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EPIDEMIOLOGY

Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis

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Abstract Evidence on non-steroidal anti-inflammatory drugs (NSAID) use and breast cancer risk shows a slightly protective effect of these drugs, but previous studies lack randomized clinical trial results and present high heterogeneity in exposure measurement. This systematic review and meta-analysis widens the knowledge about NSAID use and breast cancer risk, updating the information from the last meta-analysis, focusing on evidence on specific effects of COX-2 inhibitors and differential expression patterns of hormonal receptors. A PubMed-database search was conducted to include all entries published with the keywords "BREAST CANCER NSAID ANTI-INFLAMMATORY" until 10/24/2013 providing original results from cohort studies, case–control studies, or randomized clinical trials with at least one reported relative risk (RR) or odds ratio (OR) on the association between any NSAID use and incidence of invasive breast cancer. This resulted in 49 publications, from which the information was retrieved about type of study, exposure characteristics, breast cancer characteristics, and breast cancer-NSAID association. Meta-analyses were performed separately for case–control and cohort studies and for different hormone-receptor status. NSAID use reduced invasive breast cancer risk by about 20 %. A similar effect was found for aspirin, acetaminophen, COX-2 inhibitors and, to a lesser extent, ibuprofen. The effect of aspirin was similar in preventing hormone-receptor-positive breast cancer. This meta-analysis suggests a slightly protective effect of NSAIDs-especially aspirin and COX-2 inhibitors- against breast cancer, which seems to be restricted to ER/PR+tumors.

Keywords Anti-inflammatory drugs · NSAID · Aspirin · Ibuprofen · COX-2 inhibitor · Breast cancer

Introduction

There is abundant evidence for the role of the cyclooxygenase/prostaglandin (COX/PG) inflammation pathway in

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carcinogenesis and for the chemopreventive effect of non-steroidal anti-inflammatory drugs (NSAIDs), particularly through the inhibition of the COX-2 isoform [1–6]. The first experimental studies demonstrated that NSAIDs block angiogenesis and promote apoptosis in colorectal polyps and further epidemiological studies showed a significant protective effect of NSAIDs against colorectal cancer [7, 8]. Afterward, further studies have been conducted in order to explore similar effects of NSAIDs in other neoplasms, including breast cancer, with promising results in the experimental setting. In fact, it has been proven that both in situ and invasive human breast tumor cells overexpress COX-2 and that COX-2 blockade and overexpression in mice decrease and increase, respectively, breast tumor formation [9–13].

However, epidemiological studies about NSAID use and breast cancer incidence have not yielded consistent results. Case–control studies [14–42] globally support a small decrease in breast cancer risk with NSAID use: a protective effect of NSAIDs was demonstrated in 13 studies [14, 16–20, 22, 24, 26, 33, 34, 37, 42], while only 7 papers showed a higher risk of breast cancer among anti-inflammatory drug users [15, 21, 27, 30, 32, 40, 46]. A neutral result was found in one case–control study [33] (Table 1). Cohort studies [43–71], on the other hand, show very modest risk differences both as a protective [44, 46, 48, 49, 51–56, 61, 64, 65] and as a risk factor [47, 54, 57, 58, 62, 64, 67], with one study showing a neutral OR [50] (Table 2).

There is a remarkable amount of non-significant results amongst all studies and some of them present separate data for each anti-inflammatory drug [25, 28, 35, 61, 68] with considerable difficulty to establish a unified RR/OR. Furthermore, even in studies providing a pooled RR/OR, the NSAID type, dose, frequency, intensity, and duration of use vary substantially. Additionally, the vast majority of observational studies are based on self-reported use of NSAIDs, mostly obtained as over-the-counter drugs; the few exceptions are studies based on prescriptions, which constitute a safer strategy to assess their sale but they do not necessarily assess NSAID consumption. Finally, another possible explanation for the disparities in results may lie on the fact that some anti-inflammatory drugs inhibit COX-2 more intensely than others, which leads to different risk reductions.

Data from randomized clinical trials are exceptional: only two papers [72, 73] were found in the preliminary search and both refer to the same study (Table 2).

To date, 11 meta-analyses regarding NSAID use and breast cancer incidence have been published, but one of them was a Japanese publication and it has not been reviewed here [75]. The 10 remaining studies [76–86] support a modest protective effect of these drugs (Table 3). There is an evident difficulty in performing those meta-analyses, given the differences among the studies already mentioned; but it is also difficult to compare their results, mainly due to the heterogeneity in both the inclusion criteria and in the drugs assessed in each meta-analysis: 5 of them include different types of NSAIDs [25, 28, 35, 61, 68], the rest consider either only aspirin [76, 77, 82, 83] or non-aspirin NSAIDs (85).

Here, we present a systematic review and a new meta-analysis aiming to appraise the knowledge about NSAID use and breast cancer risk, updating the information from the last meta-analysis, which was published in 2009. During this time, there have been 12 relevant studies, mainly focused on the specific effect of COX-2 inhibitors [36, 37, 40, 42] and on how differential expression patterns of hormonal receptors [33, 39, 69] and inflammation-related genes [29, 30, 34, 38, 67] modify the effect of NSAIDs on breast cancer incidence. This information may help further understand breast carcinogenesis and can also explain the inconsistency among the results of previous studies.

Methods

Search strategy

A PubMed-database search was conducted to include all the entries published with the keywords "BREAST CANCER NSAID ANTI-INFLAMMATORY" until October 24th, 2013 resulting in 1,508 articles. This initial nonspecific search was chosen in order to cover all relevant publications. Titles and abstracts were evaluated subsequently; articles were selected if they accomplished all of the following inclusion criteria: (a) They report original results from cohort studies, case–control studies, or randomized clinical trials; (b) they report at least one relative risk (RR) or odds ratio (OR) of the association between any NSAID use (aspirin and non-aspirin, COX-2-specific and nonspecific) and invasive breast cancer incidence.

Applying these criteria, 49 publications were identified: 23 case–control studies, 24 cohort studies and 2 papers from the same randomized clinical trial. Studies regarding the association between specific polymorphisms in inflammation-related genes and breast cancer according to the use of NSAIDs [29, 30, 39] have been excluded due to the lack of a general RR/OR for NSAID—breast cancer relationship irrespective of genetic features.

Data extraction

The following basic information was retrieved in each article when available: (a) Study characteristics: Type of study (controlled clinical trial/cohort study/case–control

Table 1 OR of breast cancer for NSAID users versus non-users in case–control studies

Source	Country	Type of control	Type of NSAID	OR (95 % CI, any intake)	OR (95 % CI, highest intake)	No. of cases/ no. of control subjects
Rahme et al. [14]	Canada	Population	Cox-2-inhibitors	0.81 (0.68–0.97)	–	1,090/4,4990
			Non-aspirin NSAIDs	0.65 (0.43–0.99)	–	
			Aspirin	0.75 (0.64–0.89)	–	
			Acetaminophen	0.91 (0.71–1.16)	–	
Harris et al. [15]	USA	Hospital	Any	1.12 (0.8–1.6)	0.58 (0.4–0.8)	744/767
Harris et al. [16]	USA	Population	Any	0.65 (0.5–0.9)	0.60 (0.4–0.9)	303/906
Rosenberg [17]	USA	Hospital	Any	0.8 (0.6–1.0)	–	4,485/8,391
Harris et al. [18]	USA	Population	Any	0.66 (0.52–0.83)	0.60 (0.40–0.91)	511/1,534
Neugut et al. [19]	USA	Hospital	Aspirin	0.80 (0.35–1.80)	–	252/322
Coogan et al. [20]	USA	Hospital	Any	0.70 (0.60–0.90)	0.6 (0.3–1.0)	6,558/2,925
Langman et al. [21]	UK	Hospital	Any	1.01 (0.93–1.10)	1.12 (0.90–1.40)	3,105/9,272
Cotterchio et al. [22]	Canada	Population	Any	0.76 (0.66–0.88)	0.68 (0.54–0.86)	3,133/3,062
Meier et al. [23]	UK	Population	Any	1.00 (0.9–1.1)	1.0 (0.8–1.1)	3,706/1,4155
			Acetaminophen	1.00 (0.9–1.1)	0.8 (0.7–1.0)	
Moorman et al. [24]	USA	Population	Any	0.4 (0.3–0.6)	0.3 (0.2–0.5)	930/754
Terry et al. [25]	USA	Population	Aspirin	0.80 (0.66–0.97)	0.77 (0.57–1.04)	1,442/1,420
			Ibuprofen	0.91 (0.72–1.16)	1.09 (0.70–1.70)	1,443/1,420
			Acetaminophen	1.02 (0.80–1.31)	0.91 (0.58–1.41)	1,434/1,417
Swede et al. [26]	USA	Hospital	Aspirin	0.83 (0.75–0.93)	0.85 (0.75–0.96)	1,478/3,383
Zhang et al. [27]	USA	Hospital	Any	1.01 (0.90–1.13)	0.62 (0.28–1.35)	7,006/3,622
Harris et al. [28]	USA	Hospital	Cox-2-inhibitors	0.29 (0.14–0.59)	–	323/649
			Aspirin	0.49 (0.26–0.94)	0.39 (0.22–0.72)	
			Baby aspirin	0.82 (0.40–1.40)	–	
			Ibuprofen/naproxen	0.37 (0.18–0.72)	–	
			Acetaminophen	1.02 (0.39–2.20)		
Davis y Mirick [32]	USA	Population	Any	1.1 (0.8–1.4)	1.0 (0.7–1.5)	600/647
Kirsh et al. [33]	Canada	Population	Any	0.76 (0.66–0.88)	–	3,125/3,062
Slattery et al. [34]	USA	Population	Aspirin	0.94 (0.82–1.07)	–	2,325/2,525
Brasky et al. [35]	USA	Population	Aspirin	0.80 (0.68–0.94)	0.68 (0.46–1.00)	1,170/2,115
			Ibuprofen	1.15 (0.97–1.36)	1.12 (0.94–1.34)	
			Acetaminophen	0.97 (0.83–1.15)	1.01 (0.85–1.20)	
Cronin-Fenton et al. [36]	Denmark	Population	Any	1.04 (0.99–1.10	1.01 (0.52–1.97)	8,195/8,1950
Ashok et al. [37]	USA	Population	Non-selective NSAIDs	0.85 (0.82–0.88)	0.78 (0.69–0.89)	18,368/7,3472
			Celecoxib	0.86 (0.81–0.91)	0.84 (0.73–0.97)	
			Rofecoxib	0.68 (0.62–0.74)	0.59 (0.46–0.76)	
			Valdecoxib	0.81 (0.71–0.9)	0.94 (0.52–1.68)	
			Acetaminophen	0.95 (0.85–1.06)	1.09 (0.61–1.92)	
Vinogradova et al. [40]	UK	Population (nested)	Cox-2-inhibitors	1.24 (1.08–1.42)	1.19 (0.98–1.44)	15,666/88,125
Ou et al. [42]	Taiwan	Hospital (nested)	Any	0.41 (0.19–0.89)	–	11/36

study), number of subjects at baseline, and number of recorded cases. (b) Exposure characteristics: type of NSAID, characteristics of its use (frequency, intensity, duration, and dose). (c) Breast cancer characteristics: type of breast cancer, presence or absence of hormone receptors (for estrogens or progesterone), positivity to Her-2 receptors. (d) Measure of NSAID—breast cancer association: OR/RR with their 95 % confidence interval (CI).

Table 2 RR of breast cancer for NSAID users versus non-users in cohort studies or randomized controlled trials

Source	Country	Type of NSAID	RR (95 % CI, any intake)	RR (95 % CI, highest intake)	No. of cases/ cohort size
Paganini-Hill et al. [44]	USA	Aspirin	0.96	–	214/8,818
Schreinemachers y Everson [46]	USA	Aspirin	0.72 (0.52–1.00)	–	174/11,411
Egan et al. [47]	USA	Aspirin	1.01 (0.80–1.27)	1.12 (0.76–1.66)	2,414/89,528
Harris et al. [48]	USA	Any	0.64 (0.50–0.82)	0.57 (0.44–0.74)	393/32,505
		Aspirin	0.57 (0.40–0.81),	0.64 (0.45–0.90)	76/32,505
		Acetaminophen	0.84 (0.55–1.18)	0.84 (0.47–1.50)	36/32,505
		Ibuprofen	0.53 (0.33–0.84)	0.49 (0.30–0.80)	37/32,505
Sharpe et al. [49]	USA	Any	0.95 (0.91–0.99)	0.91 (0.75–1.09)	5,882/25,317
Friis et al. [50]	Denmark	Acetaminophen	1.0 (0.9–1.2)	–	227/39,946
Johnson et al. [51]	USA	Any	0.80 (0.67–0.95)	1.01 (0.83–1.25)	938/27,616
Friis et al. [52]	Denmark	Aspirin	0.9 (0.8–1.1)	–	149/29,470
Harris et al. [53]	USA	Any	0.93 (0.78–1.10)	0.81 (0.68–0.97)	1,392/80,741
Sorensen et al. [54]	Denmark	Any	1.1 (1.0–1.2)	1.1 (0.9–1.3)	696/17,2057
Ratnasinghe et al. [55]	USA	Aspirin	0.82 (0.49–1.36)	–	131/12,834
García-Rodríguez y González-Pérez [56]	UK, Spain	Aspirin	0.84 (0.69–1.02)	0.87 (0.53–1.41)	3,708/734,899
		Non-aspirin NSAIDs	0.98 (0.88–1.09)	1.05 (0.80–1.38)	
		Acetaminophen	0.92 (0.83–1.03)	0.76 (0.60–0.97)	
Jacobs et al. [57]	USA	Any	1.16 (1.02–1.31)	1.05 (0.88–1.26)	3,008/77,413
Marshall et al. [58]	USA	Any	–	1.11 (0.96–1.30)	2,391/114,640
		Acetaminophen	–	0.96 (0.63–1.47)	
		Ibuprofen	–	1.51 (1.17–1.95)	
		Aspirin	–	0.96 (0.79–1.18)	
Gallichio et al. [60]	USA	Any	0.89 (0.72–1.09)	–	418/15,651
		Acetaminophen	0.94 (0.71–1.25)	–	
Gill et al. [61]	USA	Any	0.88 (0.75–1.04)	0.99 (0.82–1.18)	3,493/98,920
		Acetaminophen	1.14 (0.91–1.42)	1.05 (0.83–1.33)	278/98,920
Jacobs et al. [62]	USA	Aspirin	1.02 (0.88–1.19)	0.83 (0.63–1.10)	3,121/76,303
Bardia et al. [63]	USA	Aspirina	0.84 (0.77–0.90)	0.81 (0.73–0.90)	3,487/22,507
		Non-aspirin NSAIDs	0.96 (0.89–1.04)	0.94 (0.83–1.06)	
		Combined use	0.81 (0.72–0.90)	–	
Friis et al. [64]	Denmark	Any	1.34 (1.17–1.54)		847/28,695
Ready et al. [65]	USA	Any	0.99 (0.82–1.19)	0.91 (0.75–1.09)	482/35,323
Gierarch et al. [66]	USA	Any	0.95 (0.87–1.04)	–	4,501/126,124
Siemes et al. [67]	Netherlands	Any	1.19 (0.81–1.73)	1.27 (0.80–2.00)	175/7,621
Eliassen et al. [68]	USA	Aspirin	1.07 (0.89–1.29)	1.03 (0.74–1.42)	1,345/112,292
		Non-aspirin NSAIDs	1.16 (1.01–1.34)	0.86 (0.60–1.24)	
		Acetaminophen	0.99 (0.84–1.16)	1.06 (0.64–1.76)	
Bardia et al. [69]	USA	Aspirin	0.80 (0.71–0.90)	0.71 (0.60–0.83)	1,581/26,580
		Non-aspirin NSAIDs	0.95 (0.85–1.07)	1.00 (0.84–1.19)	
		Combined use	0.77 (0.65–0.91)	–	
Zhang et al. [71]	USA	Aspirin	0.91 (0.81–1.01)		4,734/84,602
		Non-aspirin NSAIDs	0.97 (0.90–1.04)		
		Acetaminophen	0.89 (0.83–0.96)		
Cook et al. [72]; Zhang et al. [73]	UK	Aspirin	0.98 (0.87–1.09)	–	1,230/39,884

RCT randomized controlled trial

Table 3 RR of breast cancer for NSAID users versus non-users in previous meta-analysis

Source	Type of NSAID	RR (95 % CI)
Algra et al. [76]	Aspirin	0.88 (0.82–0.95)
	Case–control studies	1.17 (0.50–2.71)
	RCTs	–
	Cohort studies	
Bosetti et al. [77]	Aspirin	0.91 (0.88–0.95)
Bosetti et al. [78]	Aspirin	0.90 (0.85–0.95)
González-Pérez et al. [79]	Any	0.77 (0.66–0.88)
	Aspirin	0.77 (0.69–0.86)
	Non-aspirin NSAIDs	0.86 (0.73–1.00)
Harris et al. [80]	OTC NSAIDs	0.75 (0.67–0.84)
Khuder et al. [81]	Any	0.78 (0.62–0.99)
	Cohort studies	0.87 (0.84–0.91)
	Case–control studies	
Luo et al. [82]	Aspirin	0.86 (0.81–0.92)
Mangiapane et al. [83]	Aspirin	0.75 (0.64–0.88)
Takkouche et al. [84]	Any	0.88 (0.84–0.93)
Tolentino et al. [85]	Non-aspirin NSAIDs	–
Zhao et al. [86]	Any	0.94 (0.88–1.00)
	Aspirin	0.91 (0.83–0.98)
	Ibuprofen	0.81 (0.67–0.97)

Statistical analysis

The statistical analysis has been performed separately for cohort and case–control studies; the unique controlled clinical trial found was included in the cohort study analysis. We carried out separate analysis for any combination of type of NSAID/type of breast cancer reported in at least three studies. According to the type of NSAID, we have considered the analysis of "any type of NSAID", aspirin, non-aspirin NSAID, ibuprofen, acetaminophen, or COX-2 inhibitors. Many studies reported several results for different doses or different durations of treatment with NSAIDs; the ways doses or lengths were reported were not standardized across studies, making it difficult to extract them in an analyzable form. Therefore, in order to magnify the effect of NSAIDs, we selected the OR or RR reported for the highest dose or the longest duration of treatment. According to the type of breast cancer, we contemplated all invasive breast cancers, estrogen-positive breast cancers, progesterone positive breast cancers, and receptor-negative breast cancer.

A pooled OR or RR has been estimated weighing individual results by the inverse of their variance [87]; a fixed-effect model was preferred if Q statistics were higher than 0.1, indicating no significant heterogeneity; a random-effect model was chosen otherwise [88]. OR or RR heterogeneity was measured using Q and I^2 statistics [89]. Q is an estimator of the homogeneity between studies; it allows to estimate a p value which would be used for rejecting the null hypothesis of homogeneity; however, it is well known that Q has low statistical power; therefore, the usual threshold for rejected homogeneity is $p = 0.1$. I^2 indicates the proportion of the effect variability due to heterogeneity between studies.

The presence of small-study bias was explored with Egger test [90]; due to its low sensitivity, the cut-off was set at $p = 0.1$. Funnel plots [91] and the trim and fill method [92] were applied to detect publication bias. In particular, the trim and fill method assumes that the most negative (i.e., no NSAID effect) studies are missing or suppressed; then, if it detects a bias, it simulates the results of the studies presumably missed [93]. In such a case, two pooled OR/RR are reported: the one reached with the original data and the one obtained by filling the (presumed) missing studies; this corrected OR/RR should be interpreted as a sensitivity analysis rather than as a true estimator [93]. Results from Egger test and trim and fill method are here reported only when relevant.

All the statistical analysis was carried out with the package Stata 12/SE (Stata Corporation, College Station, TX, US).

Results

Relationship between any NSAID and breast cancer

Twenty-one case–control studies and 12 cohort studies provide results on any NSAID—breast cancer relationship (Tables 1, 2). Analyzing all case–control studies [14–28, 32, 34–37], we obtained a pooled OR of 0.82, (95 % CI: 0.77–0.88) which supports a protective role of NSAID consumption against breast cancer (Table 4; Fig. 1a). We observed a high heterogeneity among the results from the different studies ($I^2 = 86.1$ %) which does not differ significantly from previous meta-analyses (Table 3). Egger test cannot rule out a small-study effect ($p = 0.05$).

The meta-analysis of cohort studies [48, 49, 51, 53, 57, 58, 60, 61, 64, 67, 69] rendered a pooled RR of 0.92 (95 %CI 0.84–1.01), which shows a non-significant protective effect (Table 4; Fig. 1b). There was a high degree of heterogeneity ($I^2 = 89.9$ %). Egger test could not exclude the possibility of a small-study bias ($p = 0.083$). However, when the trim and fill method was applied, results remain virtually unchanged in both case–control and cohort studies, rejecting the possibility of small-study and publication biases.

Three ORs from two studies [33, 73] have been identified regarding use of any NSAID and incidence of ER+breast tumors. The pooled OR is 0.72 (0.63–0.83), which suggests a protective effect. Data on NSAID use and estrogen-receptor-positive (ER+) breast cancer have been found in 5 cohort studies [58, 59, 61, 64, 69]. The pooled RR is 0.96 (0.79–1.17).

Relationship between aspirin and breast cancer

A total of 10 OR provided by 9 case–control studies [18, 19, 25–28, 36, 39, 56] evaluating aspirin use and breast cancer risk were considered for the meta-analysis, with a pooled OR of 0.87 (95 % CI 0.82–0.92) which points to a protective effect against breast cancer.

Information on aspirin use and breast cancer risk has been found in 13 cohort studies [44, 46, 47, 50, 55, 58, 60–62, 64, 71, 73], resulting in a non-significant pooled RR of 1.00 (95 % CI 0.96–1.04).

Data on aspirin use and risk of ER+breast cancer were found in 3 case–control studies [25, 33, 73], which provided 4 ORs. The pooled OR was 0.73 (0.63–0.83) (Table 4; Fig. 2a). Eight RRs provided by 7 cohort studies have been identified for aspirin use and estrogen-receptor-positive breast cancer [58, 61, 64, 68, 69, 71, 73], with a pooled RR of 0.94 (0.88–1.00) (Table 4; Fig. 2b). The trim and fill method suggested that two studies would have been missed; the trim and fill corrected RR (random-effect) was 0.93 (0.84–1.03).

Data on aspirin use and risk of PR+breast cancer were found in 3 studies [25, 27, 33], which provided 4 ORs. The pooled OR is 0.73 (0.63–0.84).

Relationship between ibuprofen and breast cancer

We found six case–control studies containing data on ibuprofen use and breast cancer incidence [18, 25, 26, 28, 35, 73], with a pooled OR of 0.83 (95 % CI 0.69–1.00) and a moderate heterogeneity ($I^2 = 72.5$ %). Only one cohort study [58] provides specific data on ibuprofen use and breast cancer risk, it provides a non-significant association: $RR = 1.09$ (95 % CI 0.99–1.20).

Only one cohort study (58) contains data for ibuprofen use and incidence of ER+breast cancer ($RR = 1.25$, 95 % CI 1.05–1.49). No meta-analysis has been performed.

Acetaminophen and breast cancer

Information about the use of acetaminophen and breast cancer was provided by 8 case–control studies [18, 25, 26, 28, 35, 37, 56, 73]. The pooled OR calculated for this meta-analysis is 0.85 (0.76–0.95) with a moderate heterogeneity ($I^2 = 63.2$ %). Small-study bias cannot be ruled out using Egger test ($p = 0.047$). However, when the trim and fill method was executed, it ensured the absence of small-study and publication biases. Data on acetaminophen use and breast cancer have been found in two cohort studies [64, 71], with a pooled RR of 0.95 (0.88–1.01) with a low heterogeneity ($I^2 = 0.75$ %).

There are 3 cohort studies providing 4 RRs for acetaminophen use and risk of ER+breast cancer [58, 68, 71]. The pooled RR is 0.93 (0.86–1.01). I^2 for heterogeneity was 0.9 % and Egger test excludes the possibility of small-study effect (0.336). The trim and fill method detected that one study had been missed; when added, the corrected RR (fixed-effects) was 0.92 (0.85–1.00).

Table 4 Results from this meta-analysis

NSAID	Receptor	Type of study	OR/RR	95 % CI	I^2 (%)[c]
Any NSAID	Any	Cohort	0.92	0.84–1.01	89.9
	Any	Case–control	0.82	0.77–0.88	86.1
	Estrogen+	Cohort	0.96	0.79–1.17	77.1
	Estrogen+	Case–control	0.72[a]	0.63–0.83[a]	0
Aspirin	Any	Cohort	1.00	0.96–1.04	11.7
	Any	Case–control	0.87	0.82–0.92	4.5
	Estrogen+	Cohort	0.94	0.88–1.00	57.2
	Estrogen+	Case–control	0.73	0.63–0.83	0
	Progesterone+	Case–control	0.73	0.63–0.84	0
Ibuprofen	Any	Cohort	1.09[b]	0.99–1.20[b]	–
	Any	Case–control	0.83	0.69–1.00	72.5
	Estrogen+	Cohort	1.25[b]	1.05–1.49[b]	–
COX-2 inhibitors	Any	Case–control	0.90	0.87–0.93	91.4
Acetaminophen	Any	Cohort	0.95[a]	0.88–1.01[a]	0.75
	Any	Case–control	0.85	0.76–0.95	63.2
	Estrogen+	Cohort	0.92	0.85–1.00	0.9
Non-aspirin NSAID	Any	Cohort	1.03	0.99–1.08	43.6
	Any	Case–control	1.02[a]	0.98–1.07[a]	3.1
	Estrogen+	Cohort	0.99	0.92–1.07	16.2

[a] Based on two studies

[b] Based on one study

[c] I^2 percent of the effect variability due to between studies heterogeneity

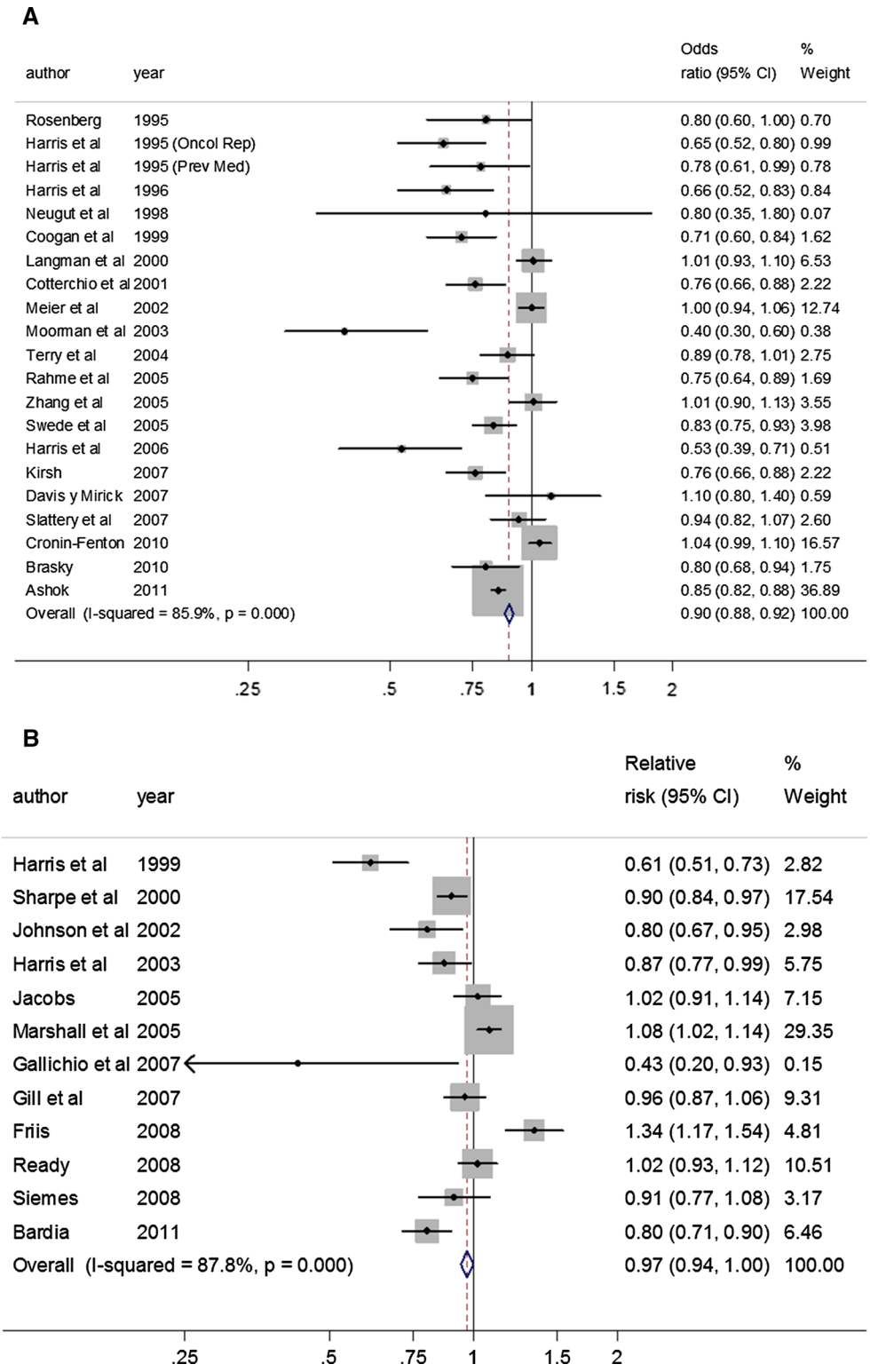

Fig. 1 Forest plot for the relationship between NSAID and breast cancer. **a** Case–control studies; **b** cohort studies. Odds ratios (OR) or relative risks (RR) lower than 1 indicate protective effect

Non-aspirin NSAID and breast cancer

Only two among all the case–control studies [36, 56] consider the use of non-aspirin NSAIDs as a group, with a pooled OR of 1.02 (0.98–1.07). There are 8 cohort studies reporting RR on breast cancer incidence and use of non-aspirin NSAIDs [51, 54, 61, 64, 65, 67, 69, 71]. The pooled RR is 1.03 (0.99–1.08) and there is a moderate heterogeneity ($I^2 = 43.6$ %). Egger test rejects the possibility of small-study bias ($p = 0.416$). The trim and fill method

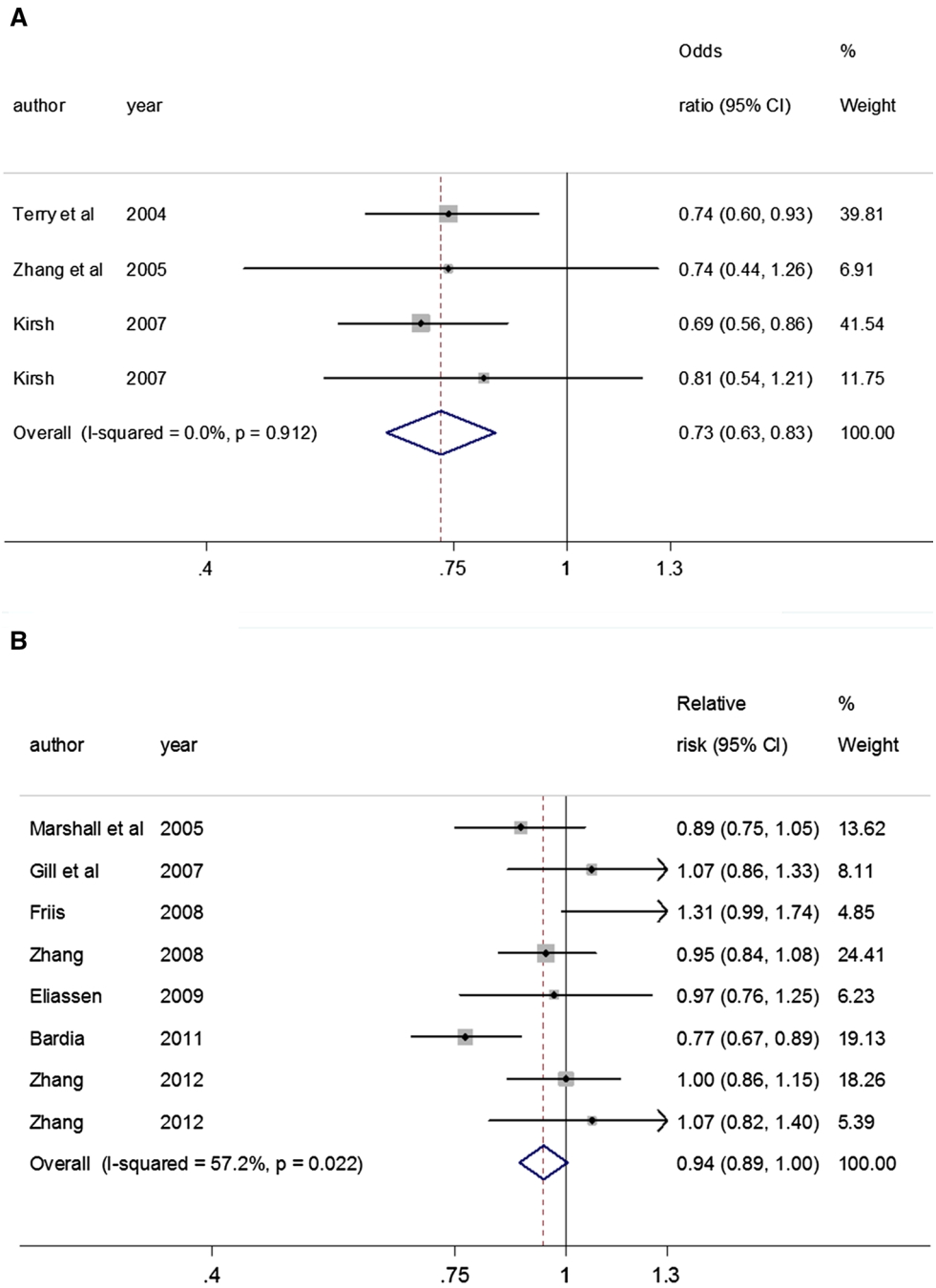

Fig. 2 Forest *plot* for the relationship between aspirin and estrogen+breast cancer. **a** Case–control studies; **b** cohort studies. Odds ratios (OR) or relative risks (RR) lower than 1 indicate protective effect

indicated that two studies had been missed; when added, the corrected RR (random-effect) was 1.02 (0.95–1.09).

Five RRs from 4 cohort studies [59, 64, 68, 71] have been identified for non-aspirin NSAID use and risk of ER+breast cancer, with a pooled RR of 0.99 (0.92–1.07).

COX-2 inhibitors and breast cancer

Data on the use of COX-2-inhibitors and breast cancer risk have been identified in 6 studies: 5 case–control studies and 1 cohort study [67], so only a meta-analysis on case–control studies could be performed. Among the 5 remaining studies, 3 of them provide different ORs for specific COX-2-inhibitors: Rahme et al. [14] and Harris et al. [28] provide separated ORs for celecoxib and rofecoxib; while Ashok et al. [37] provides separate results for celecoxib, rofecoxib, and valdecoxib [14, 28, 37]; the 2 remaining studies consider COX-2-inhibitors as a group and provide only a pooled OR [36, 40]. Therefore, a total of 9 ORs from 5 studies were included in the meta-analysis.

The combined estimate of ORs from these case–control studies in the meta-analysis is 0.90 (0.87–0.93),

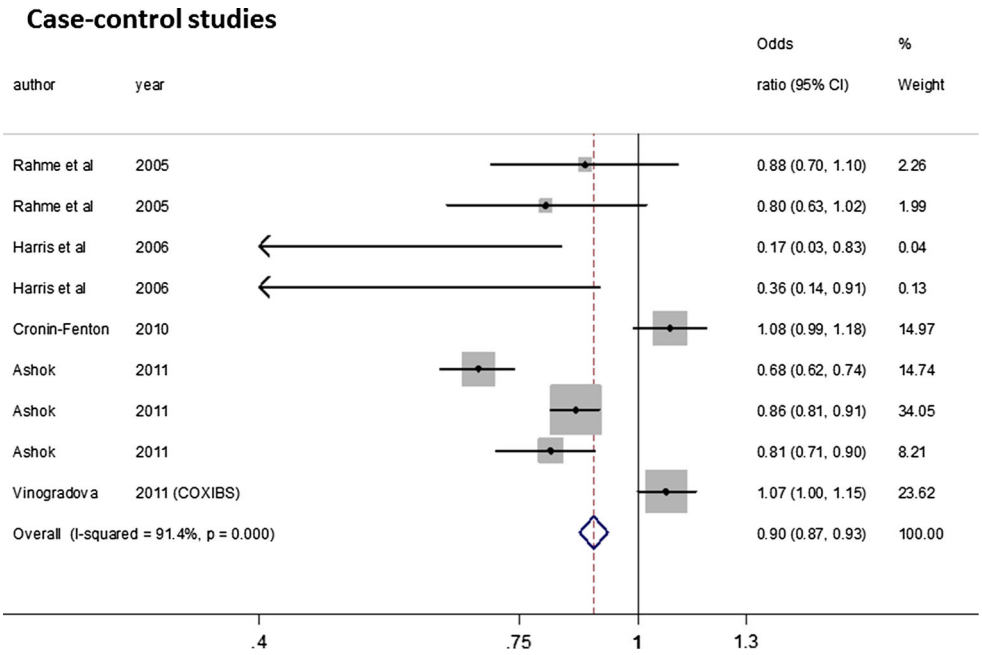

Fig. 3 Forest *plot* for the relationship between cox-2 inhibitors and breast cancer. Odds ratios (OR) lower than 1 indicate protective effect

supporting a slightly protective effect of COX-2-inhibitors against breast cancer (Table 4; Fig. 3). There was high heterogeneity among these studies ($I^2 = 91.4$ %). Both ORs from Harris et al. [28] were far lower than the others, and were based on very few patients; therefore, to further analyze whether Harris et al. would be an influential study, we performed a sensitivity analysis by deleting it; the resulting OR was virtually the same—up to the second decimal figure. Egger test and trim and fill test rejected the hypothesis of small-study or publication biases.

Discussion

The most innovative results of this meta-analysis are the protective effect of COX-2 inhibitors on breast cancer, and the protective effect of aspirin in preventing specifically ER+ and PR+ breast tumors. To our best knowledge, such results have not been reported previously in meta-analysis. Moreover, this meta-analysis confirms that consumption of NSAIDs reduced the risk of invasive breast cancer by about 20 %. A similar effect was found for consumption of different anti-inflammatory or analgesic drugs such as aspirin, acetaminophen, COX-2 inhibitors and, to a lesser extent, ibuprofen. Although similar results had been reported in previous meta-analyses, our study updates this information including recent studies.

Data concerning specific COX-2 inhibitors are still scarce [14, 28, 36, 37, 40], mainly due to discontinuation of their use after observing they were linked to an increase of thromboembolic cardiovascular risk. Nevertheless, their effect on reducing breast cancer risk seems stronger than that of traditional NSAIDs and recent reviews have reported their use to be safe if dosage is within a certain range (20).

Similarly, few studies have been published in which different molecular types of breast cancer and hormonal receptor status are considered [25, 27, 33, 39, 58, 60, 61, 64, 68, 69, 71, 73]. They had only been partially included in previous meta-analyses either because they were unpublished [27, 33, 39, 60, 61, 64, 68, 69, 71, 73, 74] or because data were insufficient for a meta-analysis [41, 68]. While two recent meta-analyses published in 2012 [82, 85] include some of these studies [25, 27, 33, 35, 58, 61, 64, 66, 68, 69] they restricted the analysis to the effect of aspirin use.

By the time our review was performed, 12 publications were available on the differential effect of NSAIDs on hormone-receptor-positive breast cancer, which made it possible to obtain separate results. We observed that NSAID use led to a higher decrease in the risk of ER+ than in breast cancer altogether (i.e., without specifying the presence or absence of hormonal receptors). Prostaglandin E2 can induce binding of several transcription factors (phosphorylated ATF-2, LRH-1, and C/EBPβ) to aromatase promoters I.3 and II, which induces up-regulating aromatase expression in adipose tissue fibroblasts. Moreover, aromatase is associated to higher exposure to estrogens in breast cancer cells (86). Use of COX-2 inhibitors would down regulate aromatase expression leading to a decrease in breast cancer risk.

It is noteworthy that case–control studies tend to report stronger effects than cohort studies. Although well-organized case–control studies would be as accurate as cohort ones, it seems on empirical basis that the latter are exposed to more frequent biases such as recall bias or selection bias. Therefore, the effect size of NSAID on breast cancer incidence would be lower than reported here. This fact is especially relevant for those effects only reported in case–control studies, as occurs with COX-2 selective inhibitors or ibuprofen. On the other hand, cohort studies rarely update the information provided by the participants at baseline, which means that NSAID consumption refers to that reported many years before breast cancer occurrence. If the protective effect of NSAID is only observed among current users, many cohort studies may suffer from an important degree of misclassification when assessing the relevant exposure.

Several limitations of our meta-analysis must be taken into account. First of all, we have not studied the effect of different NSAID doses or duration of use because original articles reported this information in very heterogeneous ways; although some meta-analyses have performed a dose–response analysis, we do believe that the lack of standardization in reporting doses or time of exposure makes such analyses unreliable. Secondly, several articles reported odds ratios on "any NSAID" without clarifying the composition of that category. In our meta-analysis, we have combined those results, regardless of the possible heterogeneity of such a group. Nevertheless, this heterogeneity should be considered in order to carefully interpret its results. Finally, NSAID use is not uniformly recorded through the different original articles, including self-reported use, NSAID prescriptions, or over-the-counter NSAID sales, which leads to an additional source of heterogeneity or bias.

In conclusion, our meta-analysis supports that NSAID use has a small protective effect on breast cancer risk, which would be stronger when using COX-2 inhibitors and regarding estrogen-responsive cancer, although the number of studies in this regard is still small. Further research on dose–response effect or duration of use would benefit from standardization in the way such variables are reported in original studies.

Conflict of interest The authors declare that they have no competing interests.

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