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Effect of Aspirin and other NSAIDs on Postmenopausal Breast Cancer Incidence by Hormone Receptor Status: Results from a Prospective Cohort Study

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Abstract

Purpose—Aspirin and other non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit aromatase activity and thus could selectively lower incidence of hormone receptor positive tumors. We assessed whether the association of aspirin and other NSAIDs with postmenopausal breast cancer risk differs by estrogen and progesterone receptor (ER, PR) status of the tumor.

Methods—A population-based cohort of 26,580 postmenopausal women was linked to a SEER Cancer Registry to identify incident breast cancers. Regular use of aspirin and other NSAIDs was reported on a self-administered questionnaire mailed in 1992. Cox proportional hazards models were used to estimate multivariate relative risks (RRs) and 95% confidence intervals (CIs) of breast cancer incidence overall and by ER and PR status, adjusting for multiple breast cancer risk factors.

Results—Through 2005, 1,581 incident breast cancer cases were observed. Compared to aspirin never users, women who regularly consumed aspirin had a lower risk of breast cancer (RR=0.80;

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95% CI: 0.71–0.90), and there was evidence for lower risk with increasing frequency of use (RR=0.71 for aspirin use 6 or more times/week versus never use; p-trend=0.00001). Inverse associations for regular aspirin use were observed for ER+ (RR=0.77; 95% CI 0.67–0.89), ER− (RR=0.78; 95% CI 0.56–1.08), PR+ (RR=0.79; 95% CI 0.68–0.92), and PR− (RR=0.73; 95% CI 0.56–0.95) breast cancers. In contrast, use of other NSAIDs was not associated with breast cancer incidence overall (RR=0.95, 95% CI: 0.85–1.07), or by ER or PR status.

Conclusions—Aspirin, but not other NSAID use, was associated with about 20% lower risk of postmenopausal breast cancer and did not vary by ER or PR status of the tumor, suggesting that the hypothesized protective effects of aspirin may either be through cellular pathways independent of estrogen or progesterone signaling, or on tumor microenvironment.

Keywords

breast cancer; aspirin; NSAIDs; hormone receptors; prevention

INTRODUCTION

Breast cancer is the most common noncutaneous cancer, and the second leading cause of cancer-related death among women in the United States [1]. It is estimated that one in eight women will develop breast cancer over her lifetime [2]. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have received considerable interest as potential cancer chemopreventive agents [3–5]. These agents block inflammation by inhibiting cyclooxygenase (COX) enzymes, leading to lower prostaglandin synthesis. Lowered levels of prostaglandins also inhibit aromatase activity, which in turn leads to lower serum estrogen levels [6,7], and thus could selectively lower incidence of hormone receptor positive tumors.

Most [8–15] but not all [16–18] epidemiologic studies have found an inverse association between breast cancer and aspirin or other NSAIDs, including an earlier report from this cohort [19]. However, breast cancer is biologically heterogeneous and it is increasingly being recognized that breast cancer risk may vary by molecular characteristics of the tumor, particularly defined by estrogen receptor (ER) and progesterone receptor (PR) status. Epidemiologic studies addressing ER and PR subtype-specific associations between breast cancer and aspirin or other NSAID use are currently more limited, with some studies supporting this hypothesis [8,11,20], while others have not [14,15,18,21–24]. However, the analyses in these studies were usually secondary and often based on small numbers of ER and PR defined subtypes.

Here, we update our previously published results for 6 years of follow up [19] to 13 years of follow up, and further present results defined by breast cancer subtype based on hormone receptor status as the primary objective. We hypothesized that aspirin use would continue to be associated with risk of postmenopausal breast cancer overall, and that these associations would be stronger for hormone receptor positive tumors.

Materials and Methods

Study population

The IWHS is a prospective cohort study of 41836 postmenopausal women aged 55–69 years at study entry; full details on study methods have been previously published [19,25]. The IWHS was reviewed and approved by the institutional review boards of the University of Iowa and the University of Minnesota. A 16-page questionnaire was mailed in 1986 to

99,826 randomly selected women and returned by 41,836 women (42.7% response rate). Follow-up questionnaires were mailed in 1987, 1989, 1992, 1997, and 2004.

Risk factor assessment

Risk factor data collected in 1986 included age, level of education, height, weight, relative weight at age 12, age at menarche, age at menopause, number of live births, age at first live birth, family history of breast cancer, use of oral contraceptives, use of hormone therapy, and level of physical activity. The use of aspirin and non-aspirin NSAIDs in the cohort was ascertained on the 1992 questionnaire. Aspirin use was ascertained by asking the respondents "How often do you take aspirin? Examples of aspirin include Bufferin, Anacin, enteric-coated aspirin, Ecotrin, and Excedrin (Do not include acetaminophen, Tylenol, Ibuprofen, Advil): never, less than one per week, one per week, 2–5 per week, and 6+ per week." Use of non-aspirin NSAIDs was ascertained by asking the respondents, "How often do you take other nonsteroidal antiinflammatory drugs or arthritis medicines? Examples include Ibuprofen, Advil, Nuprin, Motrin, Naprosyn, Feldene, and Clinoril (Do not include aspirin, acetaminophen, Tylenol, prednisone, cortisone, Deltasone): never, less than one per week, one per week, 2–5 per week, and 6+ per week." Additional data collected on the 1992 questionnaire included smoking history, lifetime use of alcohol, as well as information on rheumatoid arthritis, and osteoarthritis.

Cohort follow-up

Incident breast cancers through 2005 were identified by linking to the Iowa Cancer Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program [26]. ER and PR status of the tumor was derived from registry reports. Deaths were identified through annual linkage to Iowa state death certificates supplemented by linkage to the National Death Index.

Statistical analysis

Of the 41836 women who responded to the questionnaire in 1986, we excluded women who were premenopausal (n=569); had cancer other than nonmelanoma cancer, (n=6452); had a total or partial mastectomy (n=1884); did not return the 1992 questionnaire (n=8819); or did not answer the aspirin or other NSAID question (n=681). A total of 26,580 participants were included in the analytic cohort (exclusions were not mutually exclusive).

Follow-up for incident events was calculated as the age at completion of the 1992 questionnaire until the age at breast cancer diagnosis, age at move from Iowa, or age at death. If none of these events occurred, a woman was assumed to be alive, cancer-free, and living in Iowa through December 31, 2005. Cox proportional hazards regression analysis was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the association of breast cancer risk with aspirin and NSAID use. Incidence was modeled as a function of age [27]. Exposures were characterized by ever use for each agent as well as frequency of use. For the latter analyses, those reporting use of less than one per week or one per week were combined into one group, resulting in categories of never, 1 or less per week, 2–5 per week, and 6 or more per week. For all such analyses, never users were modeled as the referent group. Tests for trend were carried out for each frequency of use variable by ordering the values from lowest to highest and including the resulting variable as a one degree-of-freedom linear term in a Cox proportional hazards model. We also examined combinations of the two agents, defined as follows: use of aspirin only, use of non-aspirin NSAIDs only, use of both, and use of neither. We first assessed aspirin and NSAID associations with overall breast cancer risk.

We also examined associations with risk of breast cancer as defined by subsets according to ER and PR receptor status. For these analyses, the outcome variable was incident receptor status-specific breast cancer, and all other types of breast cancer were considered censored observations at the date of diagnosis.

Statistical analyses modeling overall and hormone receptor-stratified breast cancer risk did adjust for multiple potential confounding factors, as listed in Table 2. All statistical tests were two-sided, and all analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) and S-Plus (Insightful, Inc., Seattle, WA) software systems.

Results

There were 26,580 postmenopausal women aged 59 to 77 years at the 1992 baseline in the analytic data set. During 307,178 person-years of follow-up (through 2005), 1581 incident cases of breast cancer were observed. The mean age at diagnosis of breast cancer was 74.8 years (range, 62.0 – 89.1). ER status was available for 1262 of the 1581 breast cancer cases (80%), with 1060 of these ER positive and 202 ER negative. PR status was available for 1237 cases (78%), with 910 of these PR positive and 327 PR negative. Examining combinations of receptor status, 885 cases were ER+PR+, 155 were ER+PR−, 24 were ER −PR+, and 172 were ER−PR−.

As shown in Table 1, women who regularly took NSAIDs only or both NSAIDs and aspirin had a higher BMI, history of osteoarthritis or rheumatoid arthritis, and a history of use of hormone replacement therapy; there were no striking differences for other analyzed breast cancer risk factors.

Compared with women who never used aspirin, women regularly consuming aspirin had about 20% lower risk of breast cancer, after adjusting for major breast cancer risk factors (Table 2). Higher frequency of use was associated with a lower risk of breast cancer (RR=0.71 for aspirin use 6+ times/week versus never use; 95% CI: 0.60–0.83) and this trend in frequency of use was highly statistically significant (p-trend=0.00001). Inverse associations for aspirin use (any use versus never use) were observed for ER+ (RR=0.77; 95% CI 0.67–0.89), ER− (RR=0.78; 95% CI 0.56–1.08), PR+ (RR=0.79; 95% CI 0.68–0.92), and PR− (RR=0.73; 95% CI 0.56–0.95) breast cancers, although the inverse association by frequency of use was strongest for ER+ and PR+ tumors. The latter finding was mainly due to the attenuation of the RR estimates in the highest category of intake (6+ per week) for both ER− and PR− tumors. Cross classification by receptor status again showed that point estimate of the association between aspirin and breast cancer did not vary by combination of ER and PR status (Figure 1).

There was no association with use of non-aspirin NSAIDs with risk of breast cancer (RR=0.95, 95% CI: 0.85–1.07), overall or by ER or PR status, with the possible exception of a suggestive positive trend of non-aspirin NSAIDs use and risk of PR− tumors (p-trend=0.051).

In analysis of combined use of aspirin and other NSAIDs (Table 2), lower risk of breast cancer was observed for aspirin use only (RR=0.82; 95% CI 0.70–0.95) or use of both (RR=0.77; 95% CI 0.65–0.91), but not use of other non-aspirin NSAIDs only. This pattern was fairly consistent for each of the subtypes defined by ER and PR status.

Discussion

In extended follow-up of this prospective, population-based study of postmenopausal women, aspirin use continued to be inversely associated with breast cancer incidence, and a

higher frequency of use was associated with a further lower risk. Contrary to our hypothesis, the inverse association did not vary by hormone receptor status (ER or PR) of the tumor. Non-aspirin NSAID use was not associated with breast cancer, overall or by ER or PR status. Adjustment for multiple other breast cancer risk factors did not alter these results.

The study finding of an inverse association between aspirin and breast cancer, both in our previous report [19] and in this update, is consistent with most other case-control [8–11,13–15] and cohort studies [12,20,23], although there are a few exceptions [16–18,22,24]. In a meta-analysis of 11 case-control and cohort studies, aspirin use was found to be associated with a 23% lower risk of breast cancer (95% CI: 0.69–0.86). Higher frequency (> 4 times/day) of aspirin use has also been associated with lower risk of breast cancer [28], but the data on duration of aspirin use and breast cancer is not settled. While some studies have reported that aspirin use > 5 years is associated with lower risk of breast cancer [8,11,15], a recent meta-analysis of 26 case-control and cohort studies reported no association with duration of use [28]. While most of these studies have been able to adjust for a variety of potential confounders, concerns regarding bias and confounding remain from observational studies. The Women's Health Study, a randomized, placebo-controlled clinical trial [21], did not find a protective effect of low dose aspirin (100mg) taken on alternate days with risk of breast cancer after an average 10.2 years of follow-up (RR=0.98, 95% CI: 0.89–1.08). However, the trial was not able to address whether higher frequency and dose (> 100 mg/day) of aspirin could lower risk of breast cancer, as suggested by observational studies [13,29].

In our study, the inverse association between aspirin and breast cancer did not vary by hormone receptor status (ER or PR) of the tumor. Most studies have reported no difference in results based on hormone receptor status [14,15,18,21–24], with the exception of three studies [8,11,20]. In the California Teachers Study cohort there was an increased risk of ER−/PR− (RR=1.40; 95% CI: 0.96–2.05) but not ER+/PR+ (RR=0.89; 95% CI: 0.75–1.05) tumors with daily aspirin use [8]. The increased risk of ER−/PR− tumors, which was based on 279 cases, was an unexpected finding. A large case-control study [11] found that ever aspirin use was associated with lower risk of hormone receptor positive (OR=0.74; 95% CI: 0.60–0.93 for ER+PR+, ER+PR− and ER−PR+ tumors combined), but not hormone receptor negative tumors (OR=0.97; 95% CI: 0.67–1.40 for ER−PR− tumors). However, closer examination of those regularly using aspirin (rather than just ever aspirin users) showed that the associations were less discordant for hormone receptor positive (OR=0.71; 95% CI: 0.55–0.93) and negative (OR=0.83; 95% CI: 0.52–1.32) tumors. Even more striking, the results for those using aspirin for > 5 years were nearly identical for hormone receptor positive (OR=0.80; 95% CI: 0.61–1.06) or negative (OR=0.77; 95% CI: 0.46–1.23) tumors. Finally, the AARP Diet and Health Study cohort [20] found that the beneficial effect of aspirin was stronger among ER+ tumors (RR=0.84; 95% CI: 0.71–0.98), as compared to ER− tumors (RR=1.14; 95% CI: 0.81–1.62), but the number of cases were very few in the ER− group (N=52), as compared to ER+ group (N=223), limiting the power of sub-group analysis.

Overall, our findings suggest that the inverse association between aspirin and breast cancer likely does not vary by hormone receptor status (ER or PR) of the tumor within the Iowa Women's Health Study Cohort. Recently, Holmes et al reported the association between aspirin users and breast cancer survival [30]. The authors reported that women who reported using aspirin 6 to 7 days per week had a significantly lower risk of breast cancer death as compared to no users (Hazard Ratio = 0.36, 95% CI: 0.24 to 0.54), and the association did not differ by hormone receptor status. Thus, the overall evidence supports a protective effect of aspirin on breast cancer that is similar among hormone receptor positive and negative tumors, and thus suggests that the potential mechanism of prevention is likely not directly

related to estrogen or progesterone signaling pathways, but perhaps through other pathways such as inflammation pathways. It is also possible that could be that effects of aspirin are on surrounding tissue (tumor microenvironment) and not the tumor itself.

In contrast to aspirin use, non-aspirin NSAID use was not associated with breast cancer incidence. While a few prospective studies have reported that aspirin has a stronger protective effect relative to other non-aspirin NSAIDs [8,11,20], others have reported similar benefits [14,15]. This discrepancy may be due to assessment of type of NSAID used, as unlike aspirin, there are multiple different kinds of non-aspirin NSAIDs. The meta-analysis by González-Pérez et al. [31] found that protective effect of non-aspirin NSAIDs (RR=0.86; 95% CI: 0.73–1.00) on breast cancer was weaker than that of aspirin (RR=0.77; 95% CI: 0.69–0.86), and there was significant heterogeneity in the results based on study design, population studied, and exposure assessment for the non-aspirin NSAIDs. Besides these factors, heterogeneity in the doses, types, and durations of non-aspirin NSAIDs used could also account for variations in observed results, as studies have shown that not all non-aspirin NSAIDs exert similar protective effect against breast cancer [8]. Finally, the observed differences in associations could be also due to the additional biologic effects of aspirin, such as the irreversible inhibition of COX enzymes, as compared to reversible inhibition by non-aspirin NSAIDs.

The strengths of this study include its large, prospective cohort design, ascertainment of cancer incidence using high-quality Surveillance, Epidemiology, and End Results Cancer Registry data, virtually complete follow-up for mortality, and availability of information on multiple risk and protective factors to evaluate potential confounding. The study was population-based, which enhances its external validity.

There are limitations to our data. First, our questionnaire did not assess the type, dose, or duration of aspirin or non-aspirin NSAID use, although we were able to distinguish between use of these two classes of agents, and data on frequency of use was collected. Second, information about ER/PR status of breast cancer was obtained through multiple pathological laboratories, rather than a single reference laboratory. However, SEER reporting of ER and PR status is reasonably valid [32], and the ER/PR distribution in our study was similar to that reported by other studies. Finally, the observational study design has greater potential for uncontrolled confounding than an experimental (i.e., randomized controlled trial) design. However, we did adjust for known multiple confounding variables and the results changed little, adding further strength to our observation. Finally, out results can only be directly generalized to Caucasian women with post-menopausal breast cancer.

In summary, this study suggests that aspirin use may provide chemopreventive benefit with respect to incident breast cancer in postmenopausal women. Risk reduction did not vary by ER or PR status of the tumor, suggesting that the hypothesized protective effects of aspirin might be through pathways linked to inflammation or tumor microenvironment, rather than estrogen or progesterone signaling. However, these observations require confirmation in other studies.

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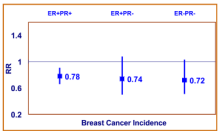

Fig. 1.
Multivariable-adjusted relative risks (RR) for aspirin use with breast cancer incidence stratified by estrogen receptor (ER) and progesterone receptor (PR) status.

Table 1

Selected demographic and breast cancer risk factors according to regular use of aspirin, NSAIDs or both, Iowa Women's Health Study (1992)

	Regular Use of Aspirin or NSAIDs			
	None (N=4,613)	**Aspirin only (N=11,472)**	**NSAIDs only (N=2,862)**	**Both (N=7,633)**
Age at baseline (1986), mean ± SD, years	68.8 ± 4.2	68.6 ± 4.2	68.3 ± 4.2	68.1 ± 4.2
Education, % greater than high school graduate	38%	41%	40%	41%
Age at menarche, mean ± SD, years	12.9 ± 1.5	12.9 ± 1.4	12.8 ± 1.5	12.8 ± 1.5
Age at menopause, mean ± SD, years	47.8 ± 6.3	48 ± 6.2	47.2 ± 6.7	47.6 ± 6.4
Body mass index in 1992, mean ± SD, kg/m^2	26.7 ± 5.0	26.6 ± 4.8	28.2 ± 5.6	27.8 ± 5.2
Body mass index at age 18, mean ± SD, kg/m^2	21.6 ± 3.0	21.5 ± 3.0	21.9 ± 3.3	21.7 ± 3.1
First degree family history of breast cancer, %	12%	12%	11%	13%
Nulliparous, %	11%	9.3%	8.1%	7.2%
3+ births and age at first live birth ≤20 years, %	20%	20%	26%	23%
Oral Contraceptive Use, % ever	17%	17%	21%	22%
Hormone therapy use, % ever	38%	41%	51%	49%
Relative weight at age 12, % above average for age and height	12%	12%	15%	15%
Osteoarthritis, % ever	11%	11%	31%	23%
Rheumatoid arthritis, % ever	7.5%	6.8%	19%	14%
Alcohol intake, % none	84%	82%	81%	80%
Ever smoker, %	28%	28%	31%	29%
Physical activity, % no regular	48%	45%	49%	46%

Table 2

Multivariable-adjusted relative risks for aspirin & other non-aspirin NSAIDs use with breast cancer incidence, overall and stratified by estrogen receptor (ER) and progesterone receptor (PR) status

	All Breast Cancer			ER +		ER−		PR+		PR−	
	Person Years	No. of Events	RR[†](95% CI)	No. of Events	RR[†](95% CI)	No. of Events	RR[†](95% CI)	No. of Events	RR[†](95% CI)	No. of Events	RR[†](95% CI)
Aspirin Use											
Never	84529	489	1.00 (reference)	331	1.00 (reference)	61	1.00 (reference)	283	1.00 (reference)	103	1.00 (reference)
Ever	222650	1092	0.80 (0.71, 0.90)	729	0.77 (0.67, 0.89)	141	0.78 (0.56, 1.08)	627	0.79 (0.68, 0.92)	224	0.73 (0.56, 0.95)
≤1/week	104210	535	0.87 (0.76, 0.99)	367	0.85 (0.72, 1.00)	62	0.78 (0.53, 1.15)	317	0.88 (0.74, 1.05)	103	0.74 (0.55, 1.01)
2–5/week	55018	268	0.78 (0.66, 0.92)	176	0.77 (0.63, 0.94)	35	0.62 (0.37, 1.03)	155	0.80 (0.64, 1.00)	52	0.61 (0.41, 0.91)
6+/week	63422	289	0.71 (0.60, 0.83)	186	0.65 (0.53, 0.79)	44	0.91 (0.59, 1.41)	155	0.64 (0.51, 0.80)	69	0.81 (0.57, 1.14)
P-trend			0.00001		0.00001		0.46		0.00005		0.11
Non-Aspirin NSAID Use											
Never	185464	948	1.00 (reference)	646	1.00 (reference)	119	1.00 (reference)	551	1.00 (reference)	194	1.00 (reference)
Ever	121715	633	0.95 (0.85, 1.07)	414	0.91 (0.79, 1.05)	83	1.16 (0.84, 1.61)	359	0.90 (0.77, 1.05)	133	1.15 (0.89, 1.48)
≤1/week	57750	275	0.90 (0.78, 1.05)	181	0.85 (0.71, 1.03)	37	1.09 (0.72, 1.64)	162	0.89 (0.73, 1.08)	53	0.96 (0.69, 1.35)
2–5/week	25057	136	1.02 (0.83, 1.25)	87	0.95 (0.74, 1.23)	22	1.50 (0.90, 2.50)	80	1.01 (0.78, 1.32)	29	1.18 (0.76, 1.84)
6+/week	38907	222	1.00 (0.84, 1.19)	146	0.97 (0.78, 1.20)	24	1.05 (0.62, 1.78)	117	0.86 (0.68, 1.09)	51	1.48 (1.02, 2.14)
P-trend			0.91		0.55		0.44		0.24		0.051
Combined Use											
Never	51950	296	1.00 (reference)	200	1.00 (reference)	42	1.00 (reference)	175	1.00 (reference)	61	1.00 (reference)
Aspirin only	133514	652	0.82 (0.70, 0.95)	446	0.83 (0.69, 0.99)	77	0.64 (0.42, 0.97)	376	0.82 (0.67, 1.00)	133	0.75 (0.53, 1.05)
NSAID only	32579	193	1.00 (0.82, 1.23)	131	1.03 (0.81, 1.32)	19	0.83 (0.46, 1.49)	108	0.97 (0.74, 1.26)	42	1.20 (0.78, 1.86)
Both	89136	440	0.77 (0.65, 0.91)	283	0.71 (0.58, 0.87)	64	0.87 (0.56, 1.34)	251	0.72 (0.58, 0.90)	91	0.85 (0.59, 1.22)

[†]Adjusted for age, education, family history of breast cancer, age at menarche, age at menopause, parity/age at first live birth, use of oral contraceptives, use of hormone therapy, body mass index in 1992, body mass index at age 18 years, relative weight at age 12, history of osteoarthritis, history of rheumatoid arthritis, smoking, use of alcohol, smoking, and physical activity level.