Recent Prediagnostic Aspirin Use, Lymph Node Involvement, and 5-Year Mortality in Women with Stage I–III Breast Cancer: A Nationwide Population-Based Cohort Study

Thomas I. Barron1,4, Evelyn M. Flahavan1, Linda Sharp2, Kathleen Bennett1, and Kala Visvanathan3,4

Abstract

Lymph node–positive breast tumors are more likely to express COX2 than node-negative tumors. In preclinical studies, COX2 inhibition prevents breast tumor spread to lymph nodes. Therefore, we examined the association between recent (1 year) prediagnostic use of aspirin (COX1/COX2 inhibitor), lymph node involvement at breast cancer diagnosis, and breast cancer–specific mortality. Women with stage I–III breast cancer diagnosed from 2001 to 2006 (N = 2,796) were identified from Ireland’s National Cancer Registry. These data were linked to prescription refill and mammographic screening databases. Relative risks (RR) were estimated for associations between prediagnostic aspirin use and lymph node–positive status at diagnosis. HRs were estimated for associations between pre- and postdiagnostic aspirin use and 5-year mortality, stratified by lymph node status. Women with prediagnostic aspirin use were statistically significantly less likely to present with a lymph node–positive tumor than nonusers [RR = 0.89; 95% confidence interval (CI), 0.81–0.97], particularly those with larger (Pinteraction = 0.036), progesterone receptor (PR)–negative (Pinteraction < 0.001) or estrogen receptor (ER)–negative (Pinteraction = 0.056) tumors. The magnitude of this association increased with dose (Ptrend < 0.01) and dosing intensity (Ptrend < 0.001) and was similar in women with or without screen-detected tumors (Pinteraction = 0.70). Prediagnostic aspirin use was associated with lower 5-year breast cancer–specific mortality among women with lymph node–negative tumors (HR, 0.55; 95% CI, 0.33–0.92) but not node-positive tumors (HR, 0.91; 95% CI, 0.37–1.22). Tests for effect-modification were, however, not statistically significant (Pinteraction = 0.087). Postdiagnostic aspirin use was not associated with breast cancer–specific mortality (HR, 0.99; 95% CI, 0.68–1.45). Our findings indicate that recent prediagnostic aspirin use is protective against lymph node–positive breast cancer. This is a plausible explanation for reductions in breast cancer mortality reported in observational studies of aspirin use.

Cancer Res; 74(15); 4065–77. © 2014 AACR.

Introduction

In a recent meta-analysis of randomized trials of aspirin for cardiovascular disease prevention, the use of aspirin, a COX1/2 inhibitor, before a cancer diagnosis, was associated with a 36% reduction in the risk of distant metastasis (1). In further subanalyses, a statistically significant reduction in metastasis was observed among patients with colorectal cancer taking aspirin [OR, 0.36; 95% confidence interval (CI), 0.18–0.74]. They made up the largest subgroup (n = 130). Aspirin use was also associated with a nonsignificant reduction in metastasis in women with breast cancer (OR, 0.50; 95% CI, 0.16–1.51; n = 86). In the same meta-analysis, prediagnostic aspirin use was also associated with lower cancer-specific mortality. This mortality benefit was only observed among individuals with nonmetastatic disease at diagnosis (1). In other observational studies, aspirin use by women with breast cancer has been associated with statistically significant reductions in breast cancer recurrence and mortality (2, 3).

Preclinical data suggest that the COX/prostaglandin pathway is involved in the development of lymph node metastases through the regulation of VEGF-C/D–mediated lymphangiogenesis (4, 5). Inhibition of the COX/prostaglandin pathway has also been shown to suppress the development of lymphatic metastases in breast cancer animal models (4, 5). The COX2 enzyme is expressed in up to 40% of breast cancers and is associated with larger tumor size, negative hormone receptor status, a high proliferation rate (identified by Ki-67), and the presence of HER2 oncogene amplification (6, 7). Women with tumors that express COX2 are also more likely to present with positive lymph nodes at diagnosis and die from breast cancer (6, 7).

In this study, we aimed to investigate the following in women with breast cancer: (i) associations between recent
prediagnostic aspirin use and the presence of lymph node metastasis at breast cancer diagnosis; (ii) associations between recent prediagnostic aspirin use and breast cancer mortality; and (iii) whether the presence of lymph node metastases at diagnosis modifies associations between recent prediagnostic aspirin use and breast cancer mortality.

Materials and Methods
Setting and data sources
We conducted this study using patient records from the National Cancer Registry Ireland (NCRI) linked to prescription dispensing data from Ireland’s General Medical Services (GMS) pharmacy claims database (8) and information on mammographic screening from BreastCheck, a national breast cancer screening program (9). The NCRI records detailed information on all incident cancers diagnosed in the population usually resident in Ireland. Information is collected by trained, hospital-based tumor registration officers from multiple sources, including pathology and radiology reports, medical records, and death certificates. The use for research of anonymized data held by the NCRI is covered by the Health (Provision of Information) Act, 1997.

Eligibility for the GMS prescription scheme is through means test or age (>70 years). The GMS database records details of all prescription drugs dispensed to GMS eligible patients since 2000. This includes all low-dose and most high-dose aspirin preparations, which are prescription-only in Ireland, as in other European countries (10). A small number of high-dose aspirin preparations are available over the counter but only for specified short-term indications, in small pack sizes (≤24–50 doses) and at increased cost. Women with GMS eligibility can obtain high-dose aspirin preparations on-prescription without charge or restriction.

We used two independent sources of information to identify women with breast tumors detected by organized or opportunistic screening mammography. First, individual screening histories from Ireland’s population-based organized screening mammography program, BreastCheck (9), were linked to NCRI patient records, allowing the accurate identification of all organized screen-detected breast cancers (12). Second, the NCRI provided information, collected by tumor registration officers, identifying breast tumors detected by any screening mammography. There was close to 100% agreement for organized screen-detected tumors between linked BreastCheck records and data collected by the NCRI (12). This enabled us to identify women with tumors detected by opportunistic screening mammography (i.e., screening mammography use outside of BreastCheck).

Cohort and exposure definitions
The study cohort included all women with a diagnosis of stage I–III invasive breast cancer (ICD-10 C50; ref. 13) between January 1, 2001 and December 31, 2006, aged 50 to 80 years at diagnosis, and with GMS eligibility from at least 1 year before diagnosis. Women were excluded if they had a prior invasive cancer other than non-melanoma skin cancer or if their breast cancer diagnosis was made at the time of death (Fig. 1). The lower age limit was set at 50 years to restrict the study population to women with similar potential for aspirin exposure (14). Of the 489 women younger than 50 years excluded from the study analyses, 97.6% did not receive any aspirin (Fig. 1). Women older than 80 years were excluded from the analysis as they are less likely to receive a definitive lymph node evaluation (15).

All prescriptions for aspirin, dispensed to women in the study cohort, were identified from the GMS database using WHO-ATC drug classifications (Supplementary Table S1; ref. 16). The dose and number of days’ supply on each prescription were abstracted. This meant we could evaluate the full range of aspirin use starting at the level of one prescription per year. Prediagnostic aspirin use was defined as having received aspirin in the year before diagnosis. Patients initiating prediagnostic aspirin use between 0–1.5, 1.5–3, and ≥3 years before diagnosis were also identified. These exposure windows were selected on the basis of prior preclinical (17) and clinical (1) data indicating that aspirin exposure in the years immediately before diagnosis can impact breast cancer progression. Aspirin dosing intensity, the proportion of days with a supply of aspirin available in the year before diagnosis, was calculated from the number of days’ supply on each prescription (18). Postdiagnostic aspirin use was defined as having received aspirin between diagnosis and the end of follow-up.

Outcomes and covariates
We used information from the NCRI database to identify lymph node status at diagnosis (positive, negative). Women were identified as lymph node–positive if they had a pathologic nodal status of pN1/2/3 or, if not available, a clinical nodal status of N1/2/3 (19). Death certificates were used to identify the date and cause of death (Supplementary Table S1) for survival analyses.
The NCRI database was also used to classify women by tumor size (T1, T2, T3, T4; ref. 13); tumor stage (I, IIa, IIb, IIIa, IIIb-c; ref. 13); tumor grade (low, intermediate, high, unspecified); tumor morphology (ductal, lobular, other; Supplementary Table S1); tumor topography (outer, inner/central, unspecified; Supplementary Table S1); estrogen receptor (ER), progesterone receptor (PR), HER2 status (positive, negative, unspecified; Supplementary Table S1); age (years); smoking status (never, past, current, unspecified); and screen-detection (organized, opportunistic, not screen-detected). We used prescription data to identify the use of other medications that could be confounders (Supplementary Table S1), including anti-diabetic medications, which were taken to indicate a diagnosis of diabetes. A medication-based comorbidity score, based on a validated measure (19), was calculated for each patient as the sum of distinct medication classes (defined by the first five ATC code characters) received in the year before breast cancer diagnosis.

Statistical analyses

The distribution of clinical and sociodemographic covariates was compared between aspirin users and nonusers. Univariate and multivariate log-binomial models (20, 21) were used to estimate relative risks (RR) with 95% CIs for associations between aspirin use before diagnosis and lymph node–positive breast cancer at diagnosis (22, 23). Covariates were identified for inclusion in the multivariate model based on prior knowledge of clinical, demographic and behavioral predictors of nodal status (tumor size; grade; morphology; topography; ER, PR, HER2 status; age; smoking status; screen detection; refs. 24–28); drugs associated with tumor invasiveness (β-blockers, biguanides, bisphosphonates, statins, estrogen, estrogen/progesterone, NSAIDs; refs. 29–34); specific comorbidities associated with lymphatic metastasis (diabetes; ref. 35); and patient characteristics associated with extent of nodal evaluation (age, comorbidity score; ref. 15). We selected the final multivariate model from these covariates using backwards elimination up to a 10% maximum cumulative change in the effect of the fully adjusted RRs (36). Covariates consistently associated with nodal status in previous studies were fixed in the model a priori (tumor size, grade, age, screen detection).

Subgroup analyses of nodal status were conducted by quartiles of prediagnostic aspirin dosing intensity; by low-dose (all prescriptions for <150 mg) and high-dose aspirin use (at least one prescription for ≥150 mg); and by duration of prediagnostic aspirin use (0–1.5, 1.5–3, ≥3 years; ref. 37). Effect-modification of associations between prediagnostic aspirin use and nodal status was assessed on an additive scale (risk difference, RD; interaction contrast, IC) and significance was tested using the Wald test (38). The separate and joint effects of aspirin exposure and effect modifier are presented using a single reference category, in addition to the within strata effects and measures of interaction (39, 40). Breast tumor characteristics known to be associated with COX2 expression were identified a priori and considered as potential effect modifiers (6, 41, 42). These were large tumor size, high grade, negative ER or PR status, positive HER2 status, and tumor morphology.

In survival analyses, multivariate Cox proportional hazards models were used to estimate HRs with 95% CIs for associations between prediagnostic aspirin use and (i) breast cancer–specific mortality and (ii) all-cause mortality. All women were followed from diagnosis to the first of either death, December 31, 2008 or 5 years. Deaths from non-breast cancer causes were censored in analyses of breast cancer–specific mortality. Covariates were selected for inclusion in the multivariate model based on prior knowledge of clinical and demographic characteristics associated with breast cancer survival. These were age, comorbidity score, tumor stage (including nodal status), grade, ER, PR, and HER2 status. Effect-modification by nodal status at diagnosis was assessed on a multiplicative scale (ratio of HRs, rHR) with 95% CIs. We repeated survival analyses with the inclusion of postdiagnostic aspirin use (unexposed, exposed; time varying; lagged 2 years) and calculated HRs with 95% CIs for associations between postdiagnostic aspirin use and (i) all-cause mortality and (ii) breast cancer–specific mortality. Postdiagnostic aspirin use was lagged in survival analyses to reduce the possibility that worsening prognosis influenced prescribing patterns (time-dependent confounding; ref. 43). This lag time was varied from 1 to 3 years in sensitivity analyses. Cumulative mortality was also estimated from directly adjusted survival curves (44). All analyses were conducted using SAS v9.2 (SAS Institute Inc). Results were considered statistically significant at a 2-sided α-level of 0.05.

Sensitivity analyses

In addition to adjusting for screen detection in nodal status analyses, the following sensitivity analyses were conducted to rule out early detection bias due to differential screening or intensity of medical surveillance among aspirin users as an explanation of our results: (i) associations between aspirin use and lymph node status were assessed in analyses stratified by screen detection and (ii) a propensity score matched analysis was conducted incorporating screening practices and comorbidities for aspirin users and nonusers. We also conducted sensitivity analyses to rule out bias due to the potential misclassification of nodal status based on clinical evaluation alone. In addition, to minimize the effect of any differential bias due to unrecorded nodal status (n = 165), we took a conservative approach in the main analysis and classified all women with unrecorded lymph node status as lymph node–positive (aspirin user, 4.9%; aspirin nonuser, 8.6%). Sensitivity analyses using complete cases were also undertaken.

To assess the presence of bias due to possible misclassification of breast cancer–specific cause of death, we repeated survival analyses with the inclusion of: (i) deaths where breast cancer was listed as a secondary cause of death on the death certificate; (ii) deaths from ill-defined or secondary cancers, cancers of unknown behavior, and unspecified causes.

Results

Cohort characteristics

The characteristics of aspirin users (n = 740) and nonusers (n = 2,056), stratified by dosing intensity, are presented in Table 1. Aspirin users were older and had a higher comorbidity score than nonusers. The proportion of organized and
Table 1. Characteristics of women selected for inclusion in the study cohort

<table>
<thead>
<tr>
<th>Characteristic at diagnosis</th>
<th>Nonuser (n = 2,056)</th>
<th>Dosing intensity (1%-37%), n = 186</th>
<th>Dosing intensity (38%-79%), n = 184</th>
<th>Dosing intensity (80%-97%), n = 185</th>
<th>Dosing intensity (98%-100%), n = 185</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient details</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>67 (58–73)</td>
<td>72 (65–77)</td>
<td>71 (64–77)</td>
<td>73 (65–76)</td>
<td>72 (66–77)</td>
</tr>
<tr>
<td>Comorbidity, median (IQR), drug classes</td>
<td>6 (3–10)</td>
<td>10 (7–14)</td>
<td>11 (8–15)</td>
<td>11 (7–15)</td>
<td>12 (9–17)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,022 (49.7)</td>
<td>92 (49.5)</td>
<td>95 (51.6)</td>
<td>100 (54.1)</td>
<td>88 (47.6)</td>
</tr>
<tr>
<td>Past</td>
<td>245 (11.9)</td>
<td>23 (12.4)</td>
<td>20 (10.9)</td>
<td>22 (11.9)</td>
<td>23 (12.4)</td>
</tr>
<tr>
<td>Current</td>
<td>456 (22.2)</td>
<td>33 (17.7)</td>
<td>31 (16.8)</td>
<td>30 (16.2)</td>
<td>34 (18.4)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>333 (16.2)</td>
<td>38 (20.4)</td>
<td>38 (20.7)</td>
<td>33 (17.8)</td>
<td>40 (21.6)</td>
</tr>
<tr>
<td><strong>Screen detected (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organized</td>
<td>257 (12.5)</td>
<td>15 (8.1)</td>
<td>24 (13.0)</td>
<td>21 (11.4)</td>
<td>21 (11.4)</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>94 (4.6)</td>
<td>7 (3.8)</td>
<td>5 (2.7)</td>
<td>8 (4.3)</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td><strong>Concomitant drugs (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td>107 (5.2)</td>
<td>6 (3.2)</td>
<td>8 (4.3)</td>
<td>9 (4.9)</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>Estrogen/Progesterone</td>
<td>164 (8.0)</td>
<td>9 (4.8)</td>
<td>7 (3.8)</td>
<td>6 (3.2)</td>
<td>10 (5.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>307 (14.9)</td>
<td>68 (36.6)</td>
<td>93 (50.5)</td>
<td>92 (50.5)</td>
<td>112 (60.5)</td>
</tr>
<tr>
<td>NSAID</td>
<td>876 (42.6)</td>
<td>101 (54.3)</td>
<td>89 (48.4)</td>
<td>94 (50.8)</td>
<td>101 (54.6)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>315 (15.3)</td>
<td>62 (33.3)</td>
<td>68 (37.0)</td>
<td>69 (37.3)</td>
<td>85 (45.9)</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>79 (3.8)</td>
<td>17 (9.1)</td>
<td>28 (15.2)</td>
<td>23 (12.4)</td>
<td>32 (17.3)</td>
</tr>
<tr>
<td>Biguandide</td>
<td>46 (2.2)</td>
<td>14 (7.5)</td>
<td>18 (9.8)</td>
<td>16 (8.6)</td>
<td>23 (12.4)</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>109 (5.3)</td>
<td>10 (5.4)</td>
<td>16 (8.7)</td>
<td>23 (12.4)</td>
<td>18 (9.7)</td>
</tr>
<tr>
<td><strong>Tumor details</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1,020 (49.6)</td>
<td>86 (46.2)</td>
<td>99 (53.8)</td>
<td>112 (60.5)</td>
<td>107 (57.8)</td>
</tr>
<tr>
<td>Positive</td>
<td>1,036 (50.4)</td>
<td>100 (53.8)</td>
<td>85 (46.2)</td>
<td>73 (39.5)</td>
<td>78 (42.2)</td>
</tr>
<tr>
<td><strong>Tumor size (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>848 (41.2)</td>
<td>71 (38.2)</td>
<td>84 (45.7)</td>
<td>78 (42.2)</td>
<td>62 (33.5)</td>
</tr>
<tr>
<td>T2</td>
<td>916 (44.6)</td>
<td>87 (46.6)</td>
<td>81 (44.0)</td>
<td>84 (45.4)</td>
<td>98 (53.0)</td>
</tr>
<tr>
<td>T3</td>
<td>130 (6.3)</td>
<td>9 (4.8)</td>
<td>12 (6.5)</td>
<td>12 (6.5)</td>
<td>13 (7.0)</td>
</tr>
<tr>
<td>T4</td>
<td>162 (7.9)</td>
<td>19 (10.2)</td>
<td>7 (3.8)</td>
<td>11 (5.9)</td>
<td>12 (6.5)</td>
</tr>
<tr>
<td><strong>Tumor stage (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>624 (30.4)</td>
<td>51 (27.4)</td>
<td>66 (35.9)</td>
<td>60 (32.4)</td>
<td>48 (25.9)</td>
</tr>
<tr>
<td>Iia/Iib</td>
<td>626/690 (30.4/23.8)</td>
<td>60/46 (32.3/24.7)</td>
<td>61/36 (32.2/19.6)</td>
<td>68/35 (36.8/18.9)</td>
<td>80/31 (43.2/16.8)</td>
</tr>
<tr>
<td>Iiia/Iib-c</td>
<td>130/186 (9.0/6.3)</td>
<td>9/20 (4.8/10.8)</td>
<td>13/8 (7.1/4.3)</td>
<td>8/14 (4.3/7.6)</td>
<td>10/16 (5.4/8.6)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Characteristics of women selected for inclusion in the study cohort (Cont'd)

<table>
<thead>
<tr>
<th>Characteristic at diagnosis</th>
<th>Nonuser (n = 2,086)</th>
<th>Dosing intensity (dosing intensity by quartiles) a</th>
<th>Dosing intensity (dosing intensity by quartiles) b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1%–37%), n = 186</td>
<td>(38%–79%), n = 184</td>
<td>(80%–100%), n = 185</td>
</tr>
<tr>
<td>Tumor grade (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>207 (10.1)</td>
<td>18 (9.8)</td>
<td>17 (9.2)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>832 (40.7)</td>
<td>105 (57.1)</td>
<td>64 (34.6)</td>
</tr>
<tr>
<td>High</td>
<td>682 (33.7)</td>
<td>59 (32.2)</td>
<td>51 (27.6)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>26 (1.3)</td>
<td>14 (7.6)</td>
<td>23 (12.4)</td>
</tr>
<tr>
<td>Tumor morphology (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>1,462 (71.1)</td>
<td>122 (66.3)</td>
<td>21 (11.4)</td>
</tr>
<tr>
<td>Lobular</td>
<td>270 (13.1)</td>
<td>25 (14.1)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Other</td>
<td>324 (16.3)</td>
<td>36 (19.6)</td>
<td>23 (12.6)</td>
</tr>
<tr>
<td>ER (%)</td>
<td>Positive/Unspecified</td>
<td>75 mg/300 mg/Other</td>
<td>75 mg/300 mg/Other</td>
</tr>
<tr>
<td>Positive/Unspecified</td>
<td>918/976/441</td>
<td>85/54/36</td>
<td>35/21/15</td>
</tr>
<tr>
<td>Negative/Unspecified</td>
<td>44/6/44</td>
<td>43/20/43</td>
<td>37/13/13</td>
</tr>
<tr>
<td>PR (%)</td>
<td>Positive/Unspecified</td>
<td>75 mg/300 mg/Other</td>
<td>75 mg/300 mg/Other</td>
</tr>
<tr>
<td>Positive/Unspecified</td>
<td>2,769/1910</td>
<td>27/1867</td>
<td>27/1867</td>
</tr>
<tr>
<td>Negative/Unspecified</td>
<td>(110/44/74)</td>
<td>(14/56/22)</td>
<td>(14/56/22)</td>
</tr>
<tr>
<td>HER2 (%)</td>
<td>Positive/Unspecified</td>
<td>75 mg/300 mg/Other</td>
<td>75 mg/300 mg/Other</td>
</tr>
<tr>
<td>Positive/Unspecified</td>
<td>2,769/1910</td>
<td>27/1867</td>
<td>27/1867</td>
</tr>
<tr>
<td>Negative/Unspecified</td>
<td>(110/44/74)</td>
<td>(14/56/22)</td>
<td>(14/56/22)</td>
</tr>
<tr>
<td>Number of Rx dispensed</td>
<td>1.2 (0.5–2.9)</td>
<td>1.2 (0.5–2.9)</td>
<td>1.2 (0.5–2.9)</td>
</tr>
<tr>
<td>Dosing intensity a, median (IQR), %</td>
<td>12 (7–21)</td>
<td>12 (7–21)</td>
<td>12 (7–21)</td>
</tr>
<tr>
<td>Aspirin exposure (diagnosis to end of follow-up)</td>
<td>23.6 (6.0–75.3)</td>
<td>74.2 (45.5–90.9)</td>
<td>89.4 (65.0–96.2)</td>
</tr>
<tr>
<td>Abbreviations: IQR, interquartile range; Rx, prescription.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Dosing intensity calculated as the number of days with a supply of aspirin available in year prior to diagnosis divided by 365.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Identified from linked BreastCheck national screening program records.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c In the year before breast cancer diagnosis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e Postdiagnostic dosing intensity calculated as number of days with supply of aspirin available from diagnosis to end of follow-up, divided by the number of days from diagnosis to end of follow-up.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f Four hundred women initiated de novo aspirin use between their breast cancer diagnosis and the end of follow-up.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
opportunistic screen-detected tumors was similar between aspirin users and nonusers (user/nonuser; organized, 11.0%/12.5%; opportunistic, 3.9%/4.6%; \( P = 0.38 \)). The reason for aspirin use was not recorded; however, 85.4% of women were taking low-dose (<150 mg/d) aspirin exclusively, which is primarily indicated for cardiovascular disease prevention. The median proportion of days using aspirin in the year before diagnosis (dosing intensity) was 80.3%.

**Aspirin and nodal status**

RRs for associations between aspirin use and lymph node–positive breast cancer are presented in Table 2. The proportion of women with node-positive breast cancer in the aspirin nonuser and user groups was 50.4% and 45.4%, respectively. In analyses adjusted for tumor size, tumor grade, screen detection, age, and comorbidity score, women taking aspirin were statistically significantly less likely to present with lymph node–positive breast cancer than women not taking aspirin (RR, 0.89; 95% CI, 0.81–0.97). This translates to a 6% (95% CI, 2%–10%) lower absolute risk of having positive lymph nodes at breast cancer diagnosis in aspirin users than in nonusers.

The risk of presenting with lymph node involvement at diagnosis decreased with increasing aspirin dosing intensity and dose (Table 2). A 19% relative reduction in node-positive breast cancer was observed among women in the highest quartile of aspirin dosing intensity when compared with nonusers (RR, 0.81; 95% CI, 0.68–0.96). A greater reduction in node-positive disease was also observed among women taking higher versus lower doses of aspirin (Table 2).

In sensitivity analyses, associations between aspirin use and lymph node metastasis were the same in women with (RD, −0.09; 95% CI, −0.21 to 0.04) and without (RD, −0.11; 95% CI, −0.17 to −0.05) screen-detected breast cancers (Supplementary Tables S2 and S3, \( P_{\text{interaction}} = 0.70 \)). Similar results were obtained in analyses matched by propensity score (Supplementary Tables S4 and S5). The results were also unchanged in sensitivity analyses classifying women with only clinical assessment of nodal status as node-positive (data not shown) and analyses of complete cases (data not shown).

**Aspirin and nodal status—effect-modification**

The associations between aspirin use and a lower risk of lymph node metastasis were statistically significantly stronger in women with larger tumors (Table 3; \( P_{\text{interaction}} = 0.04 \)) and PR-negative tumors (Table 3; \( P_{\text{interaction}} < 0.001 \)). Associations were also stronger in women with ER-negative tumors (\( P_{\text{interaction}} = 0.056 \), data not shown), HER2-positive tumors (\( P_{\text{interaction}} = 0.17 \), data not shown), and high-grade tumors (\( P_{\text{interaction}} = 0.24 \), data not shown), although these interactions did not reach statistical significance. There was no evidence of effect-modification by tumor morphology (\( P_{\text{interaction}} = 0.62 \), data not shown).

**Aspirin and mortality**

Overall, prediagnostic aspirin use was associated with a statistically significant 45% lower risk of 5-year breast cancer–specific mortality among women with node-negative tumors and no reduction in mortality among women with node-positive tumors. The interaction between aspirin exposure and nodal status did not reach statistical significance (\( P_{\text{interaction}} = 0.087 \); Table 5; Fig. 2). These results did not change after adjustment for postdiagnostic aspirin use or in sensitivity analyses for misclassification of cause of death (data not shown). Postdiagnosis aspirin dosing intensity was similar for women with node-negative (84%) and node-positive tumors (78%). We observed no association between postdiagnostic aspirin use and breast cancer–specific mortality (Table 4). These results remained unchanged in sensitivity analyses varying the lag time for postdiagnostic aspirin use from 1 to 3 years (data not shown).

**Discussion**

In this study of 2,796 women with stage I–III breast cancer, women taking aspirin in the years immediately before their breast cancer diagnosis were statistically significantly less likely to present with a lymph node–positive breast cancer than nonusers. The association was strongest among regular aspirin users and women taking higher aspirin doses. These results are not explained by differences in screening mammography use or breast cancer surveillance between aspirin users and nonusers for the following reasons: (i) there was no difference in the proportion of screen-detected tumors between aspirin users and nonusers; (ii) there was no difference in the distribution of tumor size at presentation between aspirin users and nonusers; (iii) associations between aspirin use and nodal status were unchanged in propensity score matched analyses that incorporated co-medication use and screening; and (iv) we observed the same association between aspirin use and a reduced risk of nodal involvement in women with and without screen-detected breast cancers.

We identified two prior studies that have examined associations between prediagnostic aspirin use and breast cancer nodal status (45, 46). The first of these found no association between aspirin exposure and nodal status; although, nodal status was missing in >20% of patients and analyses were not adjusted for relevant confounders such as tumor size or screening (45). The second study examined associations between antiocoagulant use (aspirin, clopidogrel, dipyridamole) at the time of breast cancer diagnosis and the risk of lymph node metastasis (46). Analyses were adjusted for some relevant confounders (tumor size) but the exposed group included patients using a variety of antiocoagulants and it is unclear what proportion of these were taking aspirin. The authors reported a nonsignificant reduction in the risk of presenting with a lymph node–positive tumor (RR, 0.94; 95% CI, 0.87–1.03) and, similar to our study, evidence of effect modification by tumor size. Information on nodal status has also been reported in two prior observational studies of NSAID exposure and breast cancer mortality from which we were able to calculate a pooled univariate estimate of the association between regular NSAID exposure (≥3 tablets/wk) and the risk of presenting with lymph node–positive disease at diagnosis (RR, 0.83; 95% CI,
Table 2. Univariate and multivariate relative risks for aspirin use and lymph node–positive breast cancer at diagnosis

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>Risk ratios for node-positive versus node-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Node positive (%)</td>
</tr>
<tr>
<td>Nonusers in year before diagnosis</td>
<td>1,036 (50.4)</td>
</tr>
<tr>
<td>Aspirin users in year before diagnosis</td>
<td>336 (45.4)</td>
</tr>
<tr>
<td>Aspirin dosing intensity</td>
<td></td>
</tr>
<tr>
<td>Dosing intensity 1%–37%bc</td>
<td>100 (53.8)</td>
</tr>
<tr>
<td>Dosing intensity 38%–79%</td>
<td>85 (46.2)</td>
</tr>
<tr>
<td>Dosing intensity 80%–97%</td>
<td>73 (39.5)</td>
</tr>
<tr>
<td>Dosing intensity 98%–100%</td>
<td>78 (42.2)</td>
</tr>
<tr>
<td>Aspirin dose</td>
<td></td>
</tr>
<tr>
<td>Low dose &lt; 150 mg</td>
<td>288 (45.6)</td>
</tr>
<tr>
<td>High dose ≥ 150 mg</td>
<td>48 (44.4)</td>
</tr>
<tr>
<td>Aspirin dosing intensity and dose</td>
<td></td>
</tr>
<tr>
<td>Low dosing intensity 1%–37%bc</td>
<td>152 (49.8)</td>
</tr>
<tr>
<td>High dose ≥ 150 mg</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td>Low dosing intensity 80%–100%</td>
<td>136 (41.6)</td>
</tr>
<tr>
<td>High dose ≥ 150 mg</td>
<td>15 (34.9)</td>
</tr>
<tr>
<td>Aspirin durationg</td>
<td></td>
</tr>
<tr>
<td>Nonuser in 3 years before diagnosis</td>
<td>543 (49.5)</td>
</tr>
<tr>
<td>Aspirin user in 3 years before diagnosis</td>
<td></td>
</tr>
<tr>
<td>Start aspirin &lt; 1.5 years before diagnosis</td>
<td>61 (50.8)</td>
</tr>
<tr>
<td>Start aspirin 1.5–3.0 years before diagnosis</td>
<td>89 (47.1)</td>
</tr>
<tr>
<td>Start aspirin ≥ 3.0 years before diagnosis</td>
<td>100 (46.1)</td>
</tr>
<tr>
<td>Aspirin dosing intensity and durationg</td>
<td></td>
</tr>
<tr>
<td>Low dosing intensity 1%–82%ad</td>
<td></td>
</tr>
<tr>
<td>Start aspirin &lt; 1.5 years before diagnosis</td>
<td>28 (47.6)</td>
</tr>
<tr>
<td>Start aspirin 1.5–3.0 years before diagnosis</td>
<td>60 (50.4)</td>
</tr>
<tr>
<td>Start aspirin ≥ 3.0 years before diagnosis</td>
<td>44 (51.8)</td>
</tr>
<tr>
<td>High dosing intensity 83%–100%</td>
<td></td>
</tr>
<tr>
<td>Start aspirin &lt; 1.5 years before diagnosis</td>
<td>33 (54.1)</td>
</tr>
<tr>
<td>Start aspirin 1.5–3.0 years before diagnosis</td>
<td>29 (41.4)</td>
</tr>
<tr>
<td>Start aspirin ≥ 3.0 years before diagnosis</td>
<td>56 (42.4)</td>
</tr>
</tbody>
</table>

*Adjusted for age (years, continuous), tumor size (T1, T2, T3, T4), tumor grade (low, intermediate, high, unspecified), comorbidity score (number of medication classes, continuous), and screen-detected tumor (organized screening, opportunistic screening, not screen detected).

bDosing intensity calculated as the number of days with supply of aspirin available in the year before diagnosis divided by 365.

*All prescriptions in the year before diagnosis were for doses < 150 mg. The 150 mg cutoff point represents twice the standard low-dose aspirin strength (75 mg) used in Ireland.

fAt least one prescription in the year before diagnosis was for a dose ≥ 150 mg.

iWomen with at least 3 years of continuous GMS eligibility before diagnosis were included in this exposure response analysis.

jDosing intensity calculated as number of days with supply of aspirin available from the first aspirin exposure in the 3 years before diagnosis up to diagnosis divided by the number of days from the first aspirin exposure in the 3 years before diagnosis up to diagnosis.

kP trend < 0.001.

lP trend < 0.01.
Table 3. Aspirin use and lymph node–positive breast cancer: effect-modification by tumor characteristics at diagnosis

<table>
<thead>
<tr>
<th>Aspirin use in the year before diagnosis</th>
<th>Nonuser</th>
<th>Low dosing intensity (1%–79%)</th>
<th>High dosing intensity (80%–100%)</th>
<th>Low dosing intensity vs. nonuser within strata</th>
<th>High dosing intensity vs. nonuser within strata</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Nonuser</td>
<td>266/582</td>
<td>55/100</td>
<td>0.02 (−0.06–0.11)</td>
<td>0.04 (−0.06–0.11)</td>
</tr>
<tr>
<td>T2–4</td>
<td>Ref (−)</td>
<td>0.02 (−0.06–0.11)</td>
<td>−0.04 (−0.13–0.04)</td>
<td>0.02 (−0.06–0.11)</td>
<td>0.04 (−0.06–0.11)</td>
</tr>
<tr>
<td><strong>Aspirin × tumor size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive scale IC (95% CI)d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR positive</td>
<td>Nonuser</td>
<td>456/462</td>
<td>80/84</td>
<td>0.00 (−0.08–0.08)</td>
<td>0.05 (−0.12–0.03)</td>
</tr>
<tr>
<td>PR negative</td>
<td>Ref (−)</td>
<td>0.00 (−0.08–0.08)</td>
<td>−0.05 (−0.12–0.03)</td>
<td>0.00 (−0.08–0.08)</td>
<td>0.05 (−0.12–0.03)</td>
</tr>
<tr>
<td><strong>Aspirin × PR status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive scale IC (95% CI)d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N+ve, node-positive; N−ve, node-negative; RD, risk difference; IC, interaction contrast.

aSeparate and joint effects of aspirin exposure and the effect modifier using a single reference category.
bDosing intensity by median. Dosing intensity calculated as number of days with supply of aspirin available in year before diagnosis, divided by 365.
cAssociation between aspirin exposure and nodal status within strata of the effect modifier.
dAdjusted for age, tumor size, tumor grade, comorbidity, and screen detection.
0.73–0.95). This is comparable to the results presented here for similar exposure intensity.

Our study did not examine associations between aspirin use and breast cancer incidence and therefore we cannot quantify the contribution that any reduction in breast cancer incidence due to aspirin exposure may have had on our results. However, studies that have evaluated aspirin use and breast cancer incidence have reported mixed results with the larger prospective cohorts and a single randomized trial finding no overall reduction in the risk of developing breast cancer (47–50). A prior study of associations between NSAID exposure and breast cancer incidence did stratify analyses by nodule status at diagnosis (51). The authors reported no difference in the incidence of node-positive or node-negative breast cancers. Three further studies have stratified their analyses by SEER summary stage classification (52–54). Differences in the incidence of localized versus regional/distant disease were only observed in one of these studies (localized: RR, 0.8; 95% CI, 0.63–1.03; regional/distant RR, 0.5; 95% CI, 0.29–0.88; ref. 54). The timing of exposure assessment in these studies of breast cancer incidence did not capture exposure close to the time of diagnosis, which is an important time window based on prior studies (1, 17). Also, none of these studies have adjusted for potential founders that may influence lymph node status such as tumor size and screen detection.

In analyses of effect-modification, we observed that recent prediagnostic aspirin use was associated with a greater reduction in the risk of presenting with node-positive disease in women with breast tumor characteristics previously associated with COX2 expression. This suggests that inhibition of lymphatic involvement by aspirin may be mediated, at least in part, through a COX2-dependent pathway. Our findings are consistent with observations from in vivo breast cancer models that have shown that COX2 inhibition suppresses the development of lymph node metastasis through the regulation of VEGF-C/-D–mediated lymphatic dysregulation (4, 5). VEGF-C/-D overexpression has been shown to induce hyperplasia in peritumoral lymphatic vessels, increasing lymphatic flow and enhancing the rate of tumor cell delivery to lymph nodes, leading to increased lymph node metastasis (4, 17). Inhibition of lymphatic dysregulation represents one possible mechanism of action for aspirin in breast cancer, although a number of other mechanisms have been proposed, including the inhibition of platelet function and reductions in serum estrogen concentrations (55, 56). It is not clear whether regulation of lymphangiogenesis can restore dysregulated lymphatics in established tumors or inhibit the development of lymphatic metastases from tumor cells that have already seeded to the lymph nodes (4, 17). This may explain why associations with reduced lymph node metastasis were only observed in women with regular aspirin use for a sustained period before diagnosis.

Survival analyses were undertaken to examine the potential effect that the inhibition of lymphatic metastasis by prediagnostic aspirin use may have on associations between aspirin use and breast cancer mortality. We hypothesized that in women using aspirin before their breast cancer diagnosis, the inhibition of lymph node involvement by aspirin would indicate women with aspirin-responsive tumors and predict a subsequent survival benefit from aspirin use. Some evidence for this was suggested in analyses stratified by nodal status at diagnosis; where, prediagnostic

---

### Table 4. Multivariate HRs for pre- and postdiagnostic aspirin use and 5 year all-cause or breast cancer–specific mortality

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>Person-years</th>
<th>Deaths</th>
<th>Multivariate HR (95% CI)</th>
<th>Deaths</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediagnostic aspirin use&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser in year before diagnosis</td>
<td>7,853</td>
<td>401</td>
<td>Ref (—)</td>
<td>274</td>
<td>Ref (—)</td>
</tr>
<tr>
<td>Aspirin user in year before diagnosis</td>
<td>2,720</td>
<td>148</td>
<td>0.81 (0.66–0.99)</td>
<td>87</td>
<td>0.80 (0.62–1.04)</td>
</tr>
<tr>
<td>Postdiagnostic aspirin use&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser postdiagnosis</td>
<td>9,096</td>
<td>459</td>
<td>Ref (—)</td>
<td>311</td>
<td>Ref (—)</td>
</tr>
<tr>
<td>Aspirin user postdiagnosis</td>
<td>1,477</td>
<td>90</td>
<td>1.11 (0.83–1.50)</td>
<td>50</td>
<td>0.99 (0.68–1.45)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age (years, continuous), tumor stage (I, IIa, IIb, IIIa, IIIb–c) tumor grade (low, intermediate, high, unspecified), ER status (positive, negative, unspecified), PR status (positive, negative, unspecified), HER2 status (positive, negative, unspecified), and comorbidity score (number of medication classes, continuous).

<sup>b</sup>Postdiagnostic aspirin use defined as exposed, unexposed, time varying, lagged by 2 years.

<sup>c</sup>Adjusted for prediagnostic aspirin use, age (years, continuous), tumor stage (I, IIa, IIb, IIIa, IIIb–c), tumor grade (low, intermediate, high, unspecified), ER status (positive, negative, unspecified), PR status (positive, negative, unspecified), HER2 status (positive, negative, unspecified), and comorbidity score (number of medication classes, continuous).
aspirin use was associated with a statistically significant reduced risk of 5-year breast cancer–specific mortality among women with lymph node–negative disease at diagnosis, but not those with lymph node–positive disease, although tests for effect-modification were not statistically significant. The length of mortality follow-up for women in our study was 5 years, and longer follow-up will be needed to generalize these results beyond this time. While this study is the first to directly assess the modification of associations between prediagnostic aspirin use and breast cancer mortality by nodal status, the results from a previous study do provide some support for our observations (3). Blair and colleagues have reported a statistically significant association between NSAID exposure and mortality in women with localized breast cancer (100% node-negative; HR, 0.37; 95% CI, 0.16–0.86) but not women with nonlocalized breast cancer (1.6% node-negative; HR, 0.67; 95% CI, 0.31–1.43). Our results are also consistent with the findings from a recent meta-analyses of cardiovascular trials (1). In this study, prediagnostic aspirin use was associated with a statistically significant reduced risk of presenting with distant metastatic disease in a range of cancers. Furthermore, a reduction in mortality due to cancer was primarily observed among patients with local disease at diagnosis. In contrast with some prior studies (2, 3, 57), we observed no association between postdiagnostic aspirin use and breast cancer–specific mortality; however, the length of postdiagnostic follow-up for women in our study was shorter than these prior studies. There are other possible reasons for this difference, unlike prior studies, we adjusted our analyses for prediagnostic aspirin use, we also identified postdiagnostic aspirin exposure using objective prescription refill data rather than patient self-report, which can be less precise (43).

The strengths of this study include its prospectively collected exposure and outcome data and the availability of high-quality patient level information on mammographic screening. In addition, the prescription-only status of low-dose aspirin in Ireland allowed the objective assessment of detailed cumulative aspirin exposure histories for all women. The study also has some limitations. It is possible that the clinically relevant window of exposure for inhibiting lymphatic metastasis extends further than 3 years before diagnosis and that distant prediagnostic exposure—in patients who discontinued aspirin before diagnosis—is also of clinical relevance; future studies should examine longer durations of prediagnostic exposure. In addition, as aspirin use was based upon prescriptions dispensed, noncompliance with treatment will have resulted in exposure misclassification. The misclassification of aspirin exposures due to this would most likely be nondifferential with respect to lymph node status and will usually, but not always, bias results toward the null (58). Information on lifestyle factors that may affect nodal involvement and disease progression, such as obesity, alcohol use, and vitamin D, was not available. The results from analyses of effect modification by PR and HER2 status should also be interpreted with caution due to the number of women with unspecified receptor status. In survival analyses, postdiagnostic exposures were lagged to reduce the possibility that changes in prognosis after diagnosis influenced postdiagnostic aspirin use. While this is an accepted approach in analyses of postdiagnostic exposures (43), it may not fully eliminate time-dependent confounding. Together, our findings provide insight into aspirin’s potential mechanism of action in breast cancer progression. They indicate that recent prediagnostic aspirin exposure inhibits the development of lymph node metastases and, in women using aspirin before a breast cancer diagnosis, negative nodal status may predict a subsequent survival benefit from aspirin use at 5 years. However, Studies with longer follow-up are required to confirm this. These results provide a plausible explanation for the reduction in breast

![Figure 2. Adjusted cumulative probability of 5-year breast cancer–specific mortality for aspirin users and nonusers in the full cohort and by lymph node status at diagnosis (positive, negative), adjusted for age, tumor stage, tumor grade, ER, PR, HER2, and comorbidity.](image-url)
cancer mortality seen in prior observational studies of aspirin use.

Disclosure of Potential Conflicts of Interest

L. Sharp reports receiving a commercial research grant from Sanofi Aventis. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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 NCI or the Irish Health Services Executive Primary Care Reimbursements Services. The Health Research Board Ireland, the Irish Cancer Society, and the Breast Cancer Research Foundation had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit for publication.

Authors’ Contributions

Conception and design: T.I. Barron, L. Sharp, K. Visvanathan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.I. Barron, L. Sharp, K. Bennett
Analysis and interpretation of data (e.g., statistical analysis, bio-statistics, computational analysis): T.I. Barron, L. Sharp, K. Bennett, K. Visvanathan
Writing, review, and/or revision of the manuscript: T.I. Barron, E.M. Flahavan, L. Sharp, K. Bennett, K. Visvanathan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.I. Barron
Study supervision: T.I. Barron

Acknowledgments

The authors thank the NCI and the Irish Health Services Executive Primary Care Reimbursements Services for providing access to the data upon which this study was based. In particular, they also thank the Data Team at the NCRI for linking the datasets and Dr. Sandra Deady for preparing these for analysis.

Grant Support

T.I. Barron is supported by the Health Research Board Ireland (HRA-2009-221, ICE-2011-9) and the Irish Cancer Society (CCRC13GAL). E.M. Flahavan is supported by the Irish Cancer Society (CRS10FLA). K. Visvanathan is supported in part by the Breast Cancer Research Foundation. This study is based upon works supported by the Irish Cancer Society Collaborative Cancer Research Centre BREAST-PREDICT (CCRC13GAL).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 26, 2013; revised May 1, 2014; accepted May 3, 2014; published online August 1, 2014.

References


Table 5. Prediagnostic aspirin use and 5-year breast cancer–specific mortality: effect-modification by lymph node status at diagnosis

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Aspirin use in the year before diagnosis</th>
<th>User vs. nonuser within stratab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonusera</td>
<td>Usera</td>
</tr>
<tr>
<td>Positive</td>
<td>Person years</td>
<td>3,750</td>
</tr>
<tr>
<td></td>
<td>Censored/death</td>
<td>827/209</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Ref (–)</td>
</tr>
<tr>
<td>Negative</td>
<td>Person years</td>
<td>4,103</td>
</tr>
<tr>
<td></td>
<td>Censored/Death</td>
<td>955/65</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.60 (0.42–0.86)</td>
</tr>
<tr>
<td>Aspirin × nodal status</td>
<td>Multiplicative scale:</td>
<td>0.60 (0.34–1.08)</td>
</tr>
</tbody>
</table>

Abbreviation: rHR, ratio of hazard ratios.

The separate and joint effects of aspirin exposure and nodal status in comparison with a single reference category.

The effects of aspirin exposure within strata of nodal status.

Adjusted for age, comorbidity, tumor stage, tumor grade, ER, PR, and HER2.

www.aacrjournals.org Cancer Res; 74(15) August 1, 2014 4075


Recent Prediagnostic Aspirin Use, Lymph Node Involvement, and 5-Year Mortality in Women with Stage I–III Breast Cancer: A Nationwide Population-Based Cohort Study
