Research Article

Cancer Epidemiology, Biomarkers & Prevention

De Novo Post-Diagnosis Aspirin Use and Mortality in Women with Stage I–III Breast Cancer

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Abstract

Background: Aspirin use has been associated with significant reductions in breast cancer–related mortality in some observational studies. However, these studies included women who initiated aspirin use before breast cancer diagnosis. It is unclear whether initiating aspirin use after diagnosis is associated with similar reductions in mortality. This study investigates associations between *de novo* post-diagnostic aspirin use and all cause, breast cancer–specific mortality.

Methods: Women, ages 50 to 80, with a diagnosis of stage I–III breast cancer were identified from Ireland's National Cancer Registry ($N = 4{,}540$). Initiation of *de novo* post-diagnostic aspirin use was identified from linked national prescription refill data ($N = 764$). Adjusted HRs were estimated for associations between *de novo* aspirin use and all-cause, breast cancer–specific mortality.

Results: The median time from diagnosis to aspirin initiation was 1.8 years. The mean number of days' supply of aspirin received was 631, and 95% of users were taking less than 150 mg/d. We found no association between *de novo* aspirin use and breast cancer–specific mortality [HR, 0.98; 95% confidence interval (CI), 0.74–1.30]. Similar null associations were found in women taking aspirin at high-intensity (HR, 1.03; 95% CI, 0.72–1.47) and women initiating use in the 1.5 years after diagnosis (HR, 1.04; 95% CI, 0.77–1.40). There was no effect modification by estrogen ($P_{\text{interaction}} = 0.81$) or progesterone ($P_{\text{interaction}} = 0.41$) receptor status.

Conclusion: Initiating aspirin use after a breast cancer diagnosis was not associated with a reduction in breast cancer–specific mortality.

Impact: On the basis of our findings, we suggest that a clearer understanding of aspirin's mechanism of action is needed to help inform the design of future studies in breast cancer. *Cancer Epidemiol Biomarkers Prev; 24(6); 898–904. ©2015 AACR.*

Introduction

The use of aspirin, a COX −1/−2 inhibitor, was associated with significant reductions in the risk of cancer-related mortality in recent meta-analyses of randomized trials for cardiovascular disease prevention (1, 2). Randomization to aspirin use was associated with a 40% reduction in the risk of developing distant metastasis after diagnosis and a 15% reduction in the risk of a cancer-related death, suggesting a potential therapeutic role for aspirin in some cancers (1, 2) In women with breast cancer, aspirin use was associated with nonsignificant reductions in the risk of developing metastasis and death (2). Of note, aspirin use was initiated before cancer diagnosis in these studies, and it is plausible that some of the observed benefit is attributable to prediagnostic use (3, 4). It is unclear whether mortality is reduced in patients starting aspirin *de novo* after a cancer is diagnosed.

In breast cancer, a number of observational studies have examined associations between aspirin use and disease recurrence or death (4–12), with three reporting statistically significant reductions in breast cancer–related mortality (5–7). Most of these studies included women taking aspirin before their breast cancer diagnosis and did not distinguish between pre- and post-diagnostic initiation of exposure in their analyses (5–9). Only two previous studies have examined associations between *de novo* post-diagnostic aspirin use and breast cancer outcomes (11, 12). In these, no association was observed between aspirin use initiated after diagnosis and breast cancer outcomes. However, these analyses were limited by either small numbers of *de novo* aspirin users ($N = 148$; ref. 11), or did not adjust for tumor stage (12).

In this study, we aimed to investigate, in a large national cancer registry and prescribing database, associations between *de novo* aspirin use, initiated after a breast cancer diagnosis, and both all-cause and breast cancer–specific mortality. We also evaluated effect modification by tumor characteristics at diagnosis.

Materials and Methods

Setting and data sources

The study was conducted using individual-level patient records from the National Cancer Registry Ireland (NCRI), which were linked to prescription dispensing data from Ireland's Primary Care Reimbursement Services (PCRS) pharmacy claims database. These linked data have been described previously (13). The NCRI database records information collected by trained hospital-based tumor registration officers on all incident cancers diagnosed in the

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population usually resident in Ireland. Completeness of registration is estimated to be at least 97% overall, and higher for breast cancer (14). The use for research of anonymized data held by the NCRI is covered by the Health (Provision of Information) Act 1997. The PCRS database records claims from pharmacies for financial reimbursement of medications dispensed through the General Medical Services (GMS) scheme. The GMS scheme provides universal healthcare, including free medications, to approximately one third (1.4 million) of the Irish population. This includes most high-dose aspirin preparations and all low-dose aspirin preparations, which are prescription-only in Ireland as in some other European countries (15). A small number of high-dose aspirin preparations are available to purchase without prescription, but only for specified short-term indications and in small pack sizes ($\leq$24–50 doses). Women with GMS eligibility can obtain these—and all other—high-dose aspirin preparations on-prescription without charge or restriction. Eligibility for the GMS scheme is assessed by a combination of means–test and age. The GMS population is, therefore, older and more socioeconomically deprived than the full Irish population.

Cohort and exposure definitions

Women not receiving aspirin before their breast cancer diagnosis were identified within the linked NCRI-PCRS database. Specifically, the study population was defined as all women with a diagnosis of stage I–III invasive breast cancer (ICD-10 C50; ref. 16) between January 1, 2001 and December 31, 2011, ages 50 to 80 years at diagnosis and with GMS eligibility starting at least 1 year before diagnosis. The lower age limit was set at 50 years to exclude women unlikely to be prescribed aspirin. Women over the age of 80 years were excluded as they are less likely to receive definitive breast cancer staging or treatment (17). Women were also excluded if they had a prior invasive cancer other than nonmelanoma skin cancer or if their cancer diagnosis was made at the time of death. We identified all prescriptions for aspirin (WHO-ATC drug classifications; Supplementary Table S1; ref. 18) dispensed in the year before breast cancer diagnosis, and women with aspirin use during this time were excluded. Within the remaining women, we identified *de novo* post-diagnostic aspirin exposure from prescriptions dispensed between breast cancer diagnosis and the end of follow-up (date of death or December 31, 2012, whichever occurred first). The number of days' supply on each prescription was used to calculate aspirin dosing intensity (in the previous 6 months), for each day of follow-up. These longitudinal aspirin exposure histories were used to define aspirin exposures as follows. First, women were identified as exposed (yes/no) from the date they received their first aspirin prescription. Second, within this group of aspirin users women were identified as having high-intensity exposure (yes/no) from the first date they had taken aspirin at an intensity of $\geq$80% for longer than 6 consecutive months. In addition, a landmark analysis was conducted in which women were identified as exposed (yes/no) if they started *de novo* aspirin use in the 1.5 years after their breast cancer diagnosis. Once allocated to an exposure category, women remained in this category to the end of follow-up.

Outcomes and covariates

We identified the date and cause of death (all-cause or breast cancer-specific) from death certificate information. Breast cancer–specific deaths were categorized using previously published SEER definitions (Supplementary Table S1; ref. 19); women who died from other causes were censored at the date of death. The following patient, tumor and treatment characteristics were abstracted from the NCRI database: age at diagnosis (years); smoking status at diagnosis (never, past, current, and unspecified); tumor stage (I, IIa, IIb, IIIa, and IIIb-c; ref. 16); tumor grade (low, intermediate, high, and unspecified); estrogen (ER), progesterone (PR), and HER2 receptor status (positive, negative, and unspecified; Supplementary Table S1); and receipt of chemotherapy (yes or no) in the year after diagnosis. Anti-estrogen therapy starting in the year after diagnosis (yes or no; Supplementary Table S1) was identified using PCRS prescription data. The PCRS database was also used to identify exposures to other potentially relevant medication in the year before diagnosis (exposed and unexposed; Supplementary Table S1). These were lipophilic statins, hydrophilic statins, bisphosphonates, antidiabetics, and other NSAIDs. The number of medication classes (WHO-ATC classification, fourth level, chemical subgroup) dispensed in the year before breast cancer diagnosis was used as a measure of comorbidity (20).

Statistical analysis

All analyses were conducted using SAS v9.3 (SAS Institute Inc.) and results were considered statistically significant at a two-sided α-level of 0.05. We tabulated the proportion of *de novo* post-diagnostic aspirin users, and compared differences in the rates of post-diagnostic aspirin initiation across baseline sociodemographic and clinical covariates by univariate Poisson regression. For women with *de novo* post-diagnostic aspirin exposure we estimated the median duration of aspirin use from first to last exposure using Kaplan–Meier analysis with censoring at death or end of follow-up (minus exposure lag time). We also calculated the number of day's supply of aspirin received during follow-up and the exposure intensity while on treatment (number of day's supply received divided by number of days from first to last exposure). Person time was calculated from the date of breast cancer diagnosis to the end of follow-up.

Adjusted HRs with 95% confidence intervals (CI) for associations between *de novo* aspirin use and breast cancer–specific and all-cause mortality were estimated using multivariate Cox models. Aspirin exposure was included in survival analyses as a time-varying covariate. Patients were identified as exposed (yes/no) from the time they received their first aspirin prescription plus a lag time. Exposures were lagged to reduce the possibility that changing prognosis influenced the probability of receiving aspirin. There are no data to indicate what the appropriate lag time should be for post-diagnostic exposures in analyses of breast cancer–specific mortality. The exposure lag was, therefore, set at 2 years, the median survival time after a breast cancer recurrence (21) and varied in sensitivity analyses (0, 1, 3, and 4 years).

We used prior knowledge of predictors of breast cancer–specific mortality to select covariates for inclusion in multivariate models. The variables included in the models were clinical and demographic characteristics (tumor stage; tumor grade; ER, PR, and HER2 status; primary treatment with chemotherapy or hormonal therapy; comorbidity-score; age); coprescribed medications (hydrophilic statins, lipophilic statins, bisphosphonates, and other NSAIDS); and the presence of specific comorbidities (diabetes, defined by receipt of an antidiabetic medication). Effect modification by baseline tumor characteristics was evaluated with the inclusion of an interaction term in the multivariate model.

Tumor characteristics previously associated with COX-2 expression were considered as potential effect modifiers (tumor size, lymph node metastasis, and ER and PR status; ref. 22).

We also conducted analyses stratified by aspirin dosing intensity (high/low). *De novo* aspirin users were identified as having high-intensity exposure if they had taken aspirin at an intensity of ≥80% for longer than 6 consecutive months (time varying, lagged by 2 years; ref. 5). Finally, we repeated analyses using a landmark approach (23) to simulate a clinically relevant scenario of adjuvant aspirin use initiated shortly after diagnosis. In this analysis, patients were identified as exposed (yes/no) if they started *de novo* aspirin use in the 1.5 years after their breast cancer diagnosis, and survival analyses were conducted with follow-up beginning at 2 years after diagnosis. Sensitivity analyses were also undertaken using a stricter definition of *de novo* aspirin use, in which the study population was restricted to those without prediagnostic aspirin exposure for at least 3 years before diagnosis (2).

We conducted two *post hoc* analyses to further explore the influence of longer-term, high-intensity *de novo* aspirin use on breast cancer outcomes. In the first of these, we defined *de novo* aspirin users as having high-intensity exposure from the first date they had taken aspirin at an intensity of ≥80% for longer than 2 consecutive years. Second, we conducted an analysis of cumulative average intensity of aspirin exposure because diagnosis (0, <50%, ≥50%) as a daily time varying covariate. Exposures were lagged by 2 years in both of these analyses.

Results

Cohort characteristics

We identified 4,540 women from the linked PCRS-NCRI database with a diagnosis of stage I–III breast cancer between the ages of 50 and 80, who were not taking aspirin before their diagnosis (Fig. 1). All women had eligibility for the GMS scheme from at least 1 year before their diagnosis, and 97.6% of women maintained continuous eligibility to the end of follow-up. The median post-diagnostic follow-up was 5.2 years.

From this cohort, we identified 764 (16.8%) women who initiated *de novo* aspirin use after diagnosis. The overall rate of post-diagnostic aspirin initiation was 35.9 *de novo* users per thousand patient years and the median time from diagnosis to initiation of aspirin was 652 days. More than 95% of aspirin users were prescribed once daily low-dose aspirin, and the median duration of post-diagnosis aspirin exposure was 1,802 days. The mean number of days' supply of aspirin received after diagnosis was 631 and the mean on-treatment exposure intensity was 86%. The characteristics of *de novo* aspirin users and non-users are presented in Table 1. The rate of aspirin initiation was higher in older women, and women with a higher baseline comorbidity score, a history of diabetes or prior NSAID use. Women with stage IIa tumors were also more likely to initiate aspirin use. The amount of person time attributed to *de novo* aspirin users and non-users was 2,302 years and 12,680 years, respectively.

Aspirin and mortality

In multivariate survival analyses, adjusted for clinical and demographic characteristics, coprescribed medications and comorbidities, we found no association between *de novo* post-diagnostic aspirin use and breast cancer–specific mortality (Table 2). These results were unchanged in sensitivity analyses varying the exposure lag time from 0 to 4 years (Table 3), and in analyses

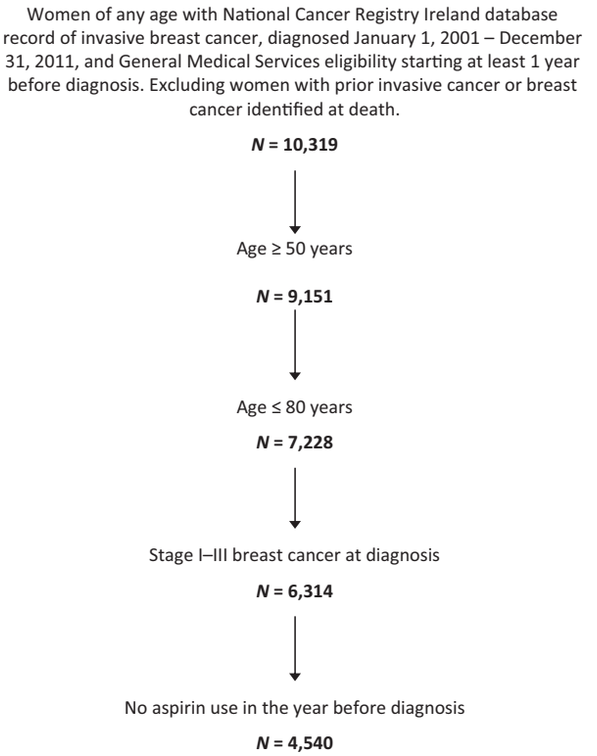

Figure 1.
Flow chart for study cohort inclusion and exclusion criteria.

restricted to the subset of women ($N = 3,578$) without aspirin exposure for at least 3 years before diagnosis (Table 3). Our results were similar for all-cause mortality, except that 0 and 1 year lagged models showed a higher risk of all-cause mortality in *de novo* aspirin users, consistent with increasing use of aspirin in the final years of life (reverse causation).

In analyses of women taking aspirin at an intensity of ≥80% for longer than 6 consecutive months (high intensity, $N = 497$), we found similar null associations with breast cancer–specific mortality. The median duration of after diagnosis aspirin exposure was 2,717 days for women in this group. The mean number of days' supply of aspirin received after diagnosis was 935 and the mean on-treatment exposure intensity was 87%. These results were unchanged in analyses of women taking aspirin at an intensity of ≥80% for longer than 2 consecutive years (low-intensity HR, 0.99; 95% CI, 0.73–1.34; high-intensity HR, 0.90; 95% CI, 0.52–1.55), and in analyses of cumulative average intensity of aspirin exposure (<50% HR, 0.99; 95% CI, 0.72–1.35; ≥50% HR, 0.98; 95% CI, 0.61–1.59). There was also no association between aspirin exposure and breast cancer–specific mortality in women who initiated use in the 1.5 year period immediately after diagnosis ($N = 380$). We found no evidence of effect modification by tumor size ($P = 0.24$), lymph node status ($P = 0.54$), ER ($P = 0.81$), or PR ($P = 0.41$) receptor status (data not shown).

Discussion

In this observational study of 4,540 women not taking aspirin before a diagnosis of early breast cancer, we found no association

Table 1. Characteristics of women selected for inclusion in the study cohort

	***De novo* aspirin use after breast cancer diagnosis[a,b]**		
Characteristic	**Non-user (*N* = 3,776)**	**User (*N* = 764)**	**Initiation rate (per 1,000 person years)**
Age, y[f]			
Median (IQR)	65 (57, 73)	68 (60, 74)	—
Comorbidity score[c,f]			
Median (IQR)	7 (3, 11)	7 (3, 12)	—
Smoking (%)			
Current	832 (22.0)	152 (19.9)	32.5
Past	447 (11.8)	85 (11.1)	34.3
Never	1,755 (46.5)	393 (51.4)	38.0
Unspecified	742 (19.7)	134 (17.5)	35.4
Hydrophilic statin (%)[c]			
Yes	760 (20.1)	147 (19.2)	39.9
No	—	—	35.1
Lipophilic statin (%)[c]			
Yes	93 (2.5)	12 (1.6)	27.2
No	—	—	36.1
NSAID (%)[c,f]			
Yes	1,564 (41.4)	368 (48.2)	40.7
No	—	—	32.3
Antidiabetic (%)[c,f]			
Yes	133 (3.5)	36 (4.7)	57.8
No	—	—	35.3
Bisphosphonate (%)[c]			
Yes	307 (8.1)	52 (6.8)	38.3
No	—	—	35.8
Tumor stage (%)[d,f]			
I	1,236 (32.7)	241 (31.5)	32.7
IIa	1,135 (30.1)	278 (36.4)	41.9
IIb	801 (21.2)	158 (20.7)	34.5
IIIa	249 (6.6)	44 (5.8)	36.5
IIIb-c	355 (9.4)	43 (5.6)	29.0
Tumor grade (%)			
Low	382 (10.1)	85 (11.1)	35.4
Intermediate	1,882 (49.8)	368 (48.2)	35.5
High	1,250 (33.1)	237 (31.0)	35.4
Unspecified	262 (6.9)	74 (9.7)	40.9
ER (%)			
Negative	668 (17.7)	115 (15.0)	33.1
Positive	2,870 (73.6)	549 (71.9)	35.9
Unspecified	328 (8.7)	100 (13.1)	40.0
PR (%)			
Negative	1,039 (27.5)	166 (21.7)	32.0
Positive	1,953 (51.7)	378 (49.5)	36.6
Unspecified	784 (20.8)	220 (28.8)	38.3
HER2 (%)[f]			
Negative	2,415 (64.0)	397 (52.0)	33.8
Positive	495 (13.1)	73 (9.6)	29.6
Unspecified	866 (22.9)	294 (38.5)	41.6
Chemotherapy (%)[e]			
Yes	1,624 (43.0)	305 (39.9)	38.1
No	—	—	33.0
Anti-estrogen (%)[e]			
Yes	2,775 (73.5)	584 (76.4)	33.2
No	—	—	36.7
***De novo* post-diagnostic aspirin exposure details**			
Number of days to first aspirin exposure			
Mean	—	913 (—)	—
Number of aspirin days' supply received			
Mean	—	631 (—)	—
Aspirin exposure intensity while on treatment			
Mean	—	0.86 (—)	—
Mean aspirin dose on exposed days (%)			
<150 mg/d	—	730 (95.5)	—
≥150 mg/d	—	34 (4.5)	—

Abbreviation: IQR, interquartile range.

[a]No aspirin use in the year before diagnosis and at least one prescription for aspirin received between diagnosis and the end of follow-up, December 31, 2011.

[b]Patients identified as aspirin users/non-users after lagging exposure by 2 years.

[c]In the year before breast cancer diagnosis.

[d]AJCC Cancer Staging Manual 6th Edition. Springer, 2002.

[e]In the year after breast cancer diagnosis.

[f]Difference in aspirin initiation rate $P < 0.05$ (Poisson regression).

Table 2. Univariate and multivariate HRs for association between *de novo* post-diagnostic aspirin use and breast cancer–related mortality

			All-cause mortality			Breast cancer–specific mortality		
***De novo* post-diagnostic aspirin exposure definition**	***N***	**Person years**	**Deaths (rate)[a]**	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)[b]**	**Deaths (rate)[a]**	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)[b]**
Aspirin exposure, yes/no[c]								
Non-user	3,061	12,680	648 (51.1)	Ref (—)	Ref (—)	390 (30.8)	Ref (—)	Ref (—)
Aspirin user	764	2,302	141 (61.3)	1.22 (1.01–1.47)	1.10 (0.90–1.33)	64 (27.8)	1.03 (0.78–1.35)	0.98 (0.74–1.30)
Dosing intensity analysis[c,d]								
Non-user	3,061	12,680	648 (51.1)	Ref (—)	Ref (—)	390 (30.8)	Ref (—)	Ref (—)
Aspirin user, low intensity	267	993	52 (52.4)	1.03 (0.77–1.34)	0.99 (0.74–1.32)	27 (27.2)	0.95 (0.64–1.41)	0.91 (0.61–1.34)
Aspirin user, high intensity (≥80% for ≥6 consecutive months)	497	1,309	89 (68.0)	1.35 (1.07–1.70)	1.19 (0.94–1.50)	37 (28.3)	1.07 (0.76–1.52)	1.03 (0.72–1.47)
Landmark analysis[e]								
Non-user	3,445	13,518	693 (51.3)	Ref (—)	Ref (—)	405 (30.0)	Ref (—)	Ref (—)
Aspirin user (initiated in the 1.5 years after diagnosis)	380	1,454	96 (66.0)	1.29 (1.04–1.60)	1.14 (0.92–1.42)	49 (33.7)	1.12 (0.84–1.51)	1.04 (0.77–1.40)

Abbreviation: Ref, referent group.

[a]Deaths/1,000 person years.

[b]Adjusted for age at diagnosis (years); smoking status (never, past, current, and unspecified); comorbidity score, tumor stage (I, IIa, IIb, IIIa, and IIIb-c); tumor grade (low, intermediate, high, and unspecified); ER, PR, and HER2 receptor status (positive, negative, and unspecified); chemotherapy in year post diagnosis (yes or no); anti-estrogen therapy in year after diagnosis (yes or no); lipophilic statin, hydrophilic statin, bisphosphonate, NSAID, and antidiabetic medication use (yes or no).

[c]Aspirin exposure lagged by 2 years in analysis.

[d]Aspirin dosing intensity of ≥80% for ≥6 consecutive months defined as high dosing intensity. All other aspirin exposures defined as low dosing intensity.

[e]Aspirin exposure initiated in the 1.5 years after breast cancer diagnosis. Follow-up from 2 years after diagnosis.

between the initiation of *de novo* post-diagnostic aspirin use and breast cancer–specific mortality. Our study included 764 *de novo* aspirin users with a median follow-up of more than 5 years. The duration and intensity of post-diagnostic aspirin exposure in this group are similar to those observed in clinical studies of daily low-dose aspirin (median duration 5 years; mean on-treatment intensity 80%–90%; refs. 24–26), and the results from this analysis provide information about the possible effectiveness of normally achievable levels of daily aspirin use in routine clinical practice. Our findings were also consistent in analyses restricted to women taking aspirin regularly for sustained periods of time after diagnosis; and analyses of aspirin use initiated shortly after diagnosis. This suggests our null results are unlikely to be due to short duration or low-intensity aspirin exposure in *de novo* users. However, the majority of women in our study were prescribed less than 150 mg/d—which is primarily indicated for cardiovascular disease prevention—our findings may not, therefore, be generalizable to the post-diagnostic use of higher doses.

We identified two prior studies that examined *de novo* post-diagnostic aspirin use in women with breast cancer (11, 12). Both of these were subgroup analyses within studies examining all post-diagnostic aspirin use. In a study of 2,292 women enrolled in

Table 3. Sensitivity analyses—univariate and multivariate HRs for association between *de novo* post-diagnostic aspirin use and breast cancer–related mortality

			All-cause mortality			Breast cancer–specific mortality		
***De novo* aspirin exposure definition**	***N***	**Person years**	**Deaths (rate)[a]**	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)[b]**	**Deaths (rate)[a]**	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)[b]**
Sensitivity analysis: aspirin exposure lagged by 0, 1, 3, and 4 years								
Aspirin exposure, yes/no (lag 0 years)								
Non-user	3,366	19,314	807 (41.8)	Ref (—)	Ref (—)	517 (26.8)	Ref (—)	Ref (—)
Aspirin user	1,174	4,258	286 (67.2)	1.50 (1.30–1.73)	1.35 (1.17–1.56)	142 (33.4)	1.26 (1.04–1.52)	1.17 (0.96–1.42)
Aspirin exposure, yes/no (lag 1 year)								
Non-user	3,408	15,926	735 (46.2)	Ref (—)	Ref (—)	463 (29.1)	Ref (—)	Ref (—)
Aspirin user	991	3,177	217 (68.3)	1.45 (1.24–1.70)	1.32 (1.12–1.55)	107 (33.7)	1.27 (1.02–1.58)	1.19 (0.95–1.48)
Aspirin exposure, yes/no (lag 3 years)								
Non-user	2,638	9,829	522 (53.1)	Ref (—)	Ref (—)	302 (30.7)	Ref (—)	Ref (—)
Aspirin user	577	1,632	96 (58.8)	1.17 (0.93–1.46)	1.07 (0.85–1.34)	39 (23.9)	0.92 (0.65–1.30)	0.90 (0.64–1.28)
Aspirin exposure, yes/no (lag 4 years)								
Non-user	2,165	7,417	377 (50.8)	Ref (—)	Ref (—)	206 (27.8)	Ref (—)	Ref (—)
Aspirin user	443	1,120	67 (59.8)	1.22 (0.93–1.59)	1.11 (0.85–1.47)	24 (21.4)	0.89 (0.57–1.37)	0.90 (0.58–1.40)
Sensitivity analysis: no aspirin exposure in 3 years before diagnosis								
Aspirin exposure, yes/no[c]								
Non-user	2,450	10,219	532 (52.1)	Ref (—)	Ref (—)	327 (32.0)	Ref (—)	Ref (—)
Aspirin user	578	1,676	110 (65.6)	1.31 (1.06–1.62)	1.13 (0.91–1.40)	54 (32.2)	1.16 (0.86–1.56)	1.04 (0.77–1.41)

Abbreviation: Ref, referent group.

[a]Deaths/1,000 person years.

[b]Adjusted for age at diagnosis (years); smoking status (never, past, current, and unspecified); comorbidity score, tumor stage (I, IIa, IIb, IIIa, and IIIb-c); tumor grade (low, intermediate, high, and unspecified); ER, PR, and HER2 receptor status (positive, negative, and unspecified); chemotherapy in year after diagnosis (yes or no); anti-estrogen therapy in year after diagnosis (yes, no); lipophilic statin, hydrophilic statin, bisphosphonate, NSAID, and antidiabetic medication use (yes or no).

[c]Exposure lagged by 2 years in analysis.

the Life After Cancer Epidemiology cohort, of whom 148 were *de novo* users, Kwan and colleagues (11) found no association between *de novo* aspirin use and breast cancer recurrence (RR, 1.23; 95% CI, 0.72–2.11). Similarly, in a larger case–control study by Murray and colleagues (12), no significant association was observed between *de novo* aspirin use and breast cancer–related mortality (OR, 0.84; 95% CI, 0.59–1.18). Several other observational studies have examined post-diagnostic aspirin use in women with breast cancer (5–9). Some of these have reported large, statistically significant reductions in breast cancer–specific mortality (5–7). However, all of these studies included women who commenced aspirin use prediagnosis and continued afterwards, and because of this it is not possible to conclude from their analyses the magnitude of effect attributable to post-diagnostic use alone. There have also been a small number of observational studies examining pre-diagnostic aspirin use and breast cancer outcomes (4, 27). Again, however, because pre- and post-diagnostic aspirin use is strongly correlated, it is unclear from these studies what time period of exposure may be most relevant. Finally, in a meta-analysis of randomized trials of aspirin for cardiovascular disease, Rothwell and colleagues (1) reported that aspirin use initiated in the pre-diagnostic setting was associated with reduced mortality from any cancer, with similar, although nonsignificant, findings for breast cancer. Their results also suggested that patients who continued aspirin use after a cancer diagnosis had greater benefit. However, the authors acknowledged it is likely that patients who remained on aspirin had a more favorable prognosis than those who did not.

In a prior study by our group, regular pre-diagnostic aspirin use was associated with a statistically significant reduction in the risk of presenting with lymph node metastasis at the time of diagnosis (27). Similarly, in their meta-analysis of randomized trials, Rothwell and colleagues (2) also found that daily aspirin use, before a cancer diagnosis, was associated with a statistically significant reduction in the risk of presenting with distant metastasis at diagnosis (2). In both of these studies, presenting with localized or nonmetastatic disease at diagnosis predicted a subsequent mortality benefit in women using aspirin before diagnosis. It has been suggested that the reduced cancer-related mortality observed in some aspirin studies could be attributable to the effects of pre-diagnostic aspirin use on the dissemination of micrometastases before diagnosis (3). It has also been suggested that, as micrometastatic disease will usually be present at the time a cancer is diagnosed, the post-diagnostic initiation of drugs that target micrometastatic dissemination may not reduce the risk of disease recurrence (28). This could explain the null associations reported in this and other studies of *de novo* post-diagnostic aspirin use; although further work is needed to clarify aspirin's exact mechanism of action in breast cancer.

The strengths of our study include the prospectively collected outcome data and the availability of longitudinal information on *de novo* aspirin exposure. The prescription-only status of low-dose aspirin in Ireland permitted the objective assessment of cumulative aspirin exposure for all women, allowing us to explore associations by intensity and timing of use. Nevertheless, as aspirin use was based upon prescriptions dispensed, treatment noncompliance will have resulted in exposure misclassification, which could have biased our results toward the null. However, it is unlikely that many women would continue to fill prescriptions for medication they were no longer using. Our study also has some limitations. This was an observational study and it is possible that unmeasured covariates could have influenced our results. For example, information on lifestyle factors that may influence disease progression, such as obesity and alcohol use, was not available. We lagged exposures in analyses to reduce the possibility that changing prognosis influenced post-diagnostic aspirin use. Although this is an accepted approach for analyses of post-diagnostic exposures, it may not fully eliminate time-dependent confounding (29). Insufficient patient follow-up has been suggested as a reason for null results in prior studies of aspirin use (9). Women in our study were followed up for a median of 5.2 years and a maximum of 12 years after diagnosis. This is less than the average follow-up in studies reporting significant reductions in breast cancer–related mortality (Fraser and colleagues, median 5.7 years; Blair and colleagues, mean 8.3 years; Holmes and colleagues, mean 10.8 years; refs. 5–7); although it is unlikely that the large mortality reductions observed in these studies would only accrue during this short difference in follow-up. Finally, our study population is a subset of breast cancer cases defined by age and socioeconomic eligibility for the GMS scheme; this should be considered when generalizing our results to a wider breast cancer population.

In conclusion, the results from our study suggest that initiating aspirin use after a breast cancer diagnosis is not associated with a reduction in breast cancer–related mortality. Currently, there is a randomized placebo-controlled study of adjuvant aspirin (100 mg–300 mg/day) ongoing in patients with early breast (N = 3,100) and other cancers; (30) although results from this are not expected for some time. On the basis of our null findings, we suggest that greater focus be given to understanding aspirin's mechanism of action, this will help inform the design of future tailored studies in breast cancer.

Disclosure of Potential Conflicts of Interest

L. Sharp reports receiving commercial research support from Sanofi-Aventis for a project on treatment and outcomes in breast cancer; 2011–2012. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The Health Research Board Ireland and the Irish Cancer Society had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit for publication. The interpretation and reporting of these data are the responsibility of the authors and should in no way be seen as the official policy or interpretation of the National Cancer Registry Ireland or the Irish Health Services Executive Primary Care Reimbursements Services.

Authors' Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.I. Barron, L.M. Murphy, C. Brown, K. Visvanathan, L. Sharp
Writing, review, and/or revision of the manuscript: T.I. Barron, L.M. Murphy, C. Brown, K. Bennett, K. Visvanathan, L. Sharp
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