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Low-dose aspirin, non-steroidal anti-inflammatory drugs, selective COX-2 inhibitors and breast cancer recurrence

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Abstract

Background—Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors may improve outcomes in breast cancer patients. We investigated the association of aspirin, NSAIDs, and use of selective COX-2 inhibitors with breast cancer recurrence.

Methods—We identified incident stage I–III Danish breast cancer patients in the Danish Breast Cancer Cooperative Group registry, who were diagnosed during 1996–2008. Prescriptions for aspirin (>99% low-dose aspirin), NSAIDs, and selective COX-2 inhibitors were ascertained from the National Prescription Registry (NPR). Follow-up began on the date of breast cancer primary surgery and continued until the first of recurrence, death, emigration, or 01/01/2013. We used Cox regression models to compute hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) associating prescriptions with recurrence, adjusting for confounders.

Results—We identified 34,188 breast cancer patients with 233,130 person-years of follow-up. Median follow-up was 7.1 years; 5,325 patients developed recurrent disease. Use of aspirin, NSAIDs, or selective COX-2 inhibitors was not associated with the rate of recurrence ($HR_{adjusted}$

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aspirin=1.0, 95% CI=0.90, 1.1; NSAIDs=0.99, 95% CI=0.92, 1.1; selective COX-2 inhibitors=1.1, 95% CI=0.98, 1.2), relative to non-use. Pre-diagnostic use of the exposure drugs was associated with reduced recurrence rates ($HR_{aspirin}$=0.92, 95%CI=0.82, 1.0; HR_{NSAIDs}=0.86, 95%CI=0.81, 0.91; $HR_{sCOX\text{-}2inhibitors}$=0.88, 95%CI=0.83, 0.95).

Conclusions—This prospective cohort study suggests that post-diagnostic prescriptions for aspirin, NSAIDs, and selective COX-2 inhibitors have little or no association with the rate of breast cancer recurrence. Pre-diagnostic use of the drugs was, however, associated with a reduced rate of breast cancer recurrence.

Keywords

breast cancer; breast cancer recurrence; cohort study; epidemiology; aspirin; non-steroidal anti-inflammatory drugs; selective COX-2 inhibitors; risk

INTRODUCTION

Breast cancer accounts for 23% of female cancers and is the most frequent cause of cancer-related death among women worldwide.[1] Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors, hereafter referred to as COX-2 inhibitors, are effective analgesic, anti-pyretic, and anti-inflammatory drugs. They exert pleiotropic effects, including the prevention of cardiovascular disease[2,3] and cancer,[4] although the latter may be confined to subpopulations.[5,6] Aspirin, NSAIDs, and COX-2 inhibitors target the cyclooxygenase enzymes, COX-1 and COX-2.[7,8] These enzymes promote angiogenesis and prevent apoptosis.[9] COX-1 is ubiquitously expressed, but COX-2 is expressed only during inflammation and in cancer.[10] Elevated COX-2 and its products, prostaglandins, correlate with shorter breast cancer survival.[11–15] Cell line and animal model research suggests that NSAIDs, aspirin, and COX-2 inhibitors impede breast cancer cell growth.[9,16,17]

Findings from epidemiologic studies of the association of these drugs with breast cancer prognosis are inconsistent.[18–27] At least three years of pre-diagnostic aspirin use has been associated with a 20% reduction in breast cancer mortality.[23] Post-diagnostic aspirin use (both low-dose and high-dose) has been associated with a 50% reduction in breast cancer recurrence/mortality in some,[18,28] but not all studies.[19,21–25] Research on the effect of NSAIDs on breast cancer recurrence or mortality also report conflicting findings.[20–22,29,30] Decreased recurrence has been correlated with perioperative use of ketorolac[29,30] and use of any NSAID.[20,21] However, protective associations have not been found in all studies,[22] and there is no evidence of a dose-response effect.[20]

Ongoing clinical trials are investigating potential survival benefits associated with use of pre- and post-operative COX-2 inhibitors in cancer patients (www.clinicaltrials.gov). A trial of 37 breast cancer patients suggested that pre-operative use of the COX-2 inhibitor celecoxib decreased Ki67 expression, a marker of tumor proliferation rate, but did not evaluate patient survival.[31] No observational study has investigated the association between COX-2 inhibitors and survival outcomes in breast cancer patients.[21]

The discordant findings regarding the association of aspirin or NSAIDs with outcomes in breast cancer patients may stem from differences in the measured confounders, or variation in the methods used to assess drug exposure, *i.e.*, self-reported versus prescription-based. Many studies investigated mortality[18–22,25] rather than disease recurrence.[18,21] Given the established protective effect of low-dose aspirin against cardiovascular disease,[32] assessing mortality rather than recurrence mixes the potential effect of the drug on cancer recurrence —which predisposes patients to mortality—with its direct effect on mortality. Further, several published aspirin studies did not adjust for statins,[18,20–22,24,28,33,34] which are frequently prescribed with aspirin to prevent cardiovascular disease, and have been consistently associated with better survival in breast cancer patients.[35,36]

To address the limitations of previous research, we conducted a large population-based study with prospectively collected data to investigate the association of aspirin (primarily low-dose aspirin, as high-dose aspirin is rarely used in Denmark), NSAIDs, and COX-2 inhibitors with the rate of breast cancer recurrence among breast cancer survivors in Denmark.

METHODS

This study was approved by the Danish Data Protection Agency (Record 2012-41-0793), the Danish Medicines Agency, and the Danish Breast Cancer Cooperative Group (DBCG). This study is based on routinely collected registry data therefore separate ethical approval was not necessary.

Source population and data collection

We included all women in Denmark diagnosed with incident invasive non-metastatic breast cancer between 1996 and 2008 registered in the DBCG (n=34,188). Since its establishment in 1976 the DBCG has registered most cases of invasive breast cancer in Denmark.[37] Registration completeness has increased over time from 87% in 1986 to 96% in 1997.[38,39] Pre-specified data on tumor, treatment, and patient characteristics are prospectively obtained from treating physicians. DBCG patients with operable disease undergo follow-up exams to detect recurrences twice-yearly for the first five years and annually up to ten years after diagnosis. Follow-up exams include a clinical evaluation and, if indicated, a chest x-ray, CT scan, bone scan, or other investigation to detect disease recurrence.[40] Patients who develop recurrent disease between follow-up exams are also reported to the DBCG. We used the DBCG registry to ascertain data on age, menopausal status at diagnosis, WHO histological tumor type and grade, lymph node status, tumor estrogen receptor (ER) status, type of primary surgery (mastectomy or breast-conserving surgery), chemotherapy, radiation therapy, endocrine therapy (ET), and date and anatomical site of recurrence. We used the Danish Civil Registration System to retrieve information on mortality and emigration.[41]

The Danish National Prescription Registry (NPR), maintained by Statistics Denmark, has recorded all prescriptions dispensed at Danish pharmacies since 1995. Recorded data include the redemption date, prescribed drug [classified by Anatomical Therapeutic Chemical (ATC) codes], and fill quantity.[42] Via Statistics Denmark, we linked prescription data from the NPR to the clinical cohort using the civil personal registration number, a

unique personal identification number assigned to each Danish citizen at birth or emigration.[43]

We used the NPR to ascertain information on prescriptions for aspirin (low dose as B01AC06 and N02BA01 in tablet sizes of 75, 100, or 150mg, and high dose as N02BA51 and N02BA01 in tablet sizes of 500mg), NSAIDs, and COX2 inhibitors, as well as potentially confounding co-medications including one or more prescriptions for simvastatin, angiotensin-converting enzyme inhibitors (ACE-inhibitors), beta-adrenergic blocking drugs (beta-blockers), and postmenopausal hormone replacement therapy (HRT) (eAppendix 1).

We obtained data on comorbid diseases from the Danish National Patient Registry (DNPR), which contains data on all non-psychiatric hospital admissions since 1977 and on outpatient hospital contacts since 1995.[44] At discharge, the DNPR records the civil personal registration number, admission and discharge dates, and up to 20 discharge diagnoses. We ascertained prevalent comorbid diseases at index date, including rheumatoid arthritis, osteoarthritis, diabetes, cancer, liver disease, arrhythmia, angina, peripheral and cerebral vascular disease, myocardial infarction, and congestive heart failure (eAppendix 2).

Analytic variables

Age at diagnosis was treated as a continuous variable in the multivariable Cox regression models. Person-time at risk for recurrence was defined as the number of days between the date of primary surgery and the date of breast cancer recurrence, death, emigration, or January 1, 2013, whichever occurred first. We used the DBCG definition of breast cancer recurrence as any local, regional, or distant recurrence, or contralateral breast cancer.[40] Histological grade was classified as low, moderate, or high. We defined surgery as either mastectomy or breast-conserving surgery with radiation therapy. Adjuvant chemotherapy was treated as a dichotomous variable. We summarized ER and ET as a joint variable (ER +/ET+, ER+/ET−, ER−/ET+, ER−/ET−).

The exposure drugs—aspirin, NSAIDs, and COX-2 inhibitors—were modeled as time-dependent post-diagnosis exposures to at least one prescription, updated daily during follow-up and lagged by one year. We also modeled exclusive use of each of the exposure drugs (*i.e.*, aspirin but not NSAIDs or COX-2 inhibitors; NSAIDs, but not aspirin or COX-2 inhibitors; and COX-2 inhibitors, but not aspirin or NSAIDs), and use of any of the three drug types as a combined category. In the latter analyses, all patients were included in these models and the reference category represented women who had not used any of the drug types. In sensitivity analyses, we changed the definition of exposure from filling ≥1 to filling ≥2 prescriptions during follow-up, and changed the lag time from one to two years.[45]

We assessed a potential dose-response effect of the exposure drugs on recurrence according to the number of prescriptions for each drug over the entire follow-up period. We assessed the mean number of days per prescription and then estimated one year supply for each drug. A one year supply equated to 3 prescriptions for aspirin, 5 prescriptions for NSAIDs, and 6 prescriptions for COX-2 inhibitors.

We modelled the association of pre-diagnostic aspirin use, and, in *post-hoc* analyses, modelled the association of pre-diagnostic use of NSAIDs and COX-2 inhibitors with the rate of breast cancer recurrence. For these analyses, we restricted the study cohort to women with at least two years of prescription history at the time of diagnosis (n=32,024). Pre-diagnostic use of each drug was defined as redemption of one or more prescriptions before breast cancer diagnosis.

Prescriptions for potentially confounding drugs—simvastatin, ACE-inhibitors, and beta-blockers—were modeled as time-varying covariates lagged by one year. HRT was modeled as a baseline covariate.[18,36]

Statistical analyses

We examined the frequency and proportion of subjects ever- versus never-prescribed aspirin, NSAIDs, and COX-2 inhibitors within categories of covariates (Table 1 and eTables 1a–c). Cox regression models were used to compute the rate of breast cancer recurrence and site of recurrent disease up to ten years after diagnosis, expressed in terms of hazard ratios (HRs) and associated Wald 95% confidence intervals (95% CIs), with and without adjustment for age, menopausal status, histological grade, estrogen receptor/endocrine therapy (ER/ET) status, stage, primary surgery type, chemotherapy, prevalent comorbidities, baseline HRT use, and post-diagnosis use of simvastatin, ACE-inhibitors, and beta-blockers. The one-year lag in the Cox models allowed for a sufficient induction period to examine drug effects on recurrence, and guarded against the possibility that subclinical recurrences affected prescribing patterns. We used Cox regression models to evaluate a dose-response association between the exposure drugs and breast cancer recurrence and mortality. We investigated effect measure modification stratifying analyses by stage and ER status. Cox models were used to evaluate the association between pre-diagnostic drug use and breast cancer recurrence, and to evaluate the association of the exposure drugs with the rate of all-cause mortality.

We also conducted analyses in a cohort restricted to patients with at least 5 years prescription history, without any pre-diagnostic prescriptions for the exposure drugs, and used Cox models to analyze “new use” of the exposure drugs. In these analyses, the exposure drugs were treated as time-varying exposures lagged by one year. All analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC).

RESULTS

The study included 34,188 breast cancer patients diagnosed between 1996 and 2008. Overall, 17%, 42%, and 17% were ever users of aspirin, NSAIDs, or COX-2 inhibitors, respectively (Table 1). Aspirin users were older than non-users, and accordingly more frequently postmenopausal at diagnosis. More users of aspirin or COX-2 inhibitors (62% versus 56%, and 59% versus 56%, respectively), but not NSAIDs (55% versus 57%), underwent mastectomy compared with non-users of each drug type. Aspirin, NSAIDs, and COX-2 inhibitor users were also more likely to have used simvastatin than non-users of each drug type. Users of the exposure drugs were less likely to receive chemotherapy. Compared with non-users, aspirin users had a higher frequency of heart, vascular, or liver diseases;

users of NSAIDs and COX-2 inhibitors had a higher frequency of rheumatoid arthritis (eTables 1a, 1b, 1c). Over 99% of aspirin prescriptions were for low-dose formulations. Ibuprofen (46%) and diclofenac (69%) were the most frequently prescribed NSAID and COX-2 inhibitors, respectively (eAppendix 3).

Overall, 5,325 (16%) patients developed recurrent disease. Compared with non-use, use of aspirin, NSAIDs, and COX-2 inhibitors had almost no effect on recurrence in models where drug exposure was lagged by one year: adjusted $HR_{aspirin}$=1.0, 95% CI=0.90, 1.1; HR_{NSAIDs}=0.99, 95% CI=0.92, 1.1; $HR_{sCOX2\ inhibitors}$=1.1, 95% CI=0.98, 1.2 (Table 2). Similar near null findings were evident in pre-planned sensitivity analyses with drug exposures lagged by two years and with the exposure threshold set to ≥2 prescriptions annually (eAppendix 4). Results also suggested no evidence of an association between use of any of the three drug types with breast cancer recurrence (HR=1.0, 95%CI=0.94, 1.1). We noted similar findings for exclusive use of aspirin, or NSAIDs, or COX-2 inhibitors, or several exposure drugs ($HR_{aspirin}$ =1.0, 95%CI=0.90, 1.2; HR_{NSAIDs} =0.99 95%CI=0.91, 1.1; $HR_{sCOX\text{-}2\ inhibitors}$ = 1.0, 95%CI=0.90, 1.2; $HR_{several}$=1.0, 95%CI=0.90, 1.2).

Analyses stratified by ER/ET status and by stage at diagnosis yielded little change in the effect estimates for the exposure drugs (Table 3). Findings for aspirin and COX-2 inhibitors were also near null in analyses accounting for cumulative number of prescriptions (Table 2). We note a reduced rate of recurrence with increasing number of NSAIDs prescriptions ($HR_{1–5\ prescriptions}$=1.0, 95%CI=0.95, 1.1; $HR_{6–10\ prescriptions}$=0.88, 95%CI=0.77, 1.0; $HR_{>10\ prescriptions}$=0.92, 95%CI=0.81, 1.0), but this was accompanied by increased all-cause mortality ($HR_{1–5\ prescriptions}$=1.0, 95%CI=1.0, 1.2; $HR_{6–10\ prescriptions}$=1.3, 95%CI=1.1, 1.4; $HR_{>10\ prescriptions}$=1.7, 95%CI=1.6, 1.9).

Most recurrent events occurred in the bone, followed by the ipsilateral breast, contralateral breast, lymph nodes, and lungs. Associations for aspirin remained near null by site of recurrence (data not presented). Use of pre-diagnostic aspirin, NSAIDs, and COX-2 inhibitors correlated with a decreased rate of breast cancer recurrence (adjusted $HR_{Aspirin}$=0.92, 95% CI=0.82, 1.0; adjusted HR_{NSAIDs}=0.86, 95% CI=0.81, 0.91; adjusted $HR_{sCOX\text{-}2\ inhibitors}$=0.89, 95% CI=0.83, 0.95).

DISCUSSION

Evidence from our large clinical cohort study does not support a protective effect of post-diagnostic use of aspirin, NSAIDs, or COX2 inhibitors on breast cancer recurrence. These near null findings were not modified by stratification on ER status/receipt of endocrine therapy or stage at diagnosis, and also remained null in analyses examining drug exposure and site-specific cancer recurrence. We observed a slightly protective association between NSAIDs and breast cancer recurrence, but higher mortality among patients with increasing numbers of NSAIDs prescriptions, suggesting confounding by indication. Our findings from pre-planned analyses of pre-diagnostic aspirin use, and *post-hoc* analyses of pre-diagnostic NSAIDs and COX-2 inhibitor use, suggest a protective association with breast cancer recurrence.

The near null associations we observed for post-diagnostic aspirin exposure agree with several published studies on the effect of post-diagnostic aspirin prescriptions and breast cancer-specific mortality.[19,21,23–25] However, our findings contrast with the strong protective associations for aspirin observed in two US-based studies (the Nurses' Health Study (NHS) and the Iowa Women's Health Study) and a Scottish cohort study.[18,20,28] The mortality reductions observed in the US-based studies [18,20] could be attributed to a higher prevalence of high-dose aspirin use compared with the European studies. Over one-third of aspirin users in the NHS cohort took high-dose aspirin.[18] High-dose aspirin inhibits prostaglandin production to exert an analgesic effect, whereas low-dose aspirin exerts an anti-platelet effect.[19,46] Still, if the reduced mortality rates in the US-based studies stem from high-dose aspirin inhibiting prostaglandins, we would expect to observe a similar decreased rate of recurrence associated with post-diagnostic NSAID and COX-2 inhibitor use in our study. The near null associations that we and others[22] observed for post-diagnostic NSAIDs and COX-2 inhibitor use do not support such a protective effect of prostaglandin inhibition on breast cancer recurrence. Our findings for post-diagnostic aspirin use also seem at odds with results from studies nested within randomized trials of aspirin and vascular events[26] and a meta-analysis of trials and observational studies.[26,27] Both suggest that cancers that developed in aspirin users were less likely to have distant metastases compared with cancers that developed in non-users. However, these studies do not isolate the specific effect of aspirin and NSAIDs on the risk of distant metastases in breast cancer patients.

The Scottish study suggested substantially reduced breast cancer mortality associated with aspirin exposure. However, the study had large proportions of missing data (40% for some variables), seemingly contradictory effects of pre- and post-diagnostic aspirin use on breast cancer mortality (over two-fold risk versus half the risk, respectively), and substantial differences between crude and adjusted estimates. The last of these suggests implausibly strong confounding. The Scottish study also may be prone to confounding by indication due to the inclusion of patients with stage IV disease.

Our results for NSAIDs contrast with two other US-based cohort studies, which observed almost 50% reduction in breast cancer-specific or all-cause mortality associated with NSAID use.[20,21] However, drug exposure in both studies was based on questionnaire data ascertained at only one time point, and in one study was not modeled as a time-varying factor.[21]

Contrary to most published studies, our study investigated breast cancer recurrence rather than cancer-specific or all-cause mortality. Due to the definition of recurrent disease in the DBCG, a proportion (16%) of the DBCG-designated "recurrent disease" is actually contralateral breast cancer, and as such, may represent *de novo* disease. However, our near-null effect estimates were consistent regardless of site of disease recurrence.

The slight reduction in risk of recurrence associated with pre-diagnostic aspirin use is in keeping with a more pronounced (20%) reduction in breast cancer mortality at five years observed by Barron et al. among Irish breast cancer patients.[23] The reduced rates of recurrence we observed for pre-diagnostic use of NSAIDs and COX2 inhibitors are intriguing. They may indicate different tumor phenotypes in women routinely prescribed

these drugs,[48] but may also be attributable to detection bias, via more frequent healthcare access, and accordingly earlier stage at cancer diagnosis with a resulting lower likelihood for recurrence. The biologic mechanism(s) underlying any protective effects of pre-diagnostic drug use are difficult to deduce. Our findings suggest that both a platelet inhibitory effect (mediated by low-dose aspirin), and a prostaglandin inhibitory effect (mediated by NSAIDs and sCOX2 inhibitors) may have a role in preventing recurrence. Further exploration of these findings is necessary to determine any potential causal associations.

Several issues should be considered when interpreting our findings. The large size of our study and prospectively collected data ensured that exposure assessment occurred before outcome, eliminating recall bias. Use of the DBCG and Danish registries ensured high quality data on breast cancer diagnosis, treatment, and recurrence, and virtually complete follow-up.[37] Due to the comprehensive registry network, a strength of our study was the possibility of adjusting for several potential confounders. However, as our crude estimates were similar to the adjusted estimates, there was little evidence of confounding. The prospective prescription data enabled us to assess any evidence of a dose-response effect of the exposure drugs on recurrence. Our study substantially extends existing knowledge as we assessed the outcome of breast cancer recurrence rather than mortality. This advantage allowed us to investigate the specific effect of aspirin, NSAIDs, and COX2 inhibitors on breast cancer, rather than on breast cancer mortality—which may be misclassified—or on all-cause mortality. We linked our cohort to other population-based and medical registries to retrieve comprehensive data on comorbid diseases and co-prescriptions for each patient. In sensitivity analyses, we assessed the possibility of a latent effect of drug exposure on our outcome data, minimizing the potential for reverse causation. Some research suggests that the anticancer effect of aspirin and NSAIDs only manifests in patients with ER−/HER2− tumors.[49] However, we saw little difference in results when stratified by ER/endocrine therapy status. As HER2 testing was only implemented in Denmark in 2006, we had insufficient data to also stratify by HER2.

Our study has some limitations. We lacked information on prescription compliance, which may lead to exposure misclassification. However, in Denmark, patients pay for part of their redeemed prescriptions, so our estimates are likely to reflect actual use. Another concern is that all aspirin formulations are available over the counter in Denmark.[50] However, low-dose aspirin, which targets platelets and has anti-cancer effects,[51] is almost exclusively indicated for cardiovascular disease prevention. Over the counter analgesics are only available in pill packs, not in large quantity bottles. Regularly used low-dose aspirin is therefore usually prescribed by physicians and reimbursable via the Danish national health insurance system.[50] Research suggests that use of non-prescription low-dose aspirin is about 8% in Denmark.[52] As 17% of women in our cohort were prescribed post-diagnostic aspirin, such non-prescription low-dose aspirin use may have contributed to our null findings, but only if used regularly, which is unlikely as described above. We had no information on use of non-prescription low-dose ibuprofen (200mg tablets), which accounts for about one-third of ibuprofen use in Denmark.[52] However, non-prescription use of ibuprofen is also likely to be sporadic and short-term, for treatment of transient pain like headaches or acute injuries. The Danish prescription registry data therefore are a valid source of regular exposure to aspirin and non-aspirin NSAIDs, particularly for chronic indications. We adjusted our analyses for

rheumatoid arthritis and migraine as both may correlate with over-the-counter use of analgesics. We had no information on the indication for the exposure drug prescriptions, but adjustment for several potentially confounding comorbid conditions did not alter the effect estimates.

We note that research on colorectal cancer suggests that anti-cancer effects of aspirin depend on genetic factors (for example *BRAF* mutations),[5,6] and some individuals may be intrinsically resistant to the anti-cancer effects of aspirin. Accordingly, aspirin users who develop cancer may be a selected population with intrinsic resistance. Unfortunately, we had no genetic data on patients included in our study. However, we did explore the possibility of acquired resistance to the exposure drugs by examining recurrence rates among new users of the drugs, but our findings remained near null.

The potential for generic drugs such as aspirin, NSAIDs, and COX2 inhibitors to delay, mitigate, or prevent breast cancer mortality is compelling, with global implications for increasing access to affordable medicine to treat cancer.[8,53] Several researchers have called for clinical trials to investigate the association between aspirin and breast cancer survival.[18,24,53] Our study of over 34,000 breast cancer survivors provides little evidence to support such a protective effect of post-diagnostic use of aspirin, NSAIDs, or COX2 inhibitors on breast cancer recurrence. However, our observed reduction in recurrence rates associated with pre-diagnostic use of these drugs necessitates further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of patients diagnosed with breast cancer in Denmark, 1996 to 2008 (n=34,188), according to post-diagnosis aspirin use, NSAIDs, and COX2 inhibitor prescription use.

Variable	Aspirin non-users n=27,386 (80%)	Aspirin users n=6,802 (20%)	NSAIDs non-users n=14,141 (41%)	NSAIDs users n=20,047 (59%)	COX2 inhibitor non-users n=24,175 (71%)	COX2 inhibitor users n=10,013 (29%)
Age at diagnosis (years)						
≤29	120 (<1)	0	55 (<1)	65 (<1)	86 (<1)	34 (<1)
30–39	1,558 (6)	33 (<1)	755 (5)	836 (4)	1,173 (5)	418 (4)
40–49	5,662 (21)	300 (4)	2,550 (18)	3,412 (17)	4,302 (18)	1,660 (17)
50–59	9,020 (33)	1,375 (20)	5,243 (30)	6,152 (30)	7,196 (30)	3,199 (32)
60–69	7,665 (28)	2,785 (41)	4,212 (30)	6,238 (31)	7,419 (31)	3,031 (30)
70–79	2,887 (11)	1,855 (27)	1,897 (13)	2,845 (14)	3,287 (14)	1,455 (15)
≥80	484 (2)	454 (7)	429 (3)	857 (2)	712 (3)	216 (2)
Menopausal status at diagnosis						
Pre-menopausal	9,124 (33)	498 (7)	4,138 (30)	5,484 (27)	6,902 (29)	2,720 (27)
Post-menopausal	18,249 (67)	6,302 (93)	9,997 (71)	14,554 (73)	17,263 (71)	7,288 (73)
(Missing)	13 (<1)	2 (<1)	6 (<1)	9 (<1)	10 (<1)	5 (<1)
UICC[a] stage						
I	10,303 (38)	2,659 (39)	4,922 (35)	8,040 (40)	8,946 (37)	4,016 (40)
II	12,120 (44)	3,134 (46)	6,334 (45)	8,920 (45)	10,832 (45)	4,422 (44)
III	4,963 (18)	1,009 (15)	2,885 (20)	3,087 (15)	4,397 (18)	1,575 (16)
Histologic grade						
Sample not suitable	108 (<1)	21 (<1)	46 (<1)	83 (<1)	88 (<1)	41 (<1)
Low	7,436 (27)	2,035 (30)	3,605 (25)	5,866 (29)	6,529 (27)	2,942 (29)
Moderate	10,270 (38)	2,649 (39)	5,368 (38)	7,551 (38)	9,253 (38)	3,666 (37)
High	5,875 (21)	1,155 (17)	3,284 (23)	3,746 (19)	5,203 (22)	1,827 (18)
Unknown	3,697 (14)	942 (14)	1,838 (13)	2,801 (14)	3,102 (13)	1,537 (15)
ER[b]/adjuvant ET[c] status						
ER+/ET+	14,126 (52)	3,740 (55)	7,343 (52)	10,523 (52)	12,758 (53)	5,108 (51)
ER+/ET−	6,846 (25)	1,718 (25)	3,247 (23)	5,317 (27)	5,849 (24)	2,715 (27)
ER−/ET+	177 (<1)	27 (<1)	88 (<1)	116 (<1)	131 (<1)	73 (<1)
ER−/ET−	5,504 (20)	1,150 (17)	3,095 (22)	3,559 (18)	4,814 (20)	1,840 (18)

Variable	Aspirin non-users n=27,386 (80%)	Aspirin users n=6,802 (20%)	NSAIDs non-users n=14,141 (41%)	NSAIDs users n=20,047 (59%)	COX2 inhibitor non-users n=24,175 (71%)	COX2 inhibitor users n=10,013 (29%)
Unknown	733 (3)	167 (2)	368 (3)	532 (3)	623 (3)	277 (3)
Type of primary surgery						
Mastectomy	15,169 (55)	4,193 (62)	8,296 (59)	11,066 (55)	13,552 (56)	5,810 (58)
BCS + RT[d]	12,213 (45)	2,607 (38)	5,842 (41)	8,978 (45)	10,619 (44)	4,201 (42)
(Missing)	4 (<1)	2 (<1)	3 (<1)	3 (<1)	4 (<1)	2 (<1)
Adjuvant chemotherapy received						
Yes	17,062 (62)	5,687 (84)	9,023 (64)	13,726 (68)	15,715 (65)	7,034 (70)
No	10,324 (38)	1,115 (16)	5,118 (36)	6,321 (32)	8,460 (35)	2,979 (30)
Other drug exposures						
Aspirin (high and low doses)	0	6,802 (28)	2,254 (16)	4,548 (23)	4,355 (18)	2,447 (24)
NSAIDs[e]	15,499 (57)	4,548 (67)	0	20,047 (100)	12,668 (52)	7,379 (74)
COX-2 inhibitors[f]	7,566 (28)	2,447 (36)	2,634 (29)	7,379 (37)	0	10,013 (100)
Simvastatin	3,819 (14)	3,299 (49)	2,352 (17)	4,766 (24)	4,716 (20)	2,402 (24)
Hormone replacement therapy	7,963 (29)	2,594 (38)	3,376 (24)	7,181 (36)	6,692 (28)	3,865 (39)
Medical history at diagnosis						
Myocardial diagnosis	50 (<1)	303 (4)	147 (1)	206 (1)	237 (<1)	116 (1)
Congestive heart disease	111 (<1)	182 (3)	146 (1)	147 (<1)	208 (<1)	85 (<1)
Peripheral vascular disease	183 (<1)	341 (5)	229 (2)	295 (1)	356 (1)	168 (2)
Cerebrovascular disease	340 (1)	651 (10)	445 (3)	546 (3)	715 (3)	276 (3)
Rheumatoid arthritis	234 (<1)	78 (1)	86 (<1)	226 (1)	178 (<1)	134 (1)
Mild liver disease	133 (<1)	45 (<1)	91 (<1)	87 (<1)	118 (<1)	60 (<1)
Moderate to severe renal disease	85 (<1)	58 (<1)	69 (<1)	74 (<1)	99 (<1)	44 (<1)
Moderate to severe liver disease	422 (2)	999 (15)	574 (4)	847 (4)	969 (4)	452 (5)
Angina pectoris	244 (<1)	726 (11)	370 (3)	580 (3)	637 (3)	313 (3)
Migraine	124 (<1)	38 (<1)	49 (<1)	113 (<1)	76 (<1)	86 (<1)

[a] UICC= Union Internationale Contre Cancer.

[b] ER= estrogen receptor.

[c] ET= endocrine therapy.

[d] BCS + RT = breast conserving surgery and radiotherapy.

[e] NSAIDs = non-steroidal anti-inflammatory drugs.

[f] COX-2 inhibitors = selective COX-2 inhibitors

Table 2

Breast cancer recurrence up to ten years after diagnosis, hazard ratios, and associated 95% confidence intervals (95% CIs) for stages I, II, or III breast cancer patients in Denmark from 1996 through 2008, by aspirin, NSAID, or selective COX-2 inhibitor use.

Exposure definition	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI) [a]
Aspirin		
Non-use	1.0	1.0
Aspirin use	0.92 (0.84, 1.0)	1.0 (0.90, 1.1)
Dose-response Aspirin		
Non-use	1.0	1.0
1–3 prescriptions	0.91 (0.78, 1.1)	0.97 (0.83, 1.1)
>3 prescriptions	0.91 (0.83, 1.0)	0.99 (0.88, 1.1)
"New users" Aspirin[b]		
Non-use	1.0	1.0
Aspirin use	0.98 (0.81, 1.2)	1.0 (0.85, 1.3)
Pre-diagnostic Aspirin		
Non-use	1.0	1.0
Aspirin use	0.88 (0.80, 0.96)	0.92 (0.82, 1.0)
NSAIDs[c]		
Non-use	1.0	1.0
NSAID use	0.94 (0.88, 1.0)	0.99 (0.92, 1.1)
Dose-response NSAIDs		
Non-use	1.0	1.0
1–5 prescriptions	0.98 (0.92, 1.0)	1.0 (0.95, 1.1)
6–10 prescriptions	0.84 (0.74, 0.96)	0.88 (0.77, 1.0)
>10 prescriptions	0.84 (0.74, 0.96)	0.92 (0.81, 1.0)
"New users" NSAIDs[b]		
Non-use	1.0	1.0
NSAID use	1.0 (0.89, 1.2)	1.0 (0.93, 1.2)
Pre-diagnostic NSAIDs		
Non-use	1.0	1.0
NSAID use	0.80 (0.75, 0.84)	0.86 (0.81, 0.91)
COX-2 inhibitors[d]		
Non-use	1.0	1.0
COX-2 inhibitor use	1.1 (0.97, 1.2)	1.1 (0.98, 1.2)
Dose-response COX-2 inhibitors		
Non-use	1.0	1.0
1–7 prescriptions	1.0 (0.96, 1.1)	1.1 (0.99, 1.1)
>7 prescriptions	0.95 (0.82, 1.1)	0.98 (0.84, 1.1)
"New users" COX-2 inhibitors[b]		

Exposure definition	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI) [a]
Non-use	1.0	1.0
COX-2 inhibitor use	1.2 (1.0, 1.5)	1.2 (0.99, 1.5)
Pre-diagnostic COX-2 inhibitors		
Non-use	1.0	1.0
COX-2 inhibitor use	0.82 (0.77, 0.87)	0.89 (0.83, 0.95)

[a]Adjusted for age at diagnosis (as a continuous variable), menopausal status at diagnosis (pre- or post-menopausal), stage (I, II, or III), histologic grade (low, moderate, high), surgery type and radiation therapy receipt (mastectomy, breast-conserving surgery with radiation therapy), estrogen receptor (ER) status and endocrine therapy receipt (ER+/ET−, ER+/ET−, ER−/ET−, ER−/ET+), receipt of chemotherapy (yes/no), post-diagnostic simvastatin use, NSAIDs[§], sCOX2 inhibitors[§] and aspirin[§] use (as time-varying covariates lagged by one year and updated yearly), pre-diagnostic HRT (yes/no), myocardial infarction and congestive heart failure (yes/no), peripheral and cerebrovascular disease (yes/no), liver disease (yes/no), angina (yes/no), and arrhythmia (yes/no).

[b]In the analyses of “new users”, we restricted the study cohort to women who had not used the exposure drugs for at least five years before diagnosis.

[c]NSAIDs = non-steroidal anti-inflammatory drugs

[d]sCOX-2 inhibitors = selective COX-2 inhibitors

Table 3

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) associating post-diagnosis prescriptions for aspirin, NSAIDs, or sCOX2 inhibitors with breast cancer recurrence up to ten years after diagnosis, stratified by ER/ET status and stage among women with stage I, II, or III breast cancer in Denmark (1996–2008).

		Aspirin		NSAIDs[a]		sCOX2 Inhibitors[b]	
Statistical model and variable analyzed	**Total recurrences n (%)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***
ER/ET[c] status							
ER+/ET+	2,464 (46)	0.99 (0.88, 1.1)	0.97 (0.84, 1.1)	0.98 (0.89, 1.1)	1.0 (0.84, 1.2)	1.2 (1.1, 1.4)	1.2 (1.0, 1.3)
ER+/ET−	1,301 (24)	0.84 (0.69, 1.0)	1.0 (0.84, 1.3)	0.91 (0.79, 1.0)	1.0 (0.87, 1.2)	1.0 (0.82, 1.2)	1.1 (0.87, 1.3)
ER−/ET−	1,332 (25)	0.90 (0.74, 1.1)	1.0 (0.82, 1.3)	0.96 (0.83, 1.1)	0.99 (0.86, 1.1)	0.92 (0.75, 1.1)	0.92 (0.75, 1.1)
Stage							
Stage I	1,409 (26)	0.91 (0.76, 1.1)	1.0 (0.83, 1.2)	0.92 (0.81, 1.1)	0.97 (0.85, 1.1)	1.0 (0.84, 1.2)	1.0 (0.86, 1.3)
Stage II	2,118 (40)	0.93 (0.81, 1.1)	1.0 (0.86, 1.2)	0.99 (0.88, 1.1)	1.0 (0.91, 1.1)	1.1 (0.97, 1.3)	1.1 (0.97, 1.3)
Stage III	1,798 (34)	0.93 (0.79, 1.1)	0.98 (0.81, 1.2)	0.93 (0.82, 1.0)	0.96 (0.85, 1.1)	1.0 (0.87, 1.2)	1.0 (0.87, 1.2)

[a] NSAIDs = non-steroidal anti-inflammatory drugs

[b] sCOX-2 inhibitors = selective COX-2 inhibitor

[c] ER/ET = estrogen receptor/endocrine therapy