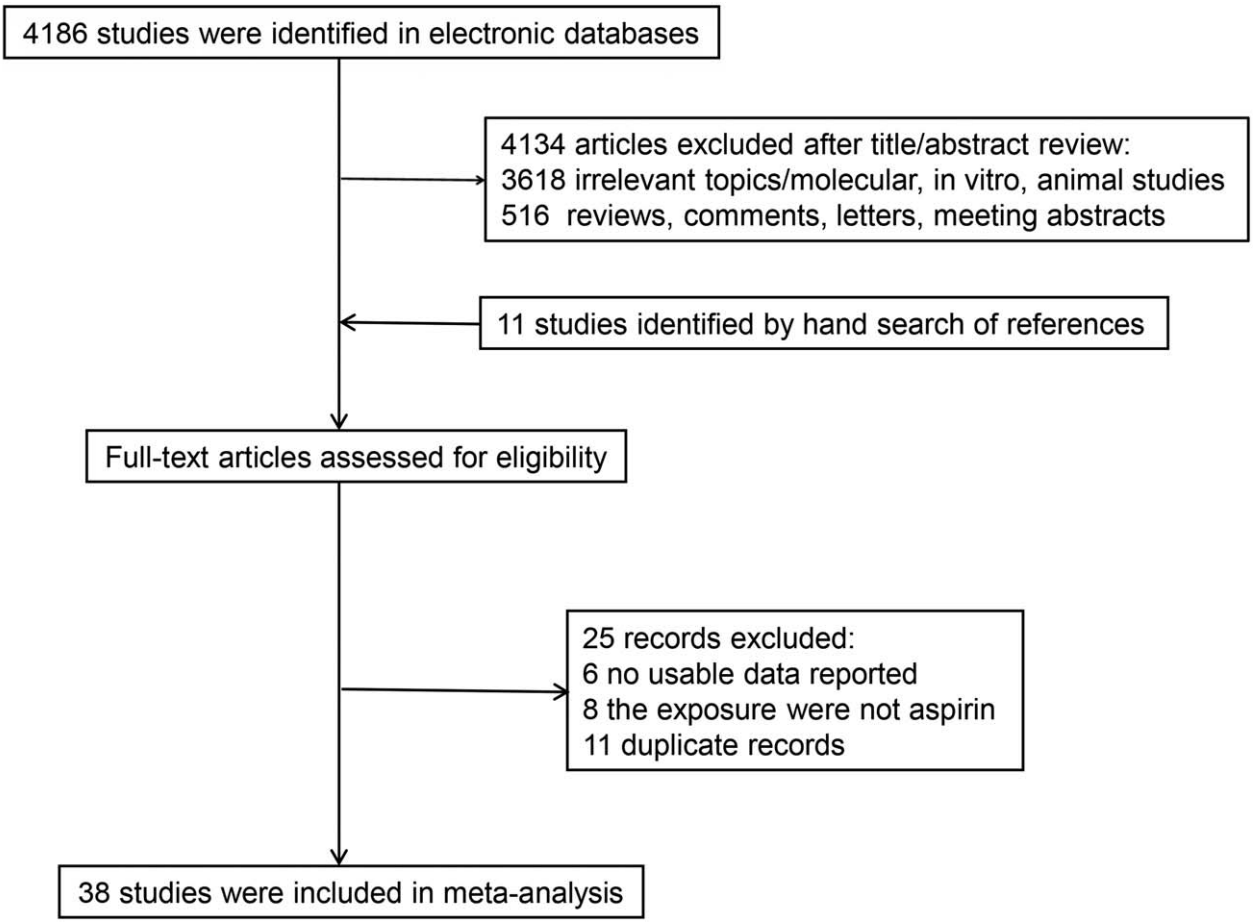

Figure 1. The flow diagram of search strategy. Flow chart of study identification and selection.

between January 1939 and April 2019. The range of enrollment periods for participants across studies was 1971 to 2017. Breast cancer was screened along with pathology reports and medical records, or through linkages with cancer registries in 36 studies (2 studies had no report of this).[52,54] Aspirin use was measured from questionnaire data in 18 studies, interviews in 10 studies, and automated database in 10 studies. Details of these studies are shown in Table 1.

3.2. Overall meta-analysis

Figure 2 illustrated the forest plot of RRs estimates with 95% CIs from individual studies and overall meta-analysis of all 38 studies. The overall summary RRs demonstrated aspirin reduced the incidence of breast cancer (RR = 0.91, 95%CI: 0.87–0.95, $P_{sig} < .001$), but there was heterogeneity between studies ($P_{het} < .001$, $I^2 = 83.0\%$). We explored the source of heterogeneity by subgroup and sensitivity analyses.

3.3. Subgroup analyses

Table 2 summarized the results of subgroup and publication bias analyses by various factors. The pooled results were 0.96 (95% CI: 0.91–1.02, $P_{sig} = .164$) for cohort studies and 0.83 (95% CI: 0.78–0.89, $P_{sig} < .001$) for case–control studies, suggesting a protective effect in case–control studies. We observed substantial statistical heterogeneity in both groups (cohort: $P_{het} < .001$, $I^2 = 85.9\%$; case–control: $P_{het} = .003$, $I^2 = 56.7\%$).

Regarding the exposure assessment, 18 studies used mailed questionnaires or in-hospital questionnaires, 10 studies used interview typically performed by trained personnel, and the rest of studies used either automated databases or medical records. Breast cancer was less likely to occur after aspirin use if exposure definition was interview (RR = 0.81, 95% CI: 0.73–0.89, $P_{sig} < .001$), however, this association was weaker for questionnaires (RR = 0.93, 95% CI: 0.87–1.00, $P_{sig} = .046$). We found that aspirin was not significantly associated with the breast cancer if recorded by automated databases (RR = 0.96, 95% CI: 0.90–1.02, $P_{sig} = .154$). Significant heterogeneity was observed when exposure definition were questionnaires ($P_{het} < .001$, $I^2 = 87.6\%$) and automated databases ($P_{het} < .001$, $I^2 = 78.4\%$), but not in interview ($P_{het} = .078$, $I^2 = 41.9\%$).

Twelve studies evaluated the relationships between exposure to aspirin and breast cancer risk in subgroup analysis based on hormone receptor status. All of them reported the relationships in hormone receptor positive tumors, and 10 studies reported the relationships in hormone receptor negative tumors. Aspirin was associated with a decreased breast cancer risk in hormone receptor positive tumors (RR = 0.91, 95% CI: 0.88–0.94, $P_{sig} < .001$), with statistical heterogeneity ($P_{het} < .001$, $I^2 = 58.5\%$). While in hormone receptor negative tumors, no associations were observed (RR = 1.06, 95% CI: 0.98–1.15,

Table 1

Characteristics of studies included in the meta-analysis.

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
Kehm-2019	The United States, Canada, and Australia	Cohort	1934–2017	Questionnaires	PO	8233/2348	503/1838	Demographics, lifestyle factors, family history, and other medication use.	Regular users: patients had ever used aspirin for at least twice a week for 1 month or longer at any time in the past.
Tsoi-2019	China	Cohort	2000–2013	Electronic medical records	PO	612,509/4478	204,170/408,339	Age, sex.	Patients being prescribed with aspirin for at least 6 months between 2000 and 2004, with no restriction on the indication and dosage of aspirin use.
Bens-2018	Denmark	Cohort	1996–2012	Prescription	PO	52,723/1444	9538/43,185	Age at first breast cancer diagnosis, calendar period of first breast cancer diagnosis, lobular histology, ER and lymph node status of first breast cancer, treatment of first breast cancer (endocrine therapy, chemotherapy, radiation therapy), highest achieved education, comorbidities (alcohol-related diseases, diabetes mellitus, pulmonary diseases, migraine, rheumatic and connective tissue diseases, ischemic heart disease, congestive heart failure, atrial flutter, cerebrovascular disease), pre-diagnosis hormone replacement therapy, post-diagnosis drug use (high-dose aspirin, non-aspirin NSAIDs, bisphosphonates, metformin, statins, digoxin).	Ever use was defined as two or more prescriptions filled after first breast cancer diagnosis; current use was defined as the period from the date of a prescription plus the number of tablets prescribed and a grace period of 60 days. Past use was defined as person-time among users not classified as current use; consistency of use was defined as current use with no prior periods of past use.
Dierssen-Sotos-2016	Spain	PCC	2008–2013	Face-to-face interview	PO	3631/1736	185/3460	Age, recruitment area, education level, tobacco smoking history, BMI family history of breast cancer, number of deliveries, age at first delivery, menarche age, and menopausal status.	Ever users were defined as women who had >2 prescriptions and never/rare users were women who used ≤2 prescriptions. Recent users were those who had ≥3 prescriptions within 2 years of index date (i.e., between 1 and 2 years before index date). Former users were those who had <3 prescriptions within that time period but >2 prescriptions (as defined by ever use) during the entire period of observation. The intensity of use was defined as low (<25%), medium (25–50%), or high (>50%), according to the number of days of prescription coverage divided by the total duration of use in days. Long-term (10 to ≤15 y, and >15 y) and shorter-term (<10 y) use.
Cao-2016	USA	Prospective cohort	1980–2015	Mailed questionnaires in1980–2012/ 1986–2010	PO	135,965/7424	13,467/12,320	Race, height, body mass index, family history of cancer, physical examination in the past 2 years, history of colonoscopy or sigmoidoscopy, smoking, physical activity, alcohol intake, current multivitamin use, total energy intake, red and processed meat intake, folate intake, calcium intake, and Alternate Healthy Eating Index 2010. For menopause status, menopausal hormone therapy and mammogram in the past 2 years. The model was also conditioned on age (months), calendar year of the questionnaire cycle, and sex or cohort.	Standard-dose (325 mg). Convert intake of 4 baby (81 mg) aspirin to 1 standard aspirin tablet. Regular aspirin users were defined as those who reported aspirin use at least 2 times per week, including standard and low-dose aspirin. Nonregular users included those who used aspirin fewer than 2 times per week or used no aspirin.
Bardia-2016	USA	Prospective cohort	1992–2005	Mailed baseline questionnaires in 1986–2004	PO	26,580/1581	19,105/7475	Age, use of oral contraceptives, use of hormone replacement therapy, body mass index (obesity), smoking, alcohol use, physical activity level, history of rheumatoid arthritis, history of osteoarthritis, first-degree relative with breast cancer, age at menarche, age at menopause, parity/age at first live birth, benign breast disease, non-steroidal anti-inflammatory drug use.	Never, less than once per week, once per week, 2 to 5 times per week, or ≥6 times per week.

(*continued*)

Table 1
(continued).

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
Kim-2015	USA	Prospective cohort	2003–2013	Telephone interview	PO	50,884/2118	NA	Race/Ethnicity, level of education, history of benign proliferative breast disease, number of 1st degree family members with breast cancer, BMI, age at 1st term birth, time since the last mammogram and menopause status at diagnosis; duration and frequency of aspirin use.	One pill-year represents use of 1 pill per week for a year. <0.75 pill-years (equivalent to <3 pills/wk for 3 months). The highest exposure category can be achieved in several ways, including by taking 1 NSAID pill/d for 7 years or by taking 1 pill/wk for 49 years. We defined regular NSAID use as use of any NSAID at least 4 times per week for ≥3 continuous months. All other use was considered nonregular.
Brasky-2014	USA	Prospective cohort	1993–2010	Prescription and over-the-counter medications	CL+PO	12,689/NA	NA	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 anti-hypertensive medication, history of coronary heart disease, use of cholesterol-lowering medication, history of arthritis, history of migraine, history of ulcer, and other NSAID use.	Regularly (≥2 times/wk) over the previous 2 weeks to their clinic visit to facilitate completion of a computer assisted interview about current medication use. Low-dose aspirin as <_x005F100 mg.
Cui-2014	USA	PCC	2001–2011	Telephone interview	PO	5034/2694	655/4379	Age, race, education, and household income 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, cigarette smoking status.	Baby aspirin (81 mg/tablet). Regular strength aspirin (325 mg).
Hollestein-2014	The Netherlands	Cohort	1998–2010	Automated database	PO	55597/585	NA	Age, sex, comedication use non-steroidal anti-inflammatory drugs (NSAID), statins, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, glucocorticoids, and other immuno suppressive drugs and comorbidities.	Low dose aspirin dispensing (100 mg daily). To calculate the duration of each dispense, the amount of dispensed drug was divided by the amount prescribed per day, as defined in the pharmacy data.
Cook-2013	USA	RCT	1993–2012	Prescription	CL+PO	39,876/2070	19,934/19,942	Age, smoking, BMI, alcohol use, physical activity, menopausal status, Family history of cancer, Vitamin E.	Aspirin (100 mg every other day). Post-trial aspirin use as >3 days per month collected on the first (or second if missing) observational questionnaire.
Zhang-2012	USA	Prospective Cohort	1980–2008	Mailed questionnaires in 1976–2008	PO	84,602/4734	NA	Age, 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, postmenopausal hormone use.	Women were classified as current users at each questionnaire in which current use was reported. The women who ceased reporting use were classified as past users, but they were eligible to become current users in subsequent follow-up years. Nonusers were those women who did not report analgesic use at baseline or on any of their follow-up questionnaires. Cumulative average dose (standard 325-mg tablet). Regular use (≥2 tablets per week).
Lee-2012	China	PCC	2002–2008	Automated database	PO	67,388/16,847	NA	Urbanization, income, diabetes mellitus, metformin usage, statin usage, estrogen usage, and progesterone usage.	(Total amount of drug)/(amount of drug in a DDD) = number of DDDs. The cumulative DDD (cDDD), or exposed drug duration, was estimated as the sum of

(*continued*)

Table 1
(continued).

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
									dispensed DDD of any medication to compare their use to the risk of breast cancer. The period of drug exposure for all participants was >5 years. Patients who received ≥28 cDDDs per year would be defined as users, whereas those who received less were defined as nonusers.
Bosco-2011	USA	Prospective cohort	1995–2007	Biennial questionnaires in 1995–2007	PO	59,000/1275	5427/47,724	Age (1-yr intervals) and questionnaire cycle and adjusted for education, BMI at age 18, vigorous activity, female hormone use, and smoking, other NSAIDs.	Currently using aspirin ≥3 days per week (regular use) and for how many years they had been taking it on a regular basis (<1, 1, 2, 3–4, ≥5 yr). Information on dose was not obtained.
Cronin-Fenton-2010	Denmark	NCC	1991–2006	Medication record	PO	90,145/8195	8802/81,343	Use of hormone replacement therapy, rheumatoid arthritis and migraine.	Low dose (B01AC06 and N02BA01 in tablet sizes of 75, 100 or 150 mg) and high dose (N02BA51 and N02BA01 in tablet size 500 mg). Ever users were defined as women who had >2 prescriptions and never/rare users were women who used less than or equal to two prescriptions. Recent users were those who had ≥3 prescriptions within 2 yr of index date (i.e., between 1 and 2 yr before index date). Former users were those who had <3 prescriptions within that time period but >2 prescriptions (as defined by ever use) during the entire period of observation. The intensity of use was defined as low (<25%), medium (25–50%), or high (>50%), according to the number of days of prescription coverage divided by the total duration of use in days. long-term (10 to ≤15 years, and >15 years) and shorter-term (<10 yr) use.
Brasky-2010	USA	PCC	1996–2001	Interview	PO	3285/1170	1470/1815	Age, race, education, age at menarche, age at menopause, parity, use of hormone therapy, benign breast disease, family history of breast cancer, and other NSAID use, history of diabetes, hypertension, coronary heart disease, cerebrovascular disease, and arthritis.	Non-users (0 d/mo), infrequent users (≤14 d/mo), and regular users (>14 d/mo). NSAID intensity was categorized into non-users (0 pills/d), low (<2 pills/d), and high (≥2 pills/d). Adult lifetime aspirin non-users (0 d/mo), irregular users (≤10 d/mo), and regular users (>10 d/mo).
Eliassen-2009	USA	Prospective cohort	1989–2003	Biennial mailed questionnaires in 1989–2003	PO	11,292/1345	NA	Age at menarche (<12, 12, 13, ≥14 years, missing), height (<1.6, 1.6 to <1.65, 1.65 to <1.7, 1.7 to <1.75, ≥1.75 m, missing), BMI at age 18 (<19, 19 to <21, 21 to <23, ≥23 kg/m^2, missing), weight change since age 18 (lost ≥2, lost/gained < 2, gained 2 to <5, 5 to <10, 10 to <20, 20 to <25, ≥25 kg), oral contraceptive use (never, current, past, missing), parity and age at first birth (nulliparous, 1−2 children/<25 yr, 1−2 children/25−29 yr, 1−2 children/≥30 yr, ≥3 children/>25 yr, ≥3 children/25−29 yr, ≥3 children/≥30 yr), alcohol consumption (never, 0−1.4, 1.5 to <5, 5 to <10, ≥10 g/d, missing), history of benign breast disease (yes, no), family history of breast cancer (yes, no).	Regularly (≥2 times per week). Women who reported regular use on a questionnaire were considered current users for the subsequent 2-year follow-up period (or the 4-year follow-up period from 1989 to 1993). Women who continued to report use on subsequent questionnaires remained classified as current users while those who ceased reporting use became past users, though these women were eligible to become current users on later questionnaires Non-users during any given follow-up period are women who had not reported use on the current or any prior questionnaire.
Ready-2008	USA	Prospective cohort	2000–2004	Mailed baseline questionnaires in 2000–2004	PO	35,323/482	7826/27,451	Age, race, BMI, family history of breast cancer, history of breast biopsy, mammogram in 2 years prior to baseline, age at menarche, age at first birth, age at menopause, history of surgical menopause, years of combined estrogen and progesterone hormone therapy,	At least once per week for a year over the previous 10 years low-dose aspirin (81 mg), regular or extra-strength aspirin. "Any use" as at least once a week for a year during the last 10 years. As a measure of cumulative use, we computed average days per week of use during the past 10 years as follows: we multiplied the

(*continued*)

Table 1
(continued).

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
								multivitamin use and alcohol use as well as adjustment for use of other categories of NSAIDs.	reported days per week of use (1–3, 4–6, 7) by years of use and divided this product by 10. Subjects could only fall into the highest category of 10-year average use if they reported long-term use.
Gierach-2008	USA	Prospective cohort	1995–2003	Annually mailed questionnaires in 1995–2003	PO	12,6124/4501	NA	Age (continuous), race, age at first birth, hormone therapy use, number of breast biopsies, alcohol intake, history of hypertension, and family history of breast cancer in first-degree relative.	Fewer than 2 times per month, 2 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, 5 to 6 times per week, 1 time per day, or ≥2 times per day-which we collapsed to categories of nonuse, <1/wk, 1 to 6/wk, and ≥1/d. The dose, duration, and indication for use were not collected. Who had not reported any aspirin use on either the questionnaire at the start of that follow-up interval or on any previous questionnaire were categorized as never users; those who were neither never users nor current daily users of adult-strength aspirin were grouped into a mixed-use category that included less than daily, low-dose, and past users.
Friis-2008	Denmark	Prospective cohort	1993–2003	Mailed questionnaires in 1993–2003	PO	28,695/847	7014/21,681	Age, school education (short, medium, long), parity (nulliparous/parous), number of births (continuous), use of HRT (current, past, never), and history of benign breast tumor surgery (yes/no).	Aspirin: ATC codes: B01AC06, N02BA01, N02BA51 (The 81 mg tablets baby aspirin. Standards 75 and 81 mg tablets). Current use (≤1 year since self-reported use or last prescription), past use (>1 year since self-reported use or last prescription), and no use (no self-reported use in questionnaire and no recorded prescriptions.
Siemes-2008	The Netherlands	Prospective cohort	1989–2004	Baseline questionnaires and prescription	PO	7621/175	214/232	Age, body mass index, C-reactive protein level, pack years of smoking, hormone replacement therapy, age at onset of menarche and menopause, and number of children.	A prescription period was calculated out of the total amount of drugs per prescription divided by de defined daily dosage (DDD) of the particular drug. A defined daily dosage is the recommended dose for an adult given for the most important indication. Consecutive periods of use were ascertained when prescription periods slightly overlap, suggesting daily drug intake.
Slattery-2007	USA	PCC	1999–2004	Interviewer-administered computerized questionnaire	CL+PO	4850/2325	2322/2525	Age, study center, referent year BMI, lifetime physical activity score, parity, and percentage Native American ancestry.	Regular use (at least thrice weekly for at least 1 month).
Kirsh-2007	Canada	PCC	1996–1998	Mailed questionnaires in 1996–1998	PO	4872/3125	5389/798	Age, history of arthritis, and benign breast disease.	Those who used NSAIDs for <2 months were considered nonusers.
Gill-2007	USA	Cohort	1993–2002	Mailed questionnaires in 1993–2002	PO	98,920/3493	48,010/48,428	Age, family history of breast cancer, mammography screening history, education, body mass index, alcohol intake, age at menarche, age at first full-term pregnancy, number of children for parous women, age at and type of menopause, oophorectomy age, hysterectomy age, use of hormone replacement therapy, pain medication use.	Daily drug intake.
Gallicchio-2007	USA	Prospective cohort	1989–2006	Mailed questionnaires in 1989–2006	PO	15,651/91	281/1128	Age.	Regular user at least once a week for 1 year.
Jacobs-2007	USA	Prospective cohort	1992–2003	Mailed self-administered questionnaires in 1982–2001	PO	76,303/3121	1083/1169	Age, race, education, smoking, BMI, physical activity level, use of hormone replacement therapy, history of mammography, history of colorectal endoscopy, use of nonaspirin NSAIDs,	All aspirin use reported in 1982 or 1992 to be adult-strength aspirin. Daily use of adult-strength aspirin was defined as use at least 30 "times" per month in 1982 and as 30 or 31 days per month in 1992, 1997, 1999, or 2001.

(*continued*)

Table 1
(continued).

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
								and history of heart attack, diabetes, and hypertension.	
Harris-2006	USA	HCC	2003–2004	Biannual mailed self-administered questionnaires	CL	770/323	55/917	Age, body mass index, parity, menopausal status, family history, alcohol intake, smoking.	At least 2 times in each of the 2 weeks for ≥2 years . No use: no more than 1 pill per week for less than a year. Aspirin dosage <100 mg/d as baby aspirin. The reference level for these analyses was 0 to 11 months of exposure to any NSAID or the related analgesic, acetaminophen.
Zhang-2005	USA	HCC	1976–2002	Interview	CL	10,628/7006	508/10,120	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 (breast cancer in a mother or sister), practice of breast self-examination, and body mass index.	Regular NSAID use as use of any NSAID at least 4 times per week for ≥3 continuous months. All other use was considered nonregular.
Swede-2005	USA	HCC	1982–1998	Automated database	CL	4861/1473	2854/2007	Age at menarche, age at 1st birth, BMI, history of 1st-degree relative with breast cancer, and history of benign breast disease.	Regular aspirin users were defined as those who had taken aspirin at least once a week for at least 1 year. Occasional users were those who had used aspirin in their lifetimes, but not to the extent of the definition of regular usage (i.e., <1 per week or <1 year in duration). Never-users were defined as those who reported never having taken aspirin during their lifetimes.
Rahme-2005	Canada	NCC	1998–2002	Medication record	PO	46,080/1090	13,720/32,360	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- these variables were risk factors for breast cancer but their inclusion in the model did not alter substantially the effect of exposure to the drugs of interest.	The primary exposure was the filling of one or more prescriptions for celecoxib and/or rofecoxib and/or any ns-NSAID for a total of ≥90 days in the year prior to the index date. We also separated exposure to ≥90 days of aspirin into 2 groups according to the mean daily dose prescribed, whether ≤100 mg or >100 mg.
Marshall-2005	USA	Prospective cohort	1995–2001	Mailed baseline questionnaires in 1995	PO	114,460/2391	25,731/88,909	Race, body mass index, 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.	Regularly (at least once a week). Not regular user: <5 years and 1–6 days per week of use, ≥5 years and 1–6 days per week of use, <5 years and daily use, and ≥5 years and daily use.
Terry-2004	USA	PCC	1996–1997	Interviewer-administered questionnaire	PO	2862/1442	646/2216	Age at diagnosis, migraine headache, body mass index, other types of medication use.	Ever use: at least once a week for 6 months or longer.
Garcia-2004	UK, Spain	NCC	1995–2001	Automated database	CL	23,708/3708	2028/21,680	Age, calendar year, BMI, alcohol intake, smoking status, HRT use, prior benign breast disease.	NA
Moorman-2003	USA	PCC	1996–2000	Interview	PO	2631/1430	NA	BMI, sex, race, poverty index, education and smoking in study with age as time metric for follow-up.	Women who reported using NSAIDs at least 8 days a month for ≥3 were categorized as regular users. Regular users were further categorized by duration of use.
Harris-1999	USA	Prospective cohort	1991–1996	Mailed questionnaire	PO	32505/393	8305/NA	Ages at menarche, pregnancy, and menopause, family history of breast cancer, history of	NA

(*continued*)

Table 1
(continued).

Study	Locale	Study design	Study time	Exposure ascertain	Setting	Sample size/ No. cases	No. of exposure/ Non-exposure	Covariate adjustment	Definition for aspirin user
								estrogen replacement therapy, and body mass index.	
Neugut-1998	USA	HCC	1989–1992	Medication record	PO+CL	574/252	NA	Age, education, parity, menopausal status, and family history of breast cancer.	Chronic use of aspirin.
Harris-1996	USA	PCC	NA	Personal interview	PO	2045/511	2045/1821	Age, parity, menopausal status, and family history.	Regular use was defined as at least 3 pills per week for at least 1 year.
Schreinemachers-1994	USA	Prospective cohort	1971–1987	Person and telephone interview	PO	11585/174	4768/2721	Age, gender, race, education, socioeconomic status, body mass index, alcohol consumption, and arthritis.	Used aspirin in last 30 d/No.
Paganini-Hill-1989	USA	Prospective cohort	1981–1988	Baseline questionnaire	CL	8964/146	2797/6021	Age.	Daily use.

BMI = body mass index; cDDD = cumulative defined daily dose; CL = clinic-based research; ER = estrogen receptor; HCC = hospital-based case–control study; HRT = hormone replacement therapy; NA = not available; NCC = nest case–control study; NSAID = nonsteroidal anti-inflammatory drugs; PCC = population-based case–control study; PO = population-based research; RCT = randomized controlled trial.

P_{sig} = .130), with no statistical heterogeneity (P_{het} = .060, I^2 = 46.4%).

When stratified by menopausal status, there were 7 studies concerned premenopausal women and 15 studies concerned postmenopausal. A significant risk reduction of breast cancer caused by aspirin was observed in postmenopausal women (RR = 0.89, 95% CI: 0.83–0.96, P_{sig} = .002), but not in premenopausal women (RR = 0.88, 95% CI: 0.72–1.08, P_{sig} = .223). Both groups had significant heterogeneity (postmenopausal: P_{het} < .001, I^2 = 72.1%; premenopausal: P_{het} = .007, I^2 = 66.1%).

When stratified by cancer stage, 13 studies were found for reporting invasive breast cancer, and 3 of them reported in situ breast cancer at the same time. A reduction in risk was observed for in situ breast cancer (RR = 0.79, 95% CI: 0.71–0.88, P_{sig} < .001), with no substantial statistical heterogeneity (P_{het} = .410, I^2 = 0.0%). For invasive breast cancer, no significant association was found (RR = 1.00, 95% CI: 0.94–1.06, P_{sig} = .988) and a substantial statistical heterogeneity was observed (P_{het} = .002, I^2 = 61.7%).

We further explored the relationships between aspirin use dosage and breast cancer risk. The risk of breast cancer was significantly reduced in participants who use aspirin for >4 times/wk (RR = 0.88, 95% CI: 0.82–0.96, P_{sig} = .003) or <4 times/wk (RR = 0.95, 95% CI: 0.91–0.99, P_{sig} = .029). Besides, a significant risk reduction of breast cancer caused by aspirin was observed in participants who use aspirin for >10 years (RR = 0.94, 95% CI: 0.89–0.99, P_{sig} = .025). And borderline significant inverse associations were observed between breast cancer risk and aspirin use for shorter than 10 years (RR = 0.97, 95% CI: 0.94–1.00, P_{sig} = .045). But, significant heterogeneity was observed in all these subgroups (all P_{het} < .05).

3.4. 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).

The publication bias was not observed (P of Egger test = .999) in overall results.

Relevant summary of RRs for subgroup were provided in Supplementary Table 1–5, http://links.lww.com/MD/E877, http://links.lww.com/MD/E878, http://links.lww.com/MD/E879, http://links.lww.com/MD/E880, http://links.lww.com/MD/E881.

4. Discussion

Based on the overall meta-analysis, we observed a 9% relative decrease in the risk of breast cancer for aspirin users. In this study, aspirin was associated with decreased breast cancer risk in hormone receptor positive tumors. We observed a decreased risk related to in situ breast cancer after aspirin use. We also found a reduction in risk of breast cancer for postmenopausal women. When the analysis was stratified by study design, a reduced risk in case–control studies was observed.

Our result of overall aspirin use and breast cancer risk was different from the article reported previously,[9] which reported that a borderline significant inverse association (RR = 0.94, 95% CI: 0.87–1.01) was observed between overall aspirin use and breast cancer risk. The difference might be explained that previous study just summarized the results of cohort studies. And we observed the similar result (RR = 0.96, 95% CI: 0.91–1.02)

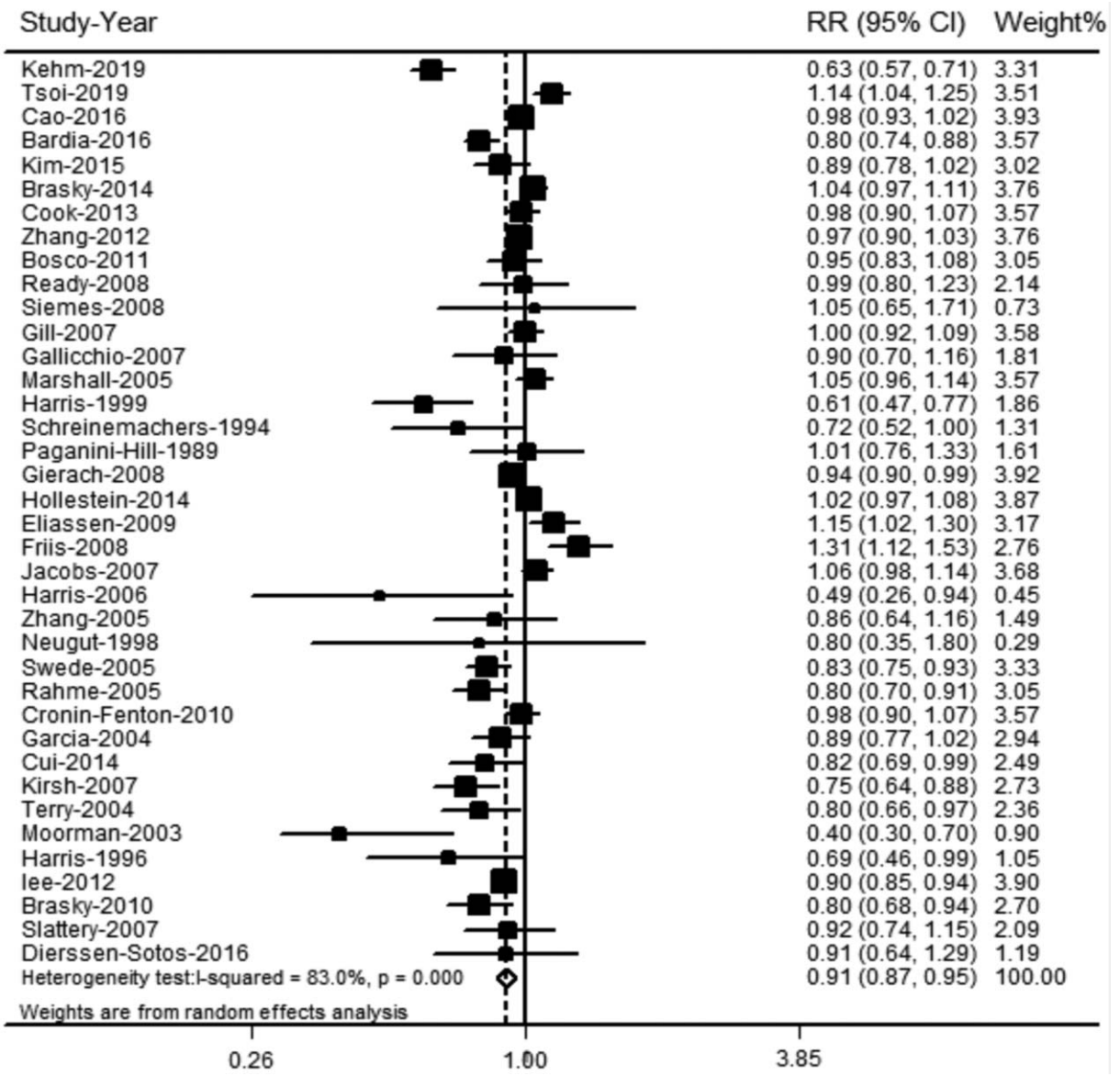

Figure 2. Forrest plot of the association between aspirin use and risk of breast cancer. Black squares and horizontal lines represent the study relative risk and 95% CIs. The size of the square is proportional to the weights of the individual studies. The diamond represents the pooled estimate (center) and 95% CI (width). CI = confidence interval; I squared = estimate for the proportion of variability between studies that is due to inter-study heterogeneity; RR = relative risk.

for cohort studies. Our result found that aspirin was associated with a decreased breast cancer risk. This could be related to aspirin not only preventing breast tumor cell growth through the induction of apoptosis, but also significantly reducing the self-renewal capacity and growth of breast tumor-initiating cells/breast cancer stem cells and delaying the formation of a palpable tumor.[71] In addition, recent study showed aspirin may suppress tumor cell-induced angiogenesis or normalizing tumor blood vessels.[21] Similar results of subgroup analysis were reported in the meta-analysis by Zhong et al.[20] They concluded that aspirin use might decrease risk of in situ breast tumors or hormone receptor positive tumors and reduce risk of breast cancer in postmenopausal women.

We observed a risk reduction of 17% in breast cancer risk for aspirin users from case–control studies, while cohort studies gave no evidence. As a result of recall bias, selection bias, and healthy-user bias introducing differential measurement error, case–control studies gave a lower level of evidence than cohort studies. However, the invalid effects reported in some cohort studies could be accounted for less detailed records of aspirin exposure, a lack of updating of exposure between initial recruitment and subsequent diagnosis of cancer. In a word, the estimates were heterogeneous and further well-characterized research is needed before reliable conclusions can be drawn.

When the analysis was examined by aspirin exposure definition, the risk of breast cancer was reduced in the interview and automated database subgroups. In contrast to self-administered questionnaires that relied heavily on the subject's ability to recall, automated database provided detailed information on dates of use and dosage of drugs used. Even so, as the weak compliance from patients may over-represent the results of automated database, we found that the estimates for the subset of

Table 2

Subgroup analyses and summary for publication bias.

	No. of studies	RR (95% CI)	*P* of ES	I^2	*P* of heterogeneity	*P* of Egger test
Ordinal exposure stratified by study design						
Cohort studies	22	0.96 (0.91,1.01)	.135	85.3%	.000	.39
Case–control studies	16	0.83 (0.78,0.89)	.000	56.7%	.003	.009
Ordinal exposure stratified by exposure ascertain						
Questionnaires	18	0.93 (0.87,1.00)	.046	87.6%	.000	.347
Interview	10	0.81 (0.73,0.89)	.000	41.9%	.078	.055
Automated database	11	0.95 (0.90,1.01)	.114	78.4%	.000	.715
Ordinal exposure stratified by hormone receptor status						
Hormone receptor positive	12	0.86 (0.82,0.92)	.000	60.5%	.000	.024
Hormone receptor negative	11	1.04 (0.93,1.17)	.505	42.7%	.074	.469
Ordinal exposure stratified by menopausal status						
Premenopausal	7	0.88 (0.72,1.08)	.223	66.1%	.007	.087
Postmenopausal	15	0.89 (0.83,0.96)	.002	72.1%	.000	.072
Ordinal exposure stratified by cancer stage						
In situ breast cancer	3	0.79 (0.71,0.88)	.000	0.0%	.410	.587
Invasive breast cancer	13	1.00 (0.94,1.06)	.988	61.7%	.002	.743
Ordinal exposure stratified by aspirin use frequency						
Frequency≤4 times/wk	15	0.95 (0.91,0.99)	.029	54.4%	.000	.31
Frequency >4 times/wk	14	0.88 (0.82,0.96)	.003	67.3%	.000	.319
Ordinal exposure stratified by aspirin use duration						
Duration ≤10 years	20	0.97 (0.94,1.00)	.033	32.9%	.011	.025
Duration >10 years	4	0.94 (0.89,0.99)	.025	0.0%	.902	.340

CI = confidence interval, ES = effect size, RR = relative risk.

studies using interview was more reliable. Considering above mentioned, we concluded that aspirin use might be associated with decreased risk of breast cancer.

Previous studies have found that in breast cancer of varying stages, COX-2 expression was shown to be inversely correlated with ER expression, and stable transfection of ER in breast cancer cells led to the repression of COX-2, in turn leading to a reduction in proliferation and migration of these cells. Huang et al[72] had already demonstrated that a novel aspirin derivative, PA-2 induced a potent cytokinetic effect on ER+ breast cancer cells by impacting potent inhibition of tumor growth. Our analysis also observed aspirin to be associated with a reduced risk of hormone receptor positive tumors.

Postmenopausal women who were regular users of aspirin showed lower incidence to suffer from breast cancer. This might be ascribed that postmenopausal women tended to suffer from hormone receptor positive tumors. Aspirin can decrease aromatase activity via suppression of COX expression and prostaglandin synthesis, which may decrease estrogen concentrations and potentially risk of breast cancer.[73,74] Postmenopausal women who were regular users of aspirin showed lower estrogen levels than nonusers.

Beneficial efficiency was found between aspirin use and the risk of in situ breast tumors. Evidence suggested that COX-2 overexpression has been observed in about 40% of cases of invasive breast carcinoma, but at a higher frequency of in situ tumors, suggesting that the potential therapeutic impact of COX-2 inhibition may be more relevant for in situ breast cancer than invasive tumors,[75] which might explain our findings.

It was widely accepted that any potential protective effects of aspirin use against cancers were likely to involve a considerable duration. We also observed statistically significant associations between any frequency and longer duration of aspirin use and risk of breast cancer in subgroup analysis. The overall association between aspirin use and cancer risk of lower frequency appeared to be similar to higher frequency but less striking, the same as when stratified by duration. Our results were consistent with the previous study. Lu et al[9] confirmed that breast cancer risk decreased as aspirin intake frequency and a trend of decreasing risk for more years of aspirin intake increased. They also concluded that the optimal aspirin dose for preventing breast cancer may be in the scope of <325 mg per day, 2 to 7 times/wk, along with long-term medication (>5 years).

It is noted that there are always concerns about the use of aspirin and the risk of serious bleeding. According to previous data, only a very modestly higher risk of extracranial and major gastrointestinal bleeds happened on aspirin users when compared with those taken placebo.[76] Experts consider that aspirin does increase the risk of bleeding, but the magnitude of this effect is likely to be over-estimated. The secondary cardiovascular disease events from aspirin are thought to be outweighed by the benefits gained from it.

In our study, we noted significant heterogeneity between included studies. We explored the source of heterogeneity using subgroup and sensitivity analysis. It was visible that the heterogeneity had declined in nearly all subgroups we stratified except for subgroup of exposure ascertain. Sensitivity analyses conducted by excluding one study at a time indicated that each individual dataset had no significant influence on the overall results. In summary, the heterogeneity between articles might come from different study designs, hormone receptor status, menopausal status, stages of cancer, aspirin use frequencies, and durations.

Our pooled study had some strengths as well as limitations. First, after searching electronic database, we carefully read the reference list of previous systematic review, making our search broad and comprehensive. This allowed for a large sample size and suitable statistical power to evaluate overall main effect associations, although the case numbers were still small and limited our power to fully perform subset of our studies with

extensive questions. Second, subgroup and sensitivity analyses based on biologically important variables gave us ability to further explore the source of heterogeneity and discuss the underlying pharmacological mechanism. However, we failed to find convincing explanations for the significant heterogeneity. Third, we used Egger test to provide quantitative evidence for publication bias. Recall bias, selection bias, and healthy-user bias could not avert although recall bias about aspirin use could be reduced by use of prescription databases. However, the misclassification of aspirin use might have a crucial impact on the effect estimates of aspirin use. Besides, the subgroup analyses based on other factors, such as obesity status, hormone replacement treatment were restricted by few studies reported interested topics.

5. Conclusions

In summary, findings from this pooled analysis support the hypothesis that aspirin use provides potential benefits in preventing breast cancer, particularly in hormone receptor positive tumors or in situ cancers and breast cancer in postmenopausal women. Future observational studies should confirm well-controlled confounding factors, and consistent assessment of aspirin use, including exposure dose, frequency and duration of use. Random controlled trials are also urgently needed.

Author contributions

Aihua Tan conceived this study. Aihua Tan and Yueqing Cao were responsible for the literature retrieval and data extraction. Yueqing Cao performed the statistical analysis. Aihua Tan oversaw the statistical analysis. Yueqing Cao wrote the paper. Aihua Tan and Yueqing Cao contributed to data interpretation and critical revision. Aihua Tan and Yueqing Cao reviewed the final version of the manuscript.

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