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Breast cancer and NSAID use: a meta-analysis

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Summary Recent epidemiological studies suggest that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of several cancers including breast cancer. This meta-analysis examined the studies on NSAID use and breast cancer. The estimators of relative risk and associated variances, which have been adjusted for the greatest number of confounders, were abstracted and included in the meta-analysis. Combined estimators of relative risk (RR) were calculated using either fixed or random effect models. Meta-analyses were performed on 6 cohort studies (number of cases ranged from 14 to 2414) and 8 case–control studies (number of cases ranged from 252 to 5882). The combined estimate of relative risk was 0.82 (95% confidence interval [CI] = 0.75–0.89). The combined estimate for cohort studies was 0.78 (95% CI = 0.62–0.99) and was 0.87 (95% CI = 0.84–0.91) for case–control studies. The findings of this meta-analysis suggest that NSAID use may be associated with a small decrease in the risk of breast cancer. However, the available data are insufficient to estimate the dose–response effect for duration and frequency of use of any particular types of NSAID. © 2001 Cancer Research Campaign http://www.bjcancer.com

Breast cancer is one of the most common cancers in women. The incidence of the disease has increased in recent years in the United States (Dinse et al, 1999). A substantial portion of the recent trend may be attributable to screening (Wun et al, 1995), however, the long-term trend remains unexplained. The established risk factors for breast cancer account for less than half of all breast cancer cases and offer few opportunities for intervention (Kelsey et al, 1993; Madigan et al, 1995).

Recently, non-steroidal anti-inflammatory drugs (NSAIDs) have received increasing attention due to their potential as chemopreventive agents against cancer. Animal studies showed inhibitory effect for NSAID on breast carcinogenesis (Lala et al, 1997; Robertson et al, 1998). However, several epidemiologic studies have examined the relation between NSAIDs and breast cancer, with inconsistent results. In some studies (Laakso et al, 1988; Gridley et al, 1993) patients with rheumatoid arthritis who use NSAIDs in high doses for symptom relief had fewer than expected cases of breast cancer.

Numerous studies have demonstrated that the level of prostaglandin is greater in breast cancer than in normal tissue (Bennett et al, 1983). In particular, the inducible form of cyclooxygenase (COX), the rate-limiting enzyme in prostaglandin biosynthesis may be overexpressed in breast cancer (Hwang et al, 1998). NSAIDs are known to block COX activity (Robertson et al, 1998) and thus become attractive agents for breast cancer prevention. A recent animal study (Harris et al, 2000) confirmed the chemopreventive activity of NSAIDs against breast cancer through COX2 blocking. In this meta-analysis we examined the epidemiological studies on NSAID use and breast cancer.

METHODS

The studies were located via a search of the MEDLINE (from 1966 to 2000) and Cancer Abstract databases (from 1980 to 2000). Abstracts of research presented at related conferences (Society for Epidemiologic Research, European Cancer Research, British Cancer Research, and American Association for Cancer Research) were also searched.

Studies were eliminated from the analyses if they included subjects used in other more-inclusive studies. The estimators of relative risk and associated variances, which has been adjusted for the greatest number of confounders, were abstracted and included in the meta-analysis.

A series of meta-analyses was conducted and the results were evaluated in the context of the published literature. The homogeneity of the estimators of relative risk was tested using Cochran's Q statistics (Cochran, 1954). This is a chi-square test with degrees of freedom equal to the number of studies minus one, and tests the null hypothesis that the within-study estimates of relative risk are homogeneous across studies. The fixed-effect model was used to obtain the combined estimator of relative risk and its standard error (SE). The random-effects model (DerSimonian and Laird, 1987) was used in situation when we detected significant heterogeneity within the groups of studies.

The potential for publication bias in published reports was investigated by constructing funnel plots of log odds ratio against the size of the study. A Kendall tau rank correlation test (Begg and Mazumdar, 1994) was used to test for the statistical significance of publication bias.

RESULTS

We identified 15 studies (Friedman and Ury, 1980; Paganini-Hill et al, 1989; Rosenberg et al, 1991; Thun et al, 1993; Schreinemachers and Emerson, 1994; Harris et al, 1995; Rosenberg, 1995; Egan et al, 1996; Harris et al, 1996; Neugut et al, 1998; Coogan et al, 1999; Harris et al, 1999; Cotterchio et al, 2000;

Table 1 Cohort studies used for meta-analyses of NSAIDs use and breast cancer

Reference	NSAID Ttype	Number of cases	OR	95% CI
Harris et al, 1999	Aspirin	76	0.60	0.47–0.77
	Acetaminophen	36	0.84	0.60–1.18
	Ibuprofen	37	0.51	0.36–0.72
Egan et al, 1996	Aspirin	2414	1.01	0.80–1.27
Schreinemachers and Everson, 1994	Aspirin	79	0.70	0.50–0.96
Thun et al, 1993	Aspirin	–	0.94	0.80–1.10
Paganini-Hill et al, 1989	Aspirin	68	0.96	0.75–1.21
Friedman and Ury, 1980	Aspirin,	2	0.20	0.05–0.80
	Indomethacin	12	0.50	0.28–0.88

Table 2 Case–control studies used for meta-analyses of NSAIDs use and breast cancer

Reference	Number of cases	NSAID type	Type of control	OR	95% CI
Sharpe et al, 2000[a]	5882	Any	General population	0.90	0.84–0.97
Cotterchio et al, 2000	2681	Any	General population	0.74	0.65–0.85
Langman et al, 2000	3105	Any	Cancer	1.00	0.92–1.09
Coogan et al, 1999	6558	Any	Cancer	0.80	0.70–1.00
			Non-cancer	0.70	0.60–0.90
		Aspirin	Cancer	0.70	0.60–0.90
			Non-cancer	0.70	0.50–0.80
Neugut et al, 1998	252	Aspirin	Non-cancer	0.80	0.35–1.80
Harris et al, 1996	106	Any	General population	0.66	0.52–0.83
		Aspirin,	General population	0.69	0.46–0.99
		Ibuprofen	General population	0.57	0.36–0.91
Roenberg, 1995	4485	Any	Cancer	0.90	0.60–1.20
			Non-cancer	0.80	0.60–1.00
Harris et al, 1995	744	Any	Cancer	0.96	0.67–1.39
			Non-cancer	0.81	0.63–1.03

[a]Nested case–control study.

Table 3 Combined analysis of studies used for meta-analysis of NSAID use and breast cancer

Reference	NSAID type	Number of studies	Test of heterogeneity		OR	95% CI
			χ^2	*P* value		
All studies	Any	16	38.1	0.001	0.80	0.73–0.87
Cohort studies	Any	6	22.8	<0.001	0.78	0.62–0.99
	Aspirin	6	17.8	<0.001	0.79	0.59–1.06
Case–control						
All	Any	10	15.2	0.09	0.83	0.79–0.88
Cancer		3	1.0	0.621	0.84	0.72–0.97
Non-cancer		7	14.2	0.03	0.79	0.72–0.86
All	Aspirin	4	0.10	0.99	0.70	0.61–0.81

Langman, 2000; Sharpe et al, 2000) evaluating the association between NSAIDs and breast cancer that were published between 1980 and 2000. One study (Rosenberg et al, 1991) was excluded from the analysis because of lack of data on the estimator of relative risk. The remaining studies were 6 cohort studies (Table 1) and 8 case–control studies (Table 2). The number of cases ranged from 14 to 2414 for cohort studies. For case–control studies the number of cases ranged from 252 to 5882 and the number of controls ranged from 42 to 89528. 5 studies (Paganini-Hill et al, 1989; Thun et al, 1993; Schreinemachers and Emerson, 1994; Egan et al, 1996; Neugut et al, 1998) were restricted to aspirin use and three studies (Harris et al, 1999; Paganini-Hill et al, 1989; Friedman and Ury, 1980) provided data stratified by NSAID type.

Twelve studies reported reduction in the risk of breast cancer with NSAID use. The estimator of relative risk for cohort studies ranged from 0.20 to 1.01 and 6 of these estimators were significant. Only one cohort study (Egan et al, 1996) reported non-significant increases in the risk of breast cancer with aspirin use. The estimator of relative risk for case–control studies ranged from 0.57 to 1.00 and 7 of these estimators were significant. None of the case–control studies reported an increase in the risk of breast cancer with any NSAID use.

The results of meta-analyses are presented in Table 3. Significant heterogeneity was detected among the studies ($\chi^2 = 53.0$, $P = 0.001$). The combined estimate of relative risk using the random-effect model was 0.82 (95% CI = 0.75–0.89). Heterogeneity among studies was significantly reduced when studies were combined within specific design and type of control. The combined estimate of relative risk for cohort studies was 0.78 (95% CI 0.62–0.99) with any NSAIDs and was 0.79 (95%

Table 4   Duration of use reported in studies used in the meta-analysis of NSAID use and breast cancer

Study	Measure	Duration	OR	95% CI
Coogan et al, 1999[a]	NSAID regular use (years) begun ≥ 1 year before admission	Never	1	–
		< 1	0.90	0.50–1.70
		1–< 2	1.10	0.70–1.70
		2–< 5	0.70	0.50–1.00
		5–< 10	0.70	0.40–1.00
		10–< 20	0.70	0.40–1.10
		20+	0.60	0.30–1.00
		Unknown	0.40	0.20–0.70
Harris et al, 1995	NSAID use, years	0	1	–
		1–4	1.09	0.80–1.50
		≥5	0.63	0.50–0.90
Egan et al, 1996	Aspirin use, years	<5	0.89	0.76–1.05
		5–9	0.98	0.81–1.19
		10–19	1.11	0.85–1.46
		≥20	1.00	0.71–1.41
Harris et al, 1996	NSAID use, years	<5	0.65	0.47–0.91
		≥5	0.60	0.40–0.91
Langman et al, 2000	Prescription of NSAID before diagnosis, months	13–24	1.03	0.93–1.13
		25–36	1.00	0.91–1.11
Sharpe et al, 2000	Highest level of NSAID exposure before diagnosis, years	1/2	1.05	0.91–1.23
		1/2–1	1.20	1.02–1.40
		2–5	0.76	0.63–0.92
		6–10	1.13	0.92–1.39
		11–15	0.83	0.63–1.11

[a]Significant dose–response relationship.

Table 5   Frequency of NSAID use in studies used in the meta-analysis of NSAID use and breast cancer

Study	Measure	Frequency	OR	95% CI
Sharpe et al, 2000[a]	Sum of NSAID mg day^{-1} dispensed ÷ maximum mg day^{-1} recommended (Σp) in 2–5 years before diagnosis	1.0	–	
		0 < Σp ≤ 1	0.93	0.85–1.01
		0.1 < Σp ≤ 0.3	0.91	0.79–1.06
		Σp >0.3	0.76	0.63–0.92
Egan et al, 1996	Number of aspirins per week	0	1.00	–
		1–3	0.99	0.89–1.11
		4–6	0.94	0.80–1.10
		7–10	1.00	0.84–1.20
		11–14	1.11	0.91–1.37
		>14	1.05	0.89–1.23
Paganini-Hill et al, 1989	Aspirin use	None	1	–
		<daily	0.95	0.68–1.34
		daily	0.96	0.69–1.34
Harris et al, 1996	NSAID dose/week	3–6	0.73	0.46–1.13
		≥7	0.63	0.49–0.81
Thun et al, 1993	Aspirin frequency/month	occasionally	0.93	0.73–1.19
		1–15	0.98	0.76–1.26
		16+	0.88	0.62–1.24
Harris et al, 1999	NSAID pills per week	0 < 1	1.00	–
		1–3	0.64	0.50–0.82
		≥4	0.57	0.44–0.74
Langman et al, 2000	Number of prescriptions of NSAID received in 13–24 months before diagnosis	0	1	–
		1	0.99	0.87–1.13
		2–6	0.96	0.83–1.11
		≥7	1.10	0.92–1.30

[a]Significant dose–response relationship.

CI = 0.59–1.06) for aspirin use. The case–control studies were relatively homogeneous within cancer and non-cancer controls. The combined estimate of relative risk for these studies was 0.87 (95% CI 0.84–0.91) with any NSAID and was 0.70 (95% CI =

0.61–0.81) for aspirin use. The combined estimate of relative risk for studies with non-cancer controls was 0.79 (95% CI 0.72–0.86) and was 0.96 (95% CI = 0.89–1.03) for studies with cancer controls.

Six studies provided results on duration of use of aspirin and that of other NSAIDs (Table 4). 9 studies provided results stratified by measures of NSAID use (Table 4). The risk reduction for highest duration of use (20+ years) ranged from 40% (Coogan et al, 1999) to zero (Egan et al, 1996). Trend tests for dose–response relations in only one of these studies was significant. The available data in Table 4 are insufficient to estimate the combined dose–response effect for duration of use of any particular types of NSAID.

Seven studies provided results on frequency of use of aspirin and that of other NSAID (Table 5). In one study (Harris et al, 1999) four or more pills of NSAID per week was associated with a 43% reduction in the risk of breast cancer (RR = 0.57, 95% CI 0.44–0.74). In another study (Paganini-Hill et al, 1989) daily use of aspirin was associated with only 4% reduction in the estimated risk of breast cancer (RR = 0.96, 95% CI 0.69–1.34). The available data in Table 5 are insufficient to estimate the combined dose–response effect for frequency of use of any particular types of NSAID.

There was no evidence of publication bias in studies included in this meta-analysis. The Kendall tau correlation coefficient for the standard error and the standardized log odds ratio was 0.96 ($P = 0.34$).

DISCUSSION

This meta-analysis showed that NSAID use may decrease the risk of breast cancer. This is evident by the consistently reduced relative risk in the majority of studies included in the analysis. The effect observed was similar in most studies regardless of design or type of cases (incident or fatal cases). The only negative study (Egan et al, 1996) may have been confounded by reproductive factors. In this meta-analysis, regular use of NSAIDs was associated with an 18% reduction in the risk of breast cancer. The reduction in risk was higher in cohort studies (21%) than case–control studies (13%). Within case–control studies, the reduction in risk was smaller in studies with cancer controls than in those with non-cancer controls. Although this finding is consistent with studies on NSAID use and colon cancer (Harris et al, 1995), it may argue against a true effect against breast cancer since this should be consistent across control groups. It is possible that some cancer subtypes (for example, gastrointestinal) were related to NSAID use and these patients discontinued the drug. If so this may overestimate the odds ratio and may bias the estimate of relative risk away from the null value. It is possible that the results of these studies are biased by a higher prevalence of pre-existing medical conditions commonly associated with NSAID use among non-cancer controls. On the other hand population-based case–control studies (Neugut et al, 1998) used as control subjects who underwent screening mammography, and their use of NSAID could have overestimated the prevalence of use in the study base.

With regard to type of NSAID, aspirin was the major type used in the studies included in this meta-analysis. In general, the reduction in risk of breast cancer with aspirin use was similar to other NSAID type. Two studies reported higher reduction in risk with ibuprofen in comparison to aspirin. However, available data were not adequate enough to test this in a meta-analysis.

Nine studies evaluated dose–response relation of NSAID use and breast cancer but only two studies reported significant dose–response relation for duration (Coogan et al, 1999) and frequency (Sharpe et al, 2000) of NSAID use. In one study (Coogan et al, 1999) the highest reduction in breast cancer risk was reported for the category 'unknown years of use'.

Although publication bias is possible because of the possibility of failure of investigators to submit negative results or failure of journals to publish negative studies our analysis did not suggest this.

The effect of NSAIDs on breast cancer risk reduction is biologically plausible. A number of animal studies have suggested a protective effect of NSAIDs against mammary cancer. A potential mechanism for anti-tumour effect of NSAIDs involves inhibition of the synthesis of prostaglandins. NSAIDs block the enzyme cyclooxygenase and in turn inhibit prostaglandin biosynthesis. Prostaglandins may serve as cofactors in carcinogenesis with potential effects ranging from direct mutagenesis to tumour promotion and immune suppression (Lupulescu, 1978; Mellemkjaer et al, 1996). One study (McCormick and Wilson, 1986) suggests that the cancer inhibitory effects of NSAIDs may be independent of their effects on prostaglandin synthesis. There is evidence from animal studies that indomethacin inhibits the effects of oestrogen in the pituitary gland (Neugut et al, 1998). In-vitro studies of human breast cancer cells indicate that acetylsalicylic acid may inhibit direct binding of oestradiol to oestrogen receptor (Thompson et al, 1995).

The majority of studies included in this meta-analysis adjusted for known risk factor for breast cancer. Our inclusion of estimators of relative risk, which were adjusted for the greatest number of confounders, would have reduced the possibility of confounding effect. The combined estimate of this study supports a protective effect for NSAIDs against breast cancer. Other support for the protective effect of NSAIDs against breast cancer comes from studies on patients with rheumatoid arthritis who use NSAIDs in high doses for symptom relief. 2 studies (Gridley et al, 1993; Baron, 1995) reported that these patients had less than expected occurrence of breast cancer. The risk pattern for NSAID users found in this meta-analysis is consistent with the pattern found in studies on patients with rheumatoid arthritis.

The limitations of this study stem from the studies included in the meta-analysis. All the studies included are observational studies and therefore subject to biases. Some are case–control studies and we cannot rule out the possibility of selection and information biases. It is possible that the relation between NSAIDs and breast cancer may reflect a recall bias by the cases or controls. Misclassification of exposure is a potential problem in observational epidemiological studies. None of the studies included in this meta-analysis utilized an objective method of exposure assessment. In all studies the NSAID use was self-reported and therefore subject to recall bias. These drugs are often taken sporadically in a pattern of intake that may be difficult to remember or summarize for some subjects. For example, some widely used brands or combination product may not be recognized as containing aspirin (Harris et al, 1995). It is possible that NSAID use may reflect a health consciousness among the control group. However, Harris et al (1995) reported no association between NSAID use and level of education, which can be taken as a proxy for health consciousness.

Currently known risk factors account for less than half of all breast cancer cases and offer limited opportunities for intervention. Therefore, any preventive measure identified will be important. This meta-analysis suggests that NSAIDs have a weak chemopreventive value against breast cancer. However, we cannot rule out the possibility of an alternate explanation for this finding due to the limitations of the studies included in the analysis.

There is a need for more studies that prospectively evaluate the reduction in risk of breast cancer utilizing a better measure of NSAID dose. There is a need to establish whether NSAIDs are

efficacious in preventing breast cancer and type and optimal dose. This can be accomplished using a randomized clinical trial on different types of NSAID.

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