Breast Cancer Res Treat (2012) 131:581–587
DOI 10.1007/s10549-011-1747-0

EPIDEMIOLOGY

Aspirin use and breast cancer risk: a meta-analysis

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Received: 10 August 2011 / Accepted: 16 August 2011 / Published online: 4 September 2011

Abstract Animal and in vitro studies suggest that the use of aspirin may be associated with reduced risk for breast cancer, but results from these studies of the association have been inconsistent. The objective of this meta-analysis was to quantitatively summarize the current evidence for such a relationship. We searched MEDLINE for studies of aspirin use and breast cancer risk that were published in any language, from January 1, 1966, to July 1, 2011. A total of 33 studies (19 cohort studies, 13 case–control studies, and 1 randomized controlled trial [RCT]) that included 1,916,448 subjects were identified. We pooled the relative risks from individual studies using a random-effects model, heterogeneity, and publication bias analyses. In a pooled analysis of all studies, aspirin use was associated with reduced risk for breast cancer (odds ratio [OR] = 0.86, 95% confidence interval [CI] = 0.81, 0.92). In the subgroup analysis by study design, results were similar except for RCT (OR = 0.98, 95% CI = 0.87, 1.09). In conclusion, this meta-analysis indicated that regular use of aspirin may be associated with reduced risk of breast cancer. More RCT were needed to confirm this association in the future.

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Keywords Aspirin · Breast cancer · Meta-analysis

Introduction

Breast cancer alone is expected to account for 26% (178,480) of all new cancer cases among women and for 15% (40,460) of all female cancer deaths in the United States of America [1]. Primary prevention of breast cancer is, therefore, very important. The mechanism of breast carcinogenesis is still not fully understood. One of the major risk factors of breast cancer is age [2]. Breast cancer may result from multiple environmental, dietary, hereditary, racial, and socioeconomic risk factors [3].

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit production of prostaglandins and cyclooxygenase, which comes in two isoforms (COX-1 and COX-2); therefore, aspirin and other NSAIDs are potential agents for chemoprevention of breast cancer. In vitro studies have shown that breast cancers produce prostaglandins in greater amounts than normal breast cells and that aspirin can inhibit growth and decrease the invasiveness of breast cancer cells, reduce cytokines involved in bony metastasis, and stimulate immune responsiveness [4]. Although an association between aspirin use and breast cancer risk is biologically plausible, epidemiologic studies on this relationship have yielded inconsistent results [5–7]. A meta-analysis and meta-regression of observational studies from 2001 to 2005 support that aspirin may reduce breast cancer risk. Moreover, a dose–response-relationship seems to exist [8]. We therefore carried out an exhaustive meta-analysis on aspirin use and risk of breast cancer. Our objective was to provide a more definitive answer about a possible inverse relationship between use of aspirin and risk for breast cancer.

Methods

Publication search

A search of the electronic databases MEDLINE (from January 1, 1966, to July 1, 2011) was performed by the following keywords: (*aspirin* or *NSAIDs* or *non-steroidal anti-inflammatory drugs*) and *breast* and (*cancer* or *neoplasm* or *carcinoma* or *tumor*). No restrictions were applied. The References lists of reviews and retrieved articles were hand searched at the same time. If necessary, we attempted to contact the corresponding authors of retrieved articles to require additional information.

Study selection

Studies were included if they met the following criteria: (1) evaluate the association between aspirin and breast cancer; (2) use a randomized controlled trial (RCT) or case–control or cohort study design; (3) provide the odds ratios (OR) or relative risk (RR) with confidence intervals (CI) or data necessary to calculate them.

Data extraction

Data were extracted independently by two investigators according to the prespecified selection criteria. We extracted the following data from each study if available: the last name of the first author, year of publication, study design, study period, the country in which the study was performed, sample size (numbers of case patients and control subjects or cohort size), and the OR or RR with corresponding 95%CI. When several estimates were available, we used the one that was adjusted for the most variables. If more than one article was published by the same author using the same population, we selected the most recent or most informative report.

Statistical analysis

The measure of effect of interest is the OR with 95%CI. Because the absolute risk of breast cancer is low, the OR mathematically approximates the RR in case–control studies; we therefore report all results as OR for simplicity [9]. The statistical heterogeneity between and within groups was measured by using the Q statistic, $P < 0.1$ was considered statistically significant. The Der-Simonian-Laird method for random effects were used to estimate pooled OR [10]. We calculated pooled estimates and confidence intervals assuming a random-effects model. Publication bias was investigated both visually by using a funnel plot and statistically by Begg funnel plots and Egger's bias test, which measures the degree of funnel plot asymmetry [11, 12]. $P < 0.1$ was considered to be representative of statistically significant publication bias. All analysis was performed by using the STATA, version 11.0 (Stata Corporation, College Station, Texas).

Results

A total of 33 studies that included 1,916,448 subjects, published from 1980 through 2011, met the inclusion criteria and were included in the meta-analysis [13–45]. Of those, 19 studies were cohort studies, 8 studies were population-based case–control (PCC) studies, 5 studies were hospital-based case–control (HCC) studies, and 1 study was RCT. Studies were conducted in USA, Denmark, and Canada (Table 1).

When all the studies were combined into the meta-analysis, we found that aspirin use was associated with reduced risk for breast cancer (OR = 0.86, 95% CI = 0.81, 0.92) (Fig. 1). In the subgroup analysis by study design, cohort studies (OR = 0.91, 95% CI = 0.84, 0.98), PCC studies (OR = 0.79, 95% CI = 0.68, 0.90), and HCC studies (OR = 0.75, 95% CI = 0.65, 0.84) yielded similar results, except for RCT (OR = 0.98, 95% CI = 0.87, 1.09) (Fig. 1).

There was significant heterogeneity for all studies ($Q = 155.39$; $P < 0.001$; $I^2 = 79.4\%$), and this heterogeneity remained significant for cohort studies ($Q = 92.25$; $P < 0.001$; $I^2 = 80.5\%$) and PCC studies ($Q = 35.53$; $P < 0.001$; $I^2 = 80.3\%$), but not for HCC studies ($Q = 3.83$; $P = 0.43$; $I^2 = 0.0\%$). Publication bias was found for all studies by the Begg rank correlation method ($P = 0.02$) (Fig. 2) and the Egger weighted regression method ($P = 0.003$) (Fig. 3).

Discussion

In this meta-analysis of 33 studies that included 1,916,448 subjects, we found that regular use of aspirin may be associated with reduced risk of breast cancer. In the subgroup analysis by study design, results were similar except for RCT.

Many studies have investigated the associations between aspirin use and risk of other cancers. A systematic review and meta-analysis supported a protective association between aspirin and NSAIDs and esophageal cancer and provided evidence for a dose effect [46]. The study by Din et al. [47] demonstrated a protective effect against colorectal cancer associated with the lowest dose of aspirin (75 mg per day) after only 5 years use in the general population. A 20-year follow-up of five randomised trials found that aspirin taken for several years at doses of at least

Table 1 Characteristics of the studies included in the meta-analysis

Study (reference)	Design	Study period	Country	Cases	Controls	OR/RR (95%CI)
Bardia et al. [13]	Cohort	1992–2005	USA	1,581	26,580	0.80 (0.71–0.90)
Cronin et al. [14]	PCC	1991–2006	Denmark	8,195	81,950	0.98 (0.90–1.07)
Brasky et al. [15]	PCC	1996–2001	USA	1,170	2,115	0.80 (0.68–0.94)
Eliassen et al. [16]	Cohort	1989–2003	USA	1,345	112,292	1.15 (0.97–1.36)
Friis et al. [17]	Cohort	1993–2003	Denmark	847	28,695	1.31 (1.12–1.53)
Ready et al. [18]	Cohort	2000–2004	USA	479	35,150	0.99 (0.80–1.23)
Gierach et al. [19]	Cohort	1996–2003	USA	4,451	126,124	0.94 (0.90–0.99)
Gill et al. [20]	Cohort	1993–2002	USA	1,457	98,920	1.00 (0.92–1.09)
Jacobs et al. [21]	Cohort	1992–2003	USA	3,121	76,303	1.06 (0.98–1.14)
Slattery et al. [22]	PCC	1999–2004	USA	1,503	1,577	0.92 (0.81–1.05)
Gallicchio et al. [23]	Cohort	1989–2006	USA	376	15,651	0.90 (0.70–1.16)
Harris et al. [24]	HCC	2003–2004	USA	15	40	0.49 (0.26–0.94)
Marshall et al. [25]	Cohort	1995–2001	USA	2,391	114,460	1.05 (0.96–1.14)
Zhang et al. [26]	HCC	1976–2002	USA	313	195	0.86 (0.64–1.16)
Swede et al. [27]	HCC	1982–1998	USA	1,478	3,383	0.80 (0.67–0.96)
Rahme et al. [28]	Cohort	1998–2002	Canada	1,090	44,990	0.80 (0.70–0.92)
Cook et al. [29]	RCT	1992–2004	USA	19,934	19,942	0.98 (0.87–1.09)
Garcia et al. [30]	PCC	1995–2001	UK	3,708	20,000	0.88 (0.75–1.04)
Terry et al. [31]	PCC	1996–1997	USA	1,442	1,420	0.80 (0.66–0.97)
Ratnasinghe et al. [32]	Cohort	1971–1980	USA	131	12,834	0.82 (0.49–1.36)
Moorman et al. [33]	PCC	1996–2000	USA	1,430	1,201	0.40 (0.30–0.70)
Harris et al. [34]	Cohort	1992–1998	USA	182	65,985	0.85 (0.73–0.99)
Johnson et al. [35]	Cohort	1986–1999	USA	938	27,616	0.82 (0.71–0.95)
Cotterchio et al. [36]	PCC	1996–1998	Canada	2,696	2,600	0.73 (0.61–0.87)
Harris et al. [37]	Cohort	1992–1998	USA	76	32,505	0.61 (0.47–0.77)
Coogan et al. [38]	HCC	1976–1996	USA	6,558	3,296	0.70 (0.50–0.80)
Neugut et al. [39]	HCC	1989–1992	USA	252	322	0.80 (0.35–1.80)
Egan et al. [40]	Cohort	1980–1992	USA	2,414	89,528	1.01 (0.80–1.27)
Harris et al. [41]	PCC	DNR	USA	511	1,534	0.69 (0.46–0.99)
Schreinemachers et al. [42]	Cohort	1971–1987	USA	174	11,411	0.70 (0.50–0.96)
Thun et al. [43]	Cohort	1982–1988	USA	DNR	635,031	0.94 (0.80–1.10)
Paganini et al. [44]	Cohort	1981–1985	USA	146	8,818	1.01 (0.76–1.33)
Friedman and Ury [45]	Cohort	1969–1976	USA	2	143,574	0.20 (0.05–0.80)

HCC hospital-based case–control, *PCC* population-based case–control, *OR* odds ratio, *RR* relative risk (rate ratio or hazard ratio), *CI* confidence interval, *DNR* data not reported

75 mg daily reduced long-term incidence and mortality because of colorectal cancer [48]. Regular use of aspirin appears to reduce the risk of colorectal cancers that over-express COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2 [49]. A meta-analysis by Yang et al. [50] indicated that regular use of aspirin may be associated with reduced risk of noncardia gastric cancer, especially among Caucasians; for *H. pylori*-infected subjects, the result was similar. Analysis of individual patient data from randomised trials found that daily aspirin reduced deaths because of several common cancers during and after the trials [51]. Many studies have shown that aspirin may have chemopreventive activity against prostate cancer [52–54].

The molecular mechanism by which regular use of aspirin may reduce the risk of breast cancer has been investigated by many experimental studies. Some human breast tumors cause in vitro osteolysis that may be inhibited by aspirin [55]. The aspirin metabolite salicylate inhibits breast cancer cells growth and their synthesis of the osteolytic cytokines interleukins-6 and -11 [56]. The aspirin metabolite, salicylate, inhibits 7,12-dimethylbenz[a]anthracene-DNA adduct formation in breast cancer cells [57]. Aspirin inhibits camptothecin-induced p21CIP1 levels and potentiates apoptosis in

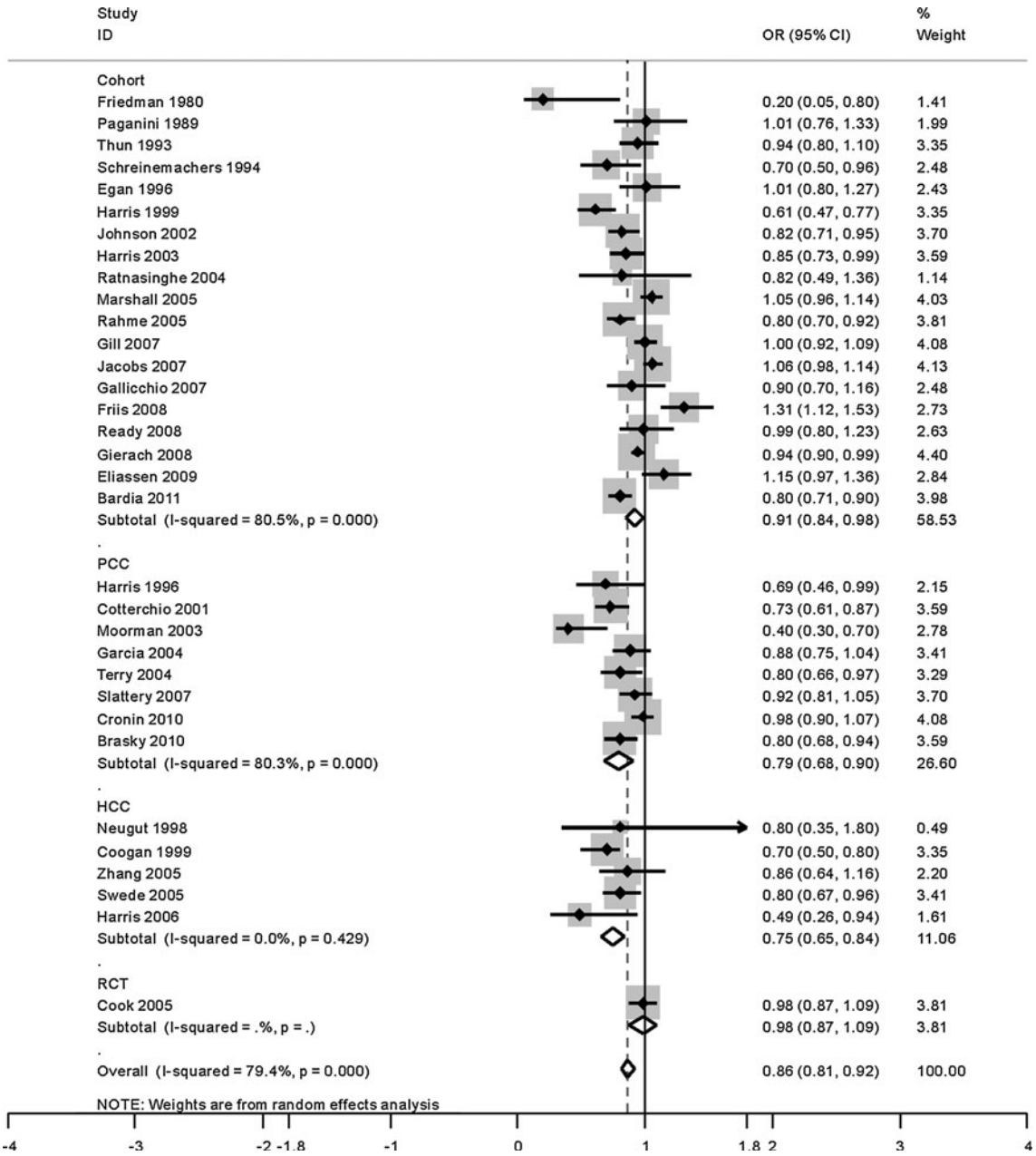

Fig. 1 Forest plot for the association between aspirin use and breast cancer risk

human breast cancer cells [58]. Maspin has been shown to inhibit the invasion and metastasis of breast cancer in an animal model. Ingestion of aspirin by breast cancer patients has been reported to restore the systemic synthesis of maspin through the stimulation of systemic nitric oxide production [59].

Several limitations needed to be discussed in this meta-analysis. First, although our results are consistent with former meta-analyses [5–8], we did not analyse a dose–response-relationship considering frequency and duration of aspirin use. Second, age is one of the major risk factors of breast cancer, but we cannot conduct stratified analyses adjusted by age because of the lack of enough data from the included studies. Third, as COX-2 expression is a very important factor for chemoprevention of breast cancer, it is reasonable to assume that the effectiveness of aspirin may also differ according to expression of COX-2. But we could not obtain information on the expression of COX-2 from most studies. Fourth, a significant heterogeneity and publication bias must be considered. Finally, all these studies are reported on Caucasians, so more studies were needed in Asians in the future.

In conclusion, this meta-analysis indicated that regular use of aspirin may be associated with reduced risk of breast

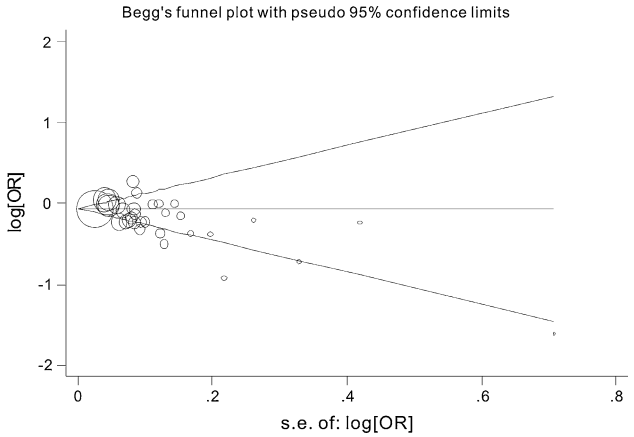

Fig. 2 Begg's funnel plot of aspirin use and breast cancer risk

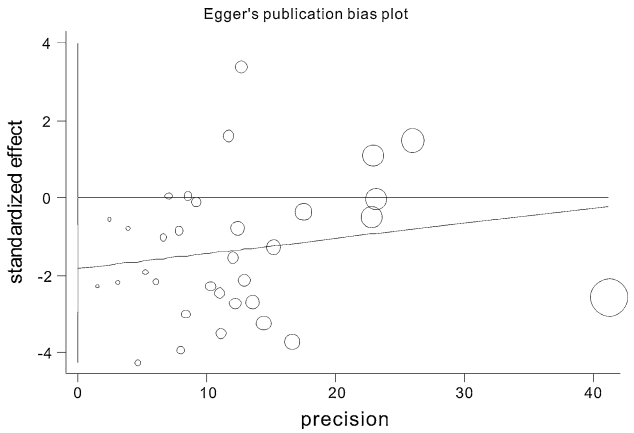

Fig. 3 Egger's publication bias plot of aspirin use and breast cancer risk

cancer. More RCT were needed to confirm this association in the future.

Conflict of interest None.

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