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ORIGINAL REPORT

Aspirin Intake and Survival After Breast Cancer

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ABSTRACT

Purpose

Animal and in vitro studies suggest that aspirin may inhibit breast cancer metastasis. We studied whether aspirin use among women with breast cancer decreased their risk of death from breast cancer.

Methods

This was a prospective observational study based on responses from 4,164 female registered nurses in the Nurses' Health Study who were diagnosed with stages I, II, or III breast cancer between 1976 and 2002 and were observed until death or June 2006, whichever came first. The main outcome was breast cancer mortality risk according to number of days per week of aspirin use (0, 1, 2 to 5, or 6 to 7 days) first assessed at least 12 months after diagnosis and updated.

Results

There were 341 breast cancer deaths. Aspirin use was associated with a decreased risk of breast cancer death. The adjusted relative risks (RRs) for 1, 2 to 5, and 6 to 7 days of aspirin use per week compared with no use were 1.07 (95% CI, 0.70 to 1.63), 0.29 (95% CI, 0.16 to 0.52), and 0.36 (95% CI, 0.24 to 0.54), respectively (test for linear trend, $P < .001$). This association did not differ appreciably by stage, menopausal status, body mass index, or estrogen receptor status. Results were similar for distant recurrence. The adjusted RRs were 0.91 (95% CI, 0.62 to 1.33), 0.40 (95% CI, 0.24 to 0.65), and 0.57 (95% CI, 0.39 to 0.82; test for trend, $P = .03$) for 1, 2 to 5, and 6 to 7 days of aspirin use, respectively.

Conclusion

Among women living at least 1 year after a breast cancer diagnosis, aspirin use was associated with a decreased risk of distant recurrence and breast cancer death.

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INTRODUCTION

Aspirin use could possibly increase survival among women with breast cancer. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit production of prostaglandins and cyclooxygenase, which comes in two isoforms (COX-1 and COX-2).

In vitro studies have shown that breast cancers produce prostaglandins in greater amounts than normal breast cells[1] and that aspirin can inhibit growth[2] and decrease the invasiveness of breast cancer cells,[3] reduce cytokines involved in bony metastasis,[2] and stimulate immune responsiveness.[4] Animal studies have shown increased COX-2 activity in metastatic breast cancer cells.[5] COX-2 knockout mice or wild-type mice treated with a NSAID had less tumor growth.[6] We hypothesized that aspirin use after diagnosis is associated with a decreased risk of breast cancer death and distant recurrence among women with stage I to III breast cancer in the Nurses' Health Study (NHS).

METHODS

Study Participants and Identification of Breast Cancer

The NHS was established in 1976 when 121,700 female registered US nurses, age 30 to 55 years, answered a mailed questionnaire on cancer and cardiovascular risk factors. We have sent questionnaires every 2 years since. Follow-up of the entire cohort's person-years is 95% complete.

For any report of breast cancer, participants gave written permission for physicians (blinded to exposure information) to review their medical records. Overall, 99% of self-reported breast cancers for which records were obtained have been confirmed. All participants in this analysis had medical record review.

The study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). We excluded women from the analysis for the following reasons: unknown birth or diagnosis date (n = 2), calculated recurrence date before 1976 (n = 3), other cancer (except nonmelanoma skin cancer) before 1976 (n = 284), death before aspirin assessment (n = 16) or recurrence

before aspirin assessment (n = 228), missing aspirin assessment (n = 2,910), first aspirin assessment more than 6 years after diagnosis (n = 119), missing stage (n = 926), stage IV disease (n = 28), and stage III disease without a metastatic work-up (n = 244). A metastatic work-up consisted of negative chest x-ray (or computed tomography), bone scan, and liver function tests (or liver scan) or physician documentation of no metastatic disease.

Exposure Assessment

Aspirin use was first assessed in 1980 and every 2 years thereafter except 1986. Aspirin use in 1984 was carried forward for 1986. Days per week of use were available as predetermined questionnaire categories. Aspirin use was then analyzed as regular use in the past 2 years according to the following categories: never, past, and current 1, 2 to 5, and 6 to 7 days per week. Past use was calculated as use after breast cancer diagnosis that was subsequently stopped. For each woman, aspirin use was first assessed using the questionnaire that occurred after the questionnaire in which the participant reported her breast cancer diagnosis and subsequently updated until end of follow-up. Duration (total number of years of aspirin use) was used in a time-dependent model and was carried forward to replace missing information for a maximum of two cycles; if duration was missing for three cycles in a row, it became permanently missing. Missing duration of aspirin use was entered as a separate category into analyses of duration. Questionnaires asked about aspirin use in the last 2 years, and we avoided aspirin use assessments during the first 12 months after diagnosis because aspirin is discouraged during chemotherapy. For example, for women diagnosed between 1976 and 1977, the 1980 questionnaire was used as the baseline aspirin assessment. For women diagnosed between 1977 and 1979, the 1982 questionnaire was used as the baseline aspirin assessment and so forth.

In 1999, a supplemental questionnaire was sent to analgesic users that asked a series of questions about the reason for aspirin use. For each question, the range of women using aspirin for that reason could be between 0% and 100%, and each question was independent of the others. Reasons for use among 3,876 women were heart disease prevention (35%), muscle or joint pain (16%), headache (13%), backache (7%), menstrual cramps (< 1%), and other reasons (9%). In a secondary analysis, we assessed the association of breast cancer death with NSAID and acetaminophen use, which was first assessed in 1990 in a similar fashion to aspirin.

End Points: Breast Cancer Death and Distant Recurrence

Deaths were reported by the family or post office. Nonresponders were searched in the National Death Index. More than 98% of deaths in the NHS have been identified by these methods. Physician reviewers blinded to exposure information ascertained cause of death from death certificates, which were supplemented with medical records if necessary. We also assessed distant breast cancer recurrence (Appendix, online only).

Numbers of patients with recurrent breast cancer calculated with these methods are similar to those found in a large (N = 5,569) radiation treatment trial in early-stage breast cancer.[7] In a sensitivity analysis, we also considered patients to have experienced recurrence 4 years before death.

Covariates

Covariates, including stage, diet, physical activity, body mass index (BMI), weight change, and reproductive factors, were those previously associated with breast cancer survival in this cohort. We also adjusted for treatment (chemotherapy, radiation, and hormonal therapy). We adjusted for smoking because it is associated with total mortality. We adjusted for calendar year to account for secular trends. Please see the Appendix for further description of covariate assessment.

Categories were created for missing data. Simple models were stratified for time since diagnosis (in months) and adjusted for age. Multivariate models were stratified for time since diagnosis and adjusted for age, calendar year, smoking status, BMI, age at first birth and parity, oral contraceptive use, menopausal status and use of hormone replacement, disease stage, treatment, protein and energy intake, physical activity, and weight change.

Statistical Analysis

Cox proportional hazards models with time since diagnosis in months as the underlying time variable were used to calculate relative risks (RRs) and 95% CIs. This means that each event was compared only with the risk set of participants who were at exactly the same time since diagnosis measured in months, providing for tight control of confounding by time since diagnosis. In these left-truncated Cox regression models, follow-up begins at the time of the first aspirin assessment after diagnosis (the baseline assessment for this study) and ends at death or June 2006, whichever occurred first. Aspirin use was entered as a time-varying covariate with records for each 2-year period. In the

Table 1. Age-Standardized Clinical Characteristics of 4,164 Women With Breast Cancer by Baseline Aspirin Use After Diagnosis

Characteristic	Aspirin Use				
	Never	Past	Current, 1 Day a Week	Current, 2 to 5 Days a Week	Current, 6 to 7 Days a Week
No. of person-years*	5,707	17,450	4,921	4,902	11,416
No. of breast cancer deaths*	56	173	44	16	49
Mean body mass index at diagnosis, kg/m^2	25.3	26.0	25.0	25.2	26.3
Mean total energy intake after treatment, kcal/d	1,613	1,713	1,705	1,716	1,694
Mean protein intake after treatment, g/d	74.1	74.0	74.5	74.1	74.6
Mean physical activity after treatment, MET-hours/wk	15.4	16.1	16.8	16.2	15.6
Mean parity, No. of children	2.9	2.9	3.0	2.9	2.9
Current smoker at diagnosis, %	16	14	20	19	17
Ever used oral contraceptives, %	37	49	38	41	45
Current users of postmenopausal hormones, %	31	42	31	38	42
Disease stage, %					
I	58	59	62	61	61
II	35	35	33	35	35
III	6	7	6	5	4
Estrogen receptor positive, %	81	81	79	76	80
Treatment, %					
Radiation	48	55	40	49	53
Chemotherapy	38	41	34	35	39
Tamoxifen or aromatase inhibitor	68	70	58	64	72
Gained weight after treatment (> 0.5 kg/m^2), %	45	47	48	50	46

*In the total population, there were 45,139 person-years and 341 breast cancer deaths; in the category of current aspirin use of unknown frequency, there were 744 person-years and three breast cancer deaths.

Table 2. Relative Risk of Breast Cancer Death According to Aspirin Intake

Factor	All Women		Aspirin Intake: None				Aspirin Intake: Past			
	No. of Person-Years*	No. of Deaths*	No. of Person-Years	No. of Deaths	Relative Risk	95% CI	No. of Person-Years	No. of Deaths	Relative Risk	95% CI
All women	45,139	341	5,707	56			17,450	173		
Simple model					1.00	—			0.85	0.62 to 1.15
Multivariate model					1.00	—			0.88	0.64 to 1.22
Multivariate model										
Stage I	26,130	111	3,133	16	1.00	—	9,914	54	0.84	0.46 to 1.55
Stage II	16,240	169	2,211	33	1.00	—	6,295	82	0.76	0.48 to 1.21
Stage III	2,769	61	363	7	1.00	—	1,241	37	0.76	0.17 to 3.38
Premenopausal	12,898	107	1,809	16	1.00	—	5,058	60	1.05	0.55 to 2.04
Postmenopausal	28,525	218	3,145	31	1.00	—	11,001	109	0.93	0.60 to 1.43
Body mass index < 25 kg/m^2	26,568	198	3,623	36	1.00	—	10,072	97	0.78	0.51 to 1.20
Body mass index ≥ 25 kg/m^2	18,571	143	2,084	20	1.00	—	7,378	76	1.05	0.59 to 1.87
Estrogen receptor positive	28,039	231	3,427	37	1.00	—	11,156	119	0.93	0.61 to 1.42
Estrogen receptor negative	7,740	49	861	8	1.00	—	2,931	21	0.94	0.27 to 3.26

(continued on following page)

main analysis, death from breast cancer was the end point, and deaths from other causes were censored. In a secondary analysis, distant breast cancer recurrence was the end point, and deaths from non–breast cancer causes were censored. Another analysis used death from any cause as the end point. After the baseline aspirin assessment, if a woman failed to report aspirin use, her use at the previous interval was carried forward. In an alternative analysis, aspirin use was carried forward for no more than one interval and then censored if it continued to be missing. If a participant indicated current aspirin use but did not indicate frequency of use, she was categorized as a current user of aspirin of unknown frequency.

RRs and 95% CIs are shown for categories of aspirin use, with never use being the reference. The two-tailed *P* value for the linear trend test across categories of current use (with past use entered as a separate term) was calculated by assigning the median value to each category. Interaction terms were calculated by multiplying the two risk factors and entering these into the relevant models, and likelihood ratio tests were used to assess their statistical significance.

Women who develop recurrent disease are likely to be treated with chemotherapy and told not to take aspirin. This may bias results in favor of a beneficial aspirin effect. The converse may also be true because women experiencing pain may take aspirin. We coped with this potential bias in several ways. First, we adjusted for treatment. Second, we performed analyses with distant recurrence as the end point.

Furthermore, time-varying indicators of disease severity (beyond stage at diagnosis) may be both risk factors for outcomes and determinants of changes in aspirin use during follow-up. For example, women whose breast cancer worsens may increase aspirin use because of symptoms or decrease use because it interferes with treatment. However, aspirin use itself may influence whether the disease worsens. In this case, standard Cox models may lead to biased estimates, whether one does or does not adjust for the potential time-dependent confounders.[8] Therefore, we used marginal structural Cox models, which appropriately adjust for measured time-dependent confounding. The parameters of marginal structural models were estimated by inverse probability weights at the current time interval, given information available up to that time.[9-11] In previous applications, marginal structural models have yielded effect estimates close to those from randomized trials.[12,13] Cook et al[14] used these methods to determine the effect of aspirin on cardiovascular mortality.

RESULTS

Among 4,164 participants for whom aspirin was assessed after breast cancer diagnosis, there were 341 breast cancer deaths, 400 distant recurrences (including the 341 breast cancer deaths), and 732 deaths from any cause. In total, 2,910 women diagnosed with breast cancer (33%) never provided an aspirin assessment after diagnosis. In general, women missing baseline aspirin assessment and women excluded for other reasons were similar to women included in the analysis in terms of age at diagnosis, BMI, dietary intake, and treatment (data not shown).

The median interval between date of diagnosis and first aspirin assessment was 48 months. Age-standardized characteristics at time of baseline aspirin assessment are listed in Table 1. Most covariates associated with survival did not have any consistent associations across aspirin use categories.

The results for simple and multivariate analyses of updated aspirin intake and breast cancer death are listed in Table 2. In addition, Table 2 includes simple and multivariate results stratified by stage at diagnosis, menopausal status, BMI, and estrogen receptor (ER) status. Aspirin use was associated with a decreased risk of breast cancer death. Relative to never aspirin users, the multivariate adjusted RRs were 0.88 (95% CI, 0.64 to 1.22), 1.07 (95% CI, 0.70 to 1.63), 0.29 (95% CI, 0.16 to 0.52), and 0.36 (95% CI, 0.24 to 0.54; test for trend, $P < .001$) for past, current 1 day per week, current 2 to 5 days per week, and current 6 to 7 days per week of use, respectively. Simple models adjusted for time since diagnosis and age were similar. Results did not differ appreciably when stratified by stage, BMI, menopausal status, or ER status. An analysis using only the first 10 years after diagnosis and an analysis that began more than 10 years after diagnosis each gave similar results (data not shown). Likewise, an analysis that carried forward aspirin use for no more than one cycle to cover missing use gave similar results

Table 2. Relative Risk of Breast Cancer Death According to Aspirin Intake (continued)

Factor	Aspirin Intake: Current, 1 Day a Week — No. of Person-Years	No. of Deaths	Relative Risk	95% CI	Current, 2 to 5 Days a Week — No. of Person-Years	No. of Deaths	Relative Risk	95% CI	Current, 6 to 7 Days a Week — No. of Person-Years	No. of Deaths	Relative Risk	95% CI	*P* (linear trend)†	*P* (interaction)
All women	4,921	44			4,902	16			11,416	49				
Simple model			1.04	0.70 to 1.55			0.27	0.15 to 0.47			0.31	0.21 to 0.46	< .001	
Multivariate model			1.07	0.70 to 1.63			0.29	0.16 to 0.52			0.36	0.24 to 0.54	< .001	
Multivariate model														
Stage I	2,688	21	1.62	0.79 to 3.32	2,764	4	0.20	0.07 to 0.63	7,631	16	0.26	0.12 to 0.56	< .001	
Stage II	1,874	20	0.77	0.42 to 1.43	1,895	7	0.17	0.07 to 0.42	3,965	27	0.36	0.20 to 0.64	.08	
Stage III	360	3	0.35	0.03 to 3.80	243	5	0.20	0.02 to 2.16	563	9	0.54	0.12 to 2.39	.74	.47
Premenopausal	2,222	18	1.00	0.45 to 2.19	1,631	3	0.16	0.04 to 0.57	2,178	10	0.30	0.12 to 0.76	.01	
Postmenopausal	2,311	24	1.36	0.76 to 2.44	2,841	13	0.42	0.21 to 0.85	9,226	41	0.43	0.26 to 0.71	< .001	.28
Body mass index < 25 kg/m^2	3,276	27	0.86	0.50 to 1.47	3,238	8	0.19	0.09 to 0.42	6,359	30	0.35	0.20 to 0.60	.02	
Body mass index ≥ 25 kg/m^2	1,646	17	1.71	0.80 to 3.67	1,663	8	0.46	0.18 to 1.15	5,800	22	0.35	0.17 to 0.70	< .001	.07
Estrogen receptor positive	2,637	25	1.04	0.59 to 1.81	2,966	10	0.32	0.15 to 0.66	7,853	40	0.42	0.26 to 0.69	.006	
Estrogen receptor negative	860	8	1.89	0.39 to 9.24	970	4	0.33	0.06 to 1.78	2,118	8	0.29	0.06 to 1.29	.03	.52

NOTE. The simple model is adjusted for time since diagnosis (by stratification) and age at diagnosis (in the model). Multivariate models are adjusted for the following factors at the time of diagnosis: age (continuous), calendar year, smoking status (never, current, or past), body mass index (< 21, 21 to 22.9, 23 to 24.9, 25 to 28.9, or ≥ 29 kg/m^2), age at first birth and parity (nulliparous, < 25 years and one to two births, < 25 years and ≥ three births, ≥ 25 years and one to two births, or ≥ 25 years and ≥ three births), oral contraceptive use (never or ever), menopausal status and use of hormone replacement (premenopausal, unknown, postmenopausal never user, postmenopausal past user, or postmenopausal current user), disease stage (I, II, or III), radiation treatment (yes or no), and systemic treatment with chemotherapy and/or hormonal therapy (chemotherapy no and hormonal therapy no, chemotherapy yes and hormonal therapy no, chemotherapy no and hormonal therapy yes, or chemotherapy yes and hormonal therapy yes). Multivariate models are additionally adjusted for the following factors after diagnosis and treatment: protein and energy intake (quintiles), physical activity (quintiles), weight change (loss ≥ 0.5 kg/m^2, gain ≥ 0.5 kg/m^2, or maintained weight), and current use of aspirin of unknown frequency (yes or no). Stratified analyses are multivariate adjusted.

*The sums of the Nos. of deaths and person-years across categories of aspirin intake shown do not add up to the total No. of deaths and person years because models were additionally adjusted for current aspirin use of unknown quantity (results not shown), which represented < 2% of the total person-years, in the main analyses. In the stratified analyses, current aspirin use of unknown quantity was categorized with current aspirin use 6 to 7 days a week.

†*P* value for linear trend is across categories of current aspirin use of known frequency.

(data not shown). There was an attenuated association for first aspirin assessment after breast cancer diagnosis (baseline). The multivariate adjusted RRs were 0.90 (95% CI, 0.64 to 1.25), 0.85 (95% CI, 0.60 to 1.20), 0.93 (95% CI, 0.63 to 1.38), and 0.68 (95% CI, 0.45 to 1.02; test for trend, $P = .30$) for past, current 1 day per week, current 2 to 5 days per week, and current 6 to 7 days per week of use, respectively.

Results with distant recurrence as the outcome were similar to results for breast cancer death (Table 3). Also, sensitivity analyses varying the definition of time of distant recurrence for patients who died showed no difference.

To apply marginal structural Cox models, we first estimated that the RR of dichotomous aspirin use (yes or no) in relation to breast

Table 3. Relative Risk of Breast Cancer Recurrence, According to Aspirin Intake

Model	All Women	Aspirin Intake: None	Past	Current, 1 Day a Week	Current, 2 to 5 Days a Week	Current, 6 to 7 Days a Week	*P* (linear trend)*
Person-years†	44,177	5,521	16,963	4,814	4,847	11,240	
Recurrences†	400	65	191	53	21	67	
Simple model							.0002
Relative risk		1.00	0.89	1.00	0.35	0.44	
95% CI			0.67 to 1.19	0.69 to 1.44	0.21 to 0.58	0.31 to 0.63	
Multivariate model							.03
Relative risk		1.00	1.03	0.91	0.40	0.57	
95% CI			0.76 to 1.39	0.62 to 1.33	0.24 to 0.65	0.39 to 0.82	

NOTE. Adjusted for the same factors as described in the footnotes of Table 2.

**P* value for linear trend is across categories of current aspirin use of known frequency.

†The sums of the Nos. of deaths and person-years across categories of aspirin intake shown do not add up to the total No. of deaths and person years because models were additionally adjusted for current aspirin use of unknown quantity (results not shown), which represented < 2% of the total person-years, in the main analyses. In the stratified analyses, current aspirin use of unknown quantity was categorized with current aspirin use 6 to 7 days a week.

cancer mortality was 0.51 (95% CI, 0.41 to 0.65). Using marginal structural models to account for potential confounding as a result of changing disease severity over time, results did not change substantially (RR = 0.53; 95% CI, 0.40 to 0.70). This provides assurance that updating the aspirin exposure and time-dependent covariates did not bias results in favor of aspirin. A 5-year duration of use (past and current) was associated with a small reduction in multivariate adjusted risk of breast cancer death (RR = 0.95; 95% CI, 0.90 to 1.00).

Aspirin use was also associated with a decreased risk of death from any cause. The multivariate RRs for overall mortality were 0.96 (95% CI, 0.76 to 1.21), 0.94 (95% CI, 0.67 to 1.32), 0.53 (95% CI, 0.37 to 0.76), and 0.54 (95% CI, 0.41 to 0.70; test for trend, $P = .004$) for past, current 1 day per week, current 2 to 5 days per week, and current 6 to 7 days per week of use, respectively; however, there was no clear evidence of a protective association for aspirin use with non–breast cancer deaths, with multivariate RRs of 1.03 (95% CI, 0.70 to 1.53), 0.45 (95% CI, 0.22 to 0.94), 0.69 (95% CI, 0.40 to 1.19), and 0.61 (95% CI, 0.40 to 0.93; test for trend $P = .65$), respectively. Therefore, the protective effect associated with aspirin seems driven by the impact on breast cancer death.

There were 10 fewer years of follow-up for nonaspirin NSAID and acetaminophen assessment and fewer breast cancer deaths (122 and 124 deaths, respectively), limiting statistical power. However, there was a suggestion of a protective association with NSAID intake but none for acetaminophen. Compared with no use or past use, the RRs for breast cancer mortality for current use of 1 day per week, 2 to 5 days per week, and 6 to 7 days per week were 1.03 (95% CI, 0.43 to 2.43), 1.17 (95% CI, 0.61 to 2.24), 0.52 (95% CI, 0.30 to 0.88; test for trend, $P = .04$), respectively, for NSAIDs and 2.40 (95% CI, 1.22 to 4.71), 1.28 (95% CI, 0.72 to 2.27), 1.44 (95% CI, 0.81 to 2.57; test for trend, $P = .17$), respectively, for acetaminophen.

DISCUSSION

We found that aspirin use after a breast cancer diagnosis was associated with a decreased risk of distant recurrence, breast cancer death, and death from any cause. This is all the more notable because the NHS did not find an association between aspirin use and breast cancer incidence.[15] We speculate that the association was stronger with breast cancer death than with recurrence because recurrence is more likely to be misclassified than death. We found a modest association with duration of aspirin use. Aspirin may influence proximal rather than distal events in the cancer pathway.

Of several large prospective studies of the association of aspirin use with breast cancer incidence, only one found a protective association,[16] whereas four others did not.[17-20] The 10-year Women's Health Study Trial found no effect of low-dose aspirin intake (100 mg every other day) on breast cancer incidence among almost 40,000 women.[21] However, meta-analyses of either NSAID or aspirin use have found a 9% to 30% reduced risk of breast cancer incidence.[22-25]

Despite inconclusive evidence linking aspirin and breast cancer incidence, aspirin may improve survival through various mechanisms. NSAIDs, including aspirin, may lower serum estradiol. A cross-sectional study of 260 postmenopausal women reported lower adjusted geometric mean estradiol levels among NSAID users versus nonusers (17.8 *v* 21.3 pmol/L, respectively; $P = .03$).[26] Aspirin and other NSAIDs may affect hormone receptor–negative tumors as well. Elevated tissue levels of prostaglandins were noted in ER-negative and progesterone receptor–negative tumors more than 20 years ago.[27] Aspirin may prevent early metastasis because COX-2 overexpression has been associated with metastatic animal[5] and human breast cancer.[28]

Until recently, there has been little direct evidence regarding the effect of aspirin and other NSAIDs on survival after breast cancer in humans. Early trials since the 1980s of NSAIDs to treat advanced or metastatic breast cancer showed little effect.[29-31] However, aspirin and NSAIDs may still have a role in preventing metastasis.[32]

Our results are consistent with two other studies reported in 2007. Kwan et al[33] reported on NSAID use and recurrence among 2,292 women with early-stage breast cancer. They found a reduced risk of recurrence for current regular ($\geq$ 3 days per week) use of ibuprofen (RR = 0.56; 95% CI, 0.32 to 0.98) but not aspirin (RR = 1.09; 95% CI, 0.74 to 1.61); short follow-up (5 years) may have precluded detecting an association. Blair et al[34] reported a borderline reduced risk of breast cancer death (RR = 0.64; 95% CI, 0.39 to 1.05) for any use of NSAIDs after diagnosis among 591 postmenopausal women with breast cancer in the Iowa Women's Health Study. In that study, aspirin and nonaspirin NSAID use was combined, but use of aspirin only (43%) was considerably more common than use of nonaspirin NSAIDs only (10%) or use of both (27%).

Despite low power, our results were suggestive for a protective association with NSAID use. The lack of association with acetaminophen suggests that the associations seen with aspirin and NSAIDs may represent biologically plausible effects and not just confounding by indication.

Limitations of our study include the following. Information on aspirin intake, treatment, and distant recurrence was self-reported. However, we believe our frequent updating improves accuracy. We lack details on aspirin dose. If there is a dose response, the effect size in the current study may be diminished because frequent aspirin users may be more likely to be low-dose users attempting to prevent heart disease. Confounding is always a limitation of observational studies. We addressed this by adjusting for all relevant covariates and through marginal structural models.

Our results may be generalizable only to longer term breast cancer survivors (ie, only women who have lived long enough after diagnosis to report aspirin use after diagnosis, which is approximately 4 years). Fortunately, almost 90% of women diagnosed with breast cancer live at least 5 years.[35] Thus, our findings have considerable clinical importance.

Strengths of our study include the prospective design, large size, and long duration. We have repeated measures of aspirin intake. We used novel statistical techniques to adjust for potential bias introduced by the changing severity of disease affecting aspirin intake over time.

To our knowledge, this is the first study reporting a survival advantage among women with breast cancer who take aspirin. Abundant scientific evidence supports why aspirin may confer this advantage. More than 2 million US women are living after a breast cancer diagnosis.[36] Survival among women with breast cancer is variable, and risks of dying of the disease are elevated even 10 or 15 years after diagnosis.[37] Aspirin has relatively benign adverse effects compared with cancer chemotherapeutic drugs and may also prevent colon cancer,[38] cardiovascular disease,[39] and stroke.[40] Aspirin seems to affect both ER-positive and -negative tumors.

The ability to affect length and quality of life after breast cancer by a common medication would be welcome. Further studies are needed to determine the possible mechanism of aspirin's action, including perhaps ultimately, a randomized trial of aspirin use after breast cancer diagnosis with survival as the end point. If confirmed, our results may broaden the scope of interventions available to reduce breast cancer–related morbidity and mortality.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Michelle D. Holmes, Wendy Y. Chen, Lisa Li, Ellen Hertzmark, Donna Spiegelman, Susan E. Hankinson
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