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Non-steroidal anti-inflammatory drug use, hormone receptor status, and breast cancer-specific mortality in the Carolina Breast Cancer Study

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Abstract

Epidemiologic studies report a protective association between non-steroidal anti-inflammatory drug (NSAID) use and hormone receptor-positive breast cancer risk, a finding consistent with

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NSAID-mediated suppression of aromatase-driven estrogen biosynthesis. However, the association between NSAID use and breast cancer-specific mortality is uncertain and it is unknown whether this relationship differs by hormone receptor status. This study comprised 935 invasive breast cancer cases, of which 490 were estrogen receptor (ER)-positive, enrolled between 1996 and 2001 in the Carolina Breast Cancer Study. Self-reported NSAID use in the decade prior to diagnosis was categorized by duration and regularity of use. Differences in tumor size, stage, node, and receptor status by NSAID use were examined using Chi-square tests. Associations between NSAID use and breast cancer-specific mortality were examined using age- and race-adjusted Cox proportional hazards analysis. Tumor characteristics did not differ by NSAID use. Increased duration and regularity of NSAID use was associated with reduced breast cancer-specific mortality in women with ER-positive tumors (long-term regular use (≥8 days/month for ≥ 3 - years) versus no use; hazard ratio (HR) 0.48; 95 % confidence interval (CI) 0.23–0.98), with a statistically significant trend with increasing duration and regularity (p-trend = 0.036). There was no association for ER-negative cases (HR 1.19; 95 %CI 0.50–2.81; p-trend = 0.891). Long-term, regular NSAID use in the decade prior to breast cancer diagnosis was associated with reduced breast cancer-specific mortality in ER-positive cases. If confirmed, these findings support the hypothesis that potential chemopreventive properties of NSAIDs are mediated, at least in part, through suppression of estrogen biosynthesis.

Keywords

Non-steroidal anti-inflammatory drugs; Breast cancer-specific mortality; Duration; Estrogen receptor; Regularity

Introduction

Non-steroidal anti-inflammatory drug (NSAID) use is associated with 10–20 % reduced risk of breast cancer [1–3], with similar effect estimates for aspirin use alone [1–5]. A previous analysis using data from the Carolina Breast Cancer Study reported that NSAID use was associated with reduced breast cancer incidence [6], and several other epidemiologic studies have reported that this protective effect of NSAID use on breast cancer risk is strongest for hormone receptor-positive tumors [7–10].

The anti-inflammatory properties of NSAIDs are mediated via cyclooxygenase (COX) inhibition which in turn reduces prostaglandin levels, resulting in down-regulation of the aromatase pathway and decreased estrogen biosynthesis [11, 12]. The inverse association between NSAID use and risk of hormone receptor-positive breast cancer is consistent with this NSAID-mediated suppression of estrogen biosynthesis. However, evidence for an association between NSAID use and breast cancer-specific mortality is conflicting. Although one study reported that aspirin use was associated with reduced breast cancer-specific mortality [13], three studies reported no association between NSAID or aspirin use and breast cancer-specific mortality [14–16]. Only a single study examined the association between aspirin use and breast cancer-specific mortality by estrogen receptor (ER) status and found no evidence of differential effects by ER status [13]. Notably, these studies were limited by small numbers of breast cancer-specific deaths [14, 16], incomplete NSAID

exposure assessment, focusing on aspirin and/or ibuprofen use only [13, 16], or examination of regularity of NSAID use without taking duration of use into account [14].

The objective of this current study was to examine the association between use of prescription and non-prescription NSAIDs and breast cancer-specific mortality within the population-based Carolina Breast Cancer Study. Given evidence that NSAIDs reduce estrogen biosynthesis via inhibition of aromatase activity, we hypothesized that there would be a stronger protective association between NSAID use and risk of breast cancer-specific mortality in women with ER-positive tumors.

Methods

Study population

The Carolina Breast Cancer Study is a population-based, case–control study conducted in North Carolina (NC) between 1993 and 2001 [17]. This study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill and informed consent was obtained from each participant. The present study includes 935 women with invasive breast cancer who were interviewed between 1996 and 2001 and provided information on NSAID use. Briefly, cases of invasive breast cancer were identified using rapid case ascertainment in cooperation with the NC Central Cancer Registry. All women who agreed to participate were interviewed in person by a registered nurse using a standardized questionnaire to collect information on established and suspected breast cancer risk factors, including prescription and non-prescription medication use. Tumor size, stage, and lymph node status were abstracted from medical records. Estrogen receptor (ER) and progesterone receptor (PR) status were abstracted from medical records for 80 % of participants [18]. For the remaining 20 % of participants, tumor tissue was sectioned and stained for ER and PR at the Immunohistochemistry Core Laboratory at the University of North Carolina.

Exposure assessment

Women were shown photographs of commonly used NSAIDs and asked to report non-prescription and prescription NSAID use during the past decade. Assessment of duration and regularity of NSAID use is described in detail by Moorman et al. [6]. Briefly, women who reported NSAID use ≥8 days a month for ≥3 months were categorized as regular users. Regular users were further categorized by duration of use (<3 vs. ≥3 years). Women who reported NSAID use <3 months or who reported sporadic use (≤7 days a month) regardless of duration were categorized as occasional users. Acetaminophen has a COX-independent mechanism of action, so was included in the “no use” category. Women were also asked the reason for NSAID use, and could select multiple reasons from a list which included arthritis, bursitis or rheumatism, back pain, surgical/dental pain, menstrual cramps, injury, or other.

Outcome assessment

Vital status was determined through December 31, 2011 through linkage with the National Death Index, which provided date and cause of death for each individual. Using international classification of disease (ICD) codes, we categorized cause of death as either

breast cancer-specific (ICD-9 code 174.9 or ICD-10 code 50.9) or other cause of death based on the first listed primary cause of death.

Statistical analysis

Age and race were selected a priori to be potential confounders of the association between NSAID use and risk of breast cancer-specific mortality. We also considered the following variables as potential confounders: education level, body mass index (BMI), and menopausal status. Chi-square tests were used to examine the distribution of these potential confounders according to NSAID use and to examine differences in tumor characteristics between NSAID users and non-users.

Individuals who died of causes other than breast cancer were censored at time of death and living individuals were censored on December 31, 2011. We modeled breast cancer-specific survival curves according to categories of duration and regularity of NSAID use versus no use using the Kaplan–Meier method and we compared survival curves using log-rank analysis. The proportional hazards assumption was met for each variable. We then conducted Cox proportional hazards analysis to test the association between categories of duration and regularity of NSAID use versus no use and risk of breast cancer-specific mortality among all invasive cases and within strata defined by hormone receptor status. We tested for linear trend with increasing duration and regularity of NSAID use using by assigning the median value to each NSAID category. We stratified both by ER status (ER + vs. ER–) and by positive hormone receptor status (ER + or PR + vs. ER– and PR–). Hazard ratios (HRs) were adjusted for age and race (African American (AA), non-AA). We also explored the effect of adjusting HRs for menopausal status (pre-, postmenopausal) and education level (< high school, high school graduate, > high school). Given the lack of association between NSAID use and BMI in this population, models were not adjusted for BMI. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). Statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

Results

Baseline characteristics of breast cancer cases stratified by NSAID use

The majority of study participants reported NSAID use; 84 (11.5 %) breast cancer survivors and 25 (12.1 %) women who died of breast cancer were categorized as non-users. Breast cancer cases who reported NSAID use were younger than non-users ($p = 0.029$), had a higher level of education ($p = 0.029$) and were more likely to be premenopausal ($p = 0.029$; Table 1). There were no differences in race or BMI according to NSAID use ($p = 0.259$ and $p = 0.634$, respectively).

We compared reasons for NSAID use between categories of duration and regularity of NSAID use (Online Resource 1). Relative to occasional users, long-term regular NSAID users were significantly more likely to cite chronic conditions including arthritis, bursitis or rheumatism (50.3 % of long-term regular users versus 14.8 % of occasional users; $p < 0.0001$), and back pain (27.1 % of long-term regular users versus 17.6 % of occasional users; $p = 0.006$) as reasons for NSAID use. Conversely, occasional users were more likely

to cite acute conditions including menstrual cramps (18.6 % of occasional users versus 11 % of long-term regular users; $p = 0.009$) and headache (68.2 % of occasional users versus 51.9 % of long-term regular users; $p < 0.0001$).

Tumor characteristics of NSAID users

Although there was a suggestion that ER-positive and ER or PR-positive breast cancer was less common among NSAID users, these associations were not statistically significant ($p = 0.149$ and $p = 0.135$, respectively; Table 2). There were no strong or significant associations between NSAID use and tumor stage, node status or tumor size (all $p > 0.5$; Table 2).

NSAID use and breast cancer-specific mortality

Overall, 181 (21.9 %) NSAID users and 25 (22.9 %) non-users died of breast cancer (log-rank $p = 0.808$; Fig. 1a) during a median follow-up period of 13 years (interquartile range; 8–14 years). Among all invasive cases, increased duration and regularity of NSAID use was not associated with breast cancer-specific mortality on unadjusted analysis (log-rank $p = 0.221$; Fig. 1b). After adjusting for age and race, although there was no association between NSAID ever use and risk of breast cancer-specific mortality (use versus no use; HR 0.93; 95 %CI 0.61–1.41; Table 3), there was a suggestion that increasing duration and regularity of NSAID use was associated with a reduced hazard ratio of breast cancer-specific mortality, although this was not significant (NSAID use ≥8 days/month for ≥3 years versus no use; HR 0.71; 95 %CI 0.42–1.21; *p-trend* = 0.105; Table 3).

Among ER-positive cases only ($n = 490$), 76 (17.8 %) NSAID users and 16 (25.0 %) non-users died of breast cancer (log-rank $p = 0.089$; Fig. 1c). Increased duration and regularity of NSAID use was not associated with breast cancer-specific mortality on unadjusted analysis (log-rank $p = 0.141$; Fig. 1d). However, after adjusting for age and race, increased duration and regularity of NSAID use was significantly associated with a reduced hazard ratio for ER-positive breast cancer-specific mortality (regular use ≥3 years versus no use; HR 0.48; 95 %CI 0.23–0.98; Table 3), with a significant trend across categories of increasing duration and regularity of NSAID use (*p-trend* = 0.036). When duration and regularity categories were collapsed to create a single NSAID use category, there was a reduced hazard ratio among women with ER-positive tumors (use versus no use; HR 0.63; 95 %CI 0.37–1.09; Table 3). In contrast, among women with ER-negative breast cancer, use of NSAIDs had an elevated, but imprecise hazard ratio (use versus no use; HR 1.46; 95 %CI 0.71–3.01; Table 3) and there was no association between increased duration and regularity of NSAID use and breast cancer-specific mortality (regular use ≥3 years versus no use; HR 1.19; 95 %CI 0.50–2.81; *p-trend* = 0.891). Further adjustment of our models for menopausal status and education level had no appreciable effect on our estimates (data not shown). Finally, these associations were similar when we stratified women into groups based on both ER and progesterone receptor (PR) positivity (ER- or PR-positive versus ER- and PR-negative; data not shown).

Discussion

Evidence from preclinical models [19, 20] and epidemiologic studies [3] supports a potential role for NSAIDs in breast cancer chemoprevention. Using data from the population-based Carolina Breast Cancer Study, we found that increasing duration and regularity of NSAID use within the decade prior to diagnosis was associated with reduced breast cancer-specific mortality in women with ER-positive tumors. This association was not observed among women with ER-negative tumors, suggesting that the protective effect of NSAID use on breast cancer-specific mortality may be limited to hormone-dependent breast cancer. These results are consistent with the hypothesis that the potential chemopreventive and tumor suppressive properties of NSAIDs are mediated, at least in part, through suppression of estrogen biosynthesis.

NSAIDs inhibit activity of COX-2, a key enzyme in prostaglandin synthesis with an established role in inflammation and carcinogenesis [21]. While normal breast tissue expresses low levels of COX-2, approximately 40 % of invasive breast tumors overexpress this enzyme [11, 22] and elevated levels are associated with increased risk of breast cancer-specific mortality [23]. Given that COX-2-mediated prostaglandin production promotes estrogen biosynthesis via up regulation of the aromatase pathway [12], there is biologic rationale to support a role for NSAIDs in ER-positive breast cancer [11]. Indeed, NSAID use is associated with reduced serum estradiol levels in women with breast cancer [24], which may impact growth of estrogen-responsive tumors. Several studies have found the protective effect of NSAID use on breast cancer incidence to be restricted to hormone receptor-positive breast cancer [7–9], although others reported no difference in this association according to hormone receptor status [25–31].

Few studies have examined the association between NSAID use and breast cancer-specific mortality, and only one conducted stratified analysis by ER status [13]. While this prior study found no evidence of effect modification by ER status (*p-interaction* = 0.52), their results were limited to assessment of aspirin use only and there was a reduced sample size for which ER status was available [13]. In this study, we were able to examine all prescription and non-prescription NSAIDs using a population-based dataset of over 900 incident cases over 13 years of follow-up.

Our results should be considered in light of the study's strengths and limitations. First, confounding by indication is an important consideration in observational studies of NSAID use. To ascertain whether long-term regular NSAID users were more likely to suffer from chronic conditions, we documented the reason for NSAID use. As anticipated, we found that long-term regular users were more likely to use NSAIDs to control symptoms of arthritis, relative to occasional users. While a possible association between arthritis and increased risk of breast cancer-specific mortality has not been consistently reported [32, 33], such an association would likely result in uncontrolled bias in our results. However, the direction of bias would likely be toward the null and, as such, our analysis may have underestimated the strength of the association between long-term regular NSAID use and risk of breast cancer-specific mortality. Moreover, a previous study found that a diagnosis of arthritis did not modify the association between NSAID use and breast cancer risk [25]. Second, we lacked

treatment data in Carolina Breast Cancer Study Phase 2, and so could not examine interactions between NSAID use and breast cancer treatment. Third, we did not collect information on post-diagnosis NSAID use. However, long-term regular users were more likely to use NSAIDs to control chronic conditions, suggesting they would be likely to continue regular NSAID use post-diagnosis. While occasional users who reported NSAID use for menstrual cramps may have been less likely to continue NSAID use if they experienced treatment-induced menopause, the majority of occasional users cited headache as the reason for NSAID use, and this condition would not be expected to be altered by breast cancer diagnosis or treatment. Thus, while we would expect similar patterns of NSAID use post-diagnosis, future studies should explore the association between post-diagnosis NSAID use and risk of breast cancer-specific mortality.

These limitations are balanced by an important strength of this study. Most previous studies did not collect complete NSAID use information, focusing solely on aspirin and ibuprofen use [13, 15, 16]. Incomplete NSAID use data may attenuate the association between NSAID use and breast cancer, since many “unexposed” women may have taken NSAIDs that were not ascertained during data collection, particularly given the widespread use of NSAIDs. In this study, we attempted to collect complete information on all prescription and non-prescription NSAID use, and improved recall to the best of our ability by showing photographs of commonly used NSAIDs to each participant. This study is also strengthened by long follow-up and by inclusion of a large number of African American women, allowing our results to be generalized to a diverse population of women.

This is the first study, to our knowledge, to report a protective association between NSAID use and breast cancer-specific mortality which is limited to ER-positive tumors. This finding is supported by extensive preclinical and epidemiologic evidence for a role of COX-2 inhibition in ER-positive breast cancer. Several clinical trials in breast cancer patients have suggested that combining COX-2 inhibitors with aromatase inhibitors may improve efficacy of aromatase inhibitors in patients with ER-positive tumors [34, 35]. However, while these trials support a role for targeting COX-2 in breast cancer treatment, the clinical utility of selective COX-2 inhibitors is limited due to increased risk of serious cardiovascular events [36, 37]. Thus, if confirmed, our results provide additional rationale for exploring a potential role for NSAIDs in breast cancer treatment.

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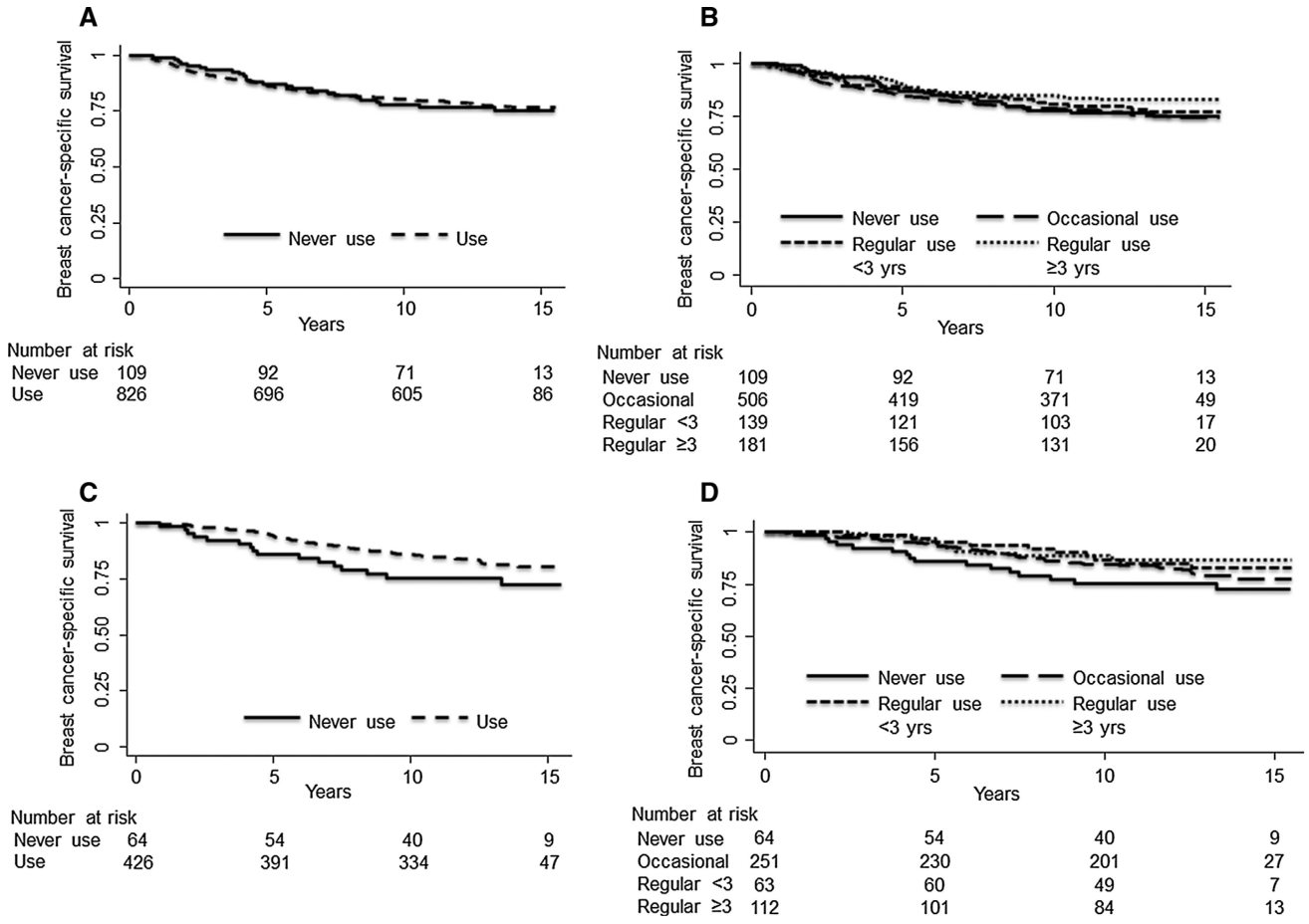

Fig. 1.

Kaplan—Meier plots showing breast cancer-specific mortality by NSAID use versus no use among **a** all invasive cases and **b** ER-positive cases, and categories of duration and regularity of NSAID use among **c** all invasive cases and **d** among ER-positive cases

Table 1

Characteristics of invasive breast cancer cases in the Carolina Breast Cancer Study Phase 2 according to NSAID use

	No use of NSAIDs, *n* (%)	Use of NSAIDs, *n* (%)	*p* value*
Race			
Non-African American	51 (46.8)	434 (52.5)	0.259
African American	58 (53.2)	392 (47.5)	
Age at selection			
< 40	9 (8.3)	128 (15.5)	0.029
40-49	37 (33.9)	292 (35.4)	
50-59	22 (20.2)	194 (23.5)	
60-74	41 (37.6)	212 (25.7)	
Education			
< High school	27 (24.8)	143 (17.3)	0.029
High school graduate	35 (32.1)	219 (26.5)	
> High school	47 (43.1)	464 (56.2)	
Body mass index (kg/m^2)			
< 25	35 (34.0)	259 (31.8)	0.634
25-29	32 (31.1)	231 (28.4)	
30+	36 (35.0)	324 (39.8)	
Missing	6	12	
Menopausal status			
Premenopausal	39 (35.8)	387 (46.9)	0.029
Postmenopausal	70 (64.2)	439 (53.1)	

*Chi-square test

Table 2

Tumor characteristics of invasive breast cancer cases in the Carolina Breast Cancer Study Phase 2 according to NSAID use

	No use of NSAIDs, *n* (%)	Use of NSAIDs, *n* (%)	*p* value*
Tumor stage			
Stage I	48 (44.9)	328 (41.5)	0.515
Stage II	42 (39.3)	355 (44.9)	
Stage III	15 (14.0)	84 (10.6)	
Stage IV	2 (1.9)	23 (2.9)	
Missing	2	36	
Node status			
Negative	74 (67.9)	533 (64.7)	0.510
Positive	35 (32.1)	291 (35.3)	
Missing	0	2	
Tumor size			
≤ 2 cm	52 (50.5)	406 (52.3)	0.939
> 2–5 cm	38 (36.9)	279 (35.9)	
> 5 cm	13 (12.6)	92 (11.8)	
Missing	6	49	
ER status			
Positive	64 (62.1)	426 (54.6)	0.149
Negative	39 (37.9)	354 (45.4)	
Missing	6	46	
ER/PR status			
ER + or PR+	72 (69.9)	485 (62.3)	0.135
ER– and PR–	31 (30.1)	293 (37.7)	
Missing	6	48	

*Chi-square test

Table 3

Associations between NSAID use and risk of breast cancer-specific mortality among invasive cases in the Carolina Breast Cancer Study Phase 2, overall and stratified by estrogen receptor status

	All invasive cases	
	***n*, cases (deaths)**	**HR* (95 % CI)**
NSAID use		
No use	109 (25)	1.00 (ref)
Use	826 (181)	0.93 (0.61–1.41)
NSAID regularity and duration of use		
No use	109 (25)	1.00 (ref)
Occasional	506 (122)	1.02 (0.66–1.59)
Regular < 3 years	139 (30)	0.90 (0.53–1.53)
Regular ≥ 3 years	181 (29)	0.71 (0.42–1.21)
p-trend		0.105

	ER-positive cases *n*, cases (deaths) HR* (95 % CI)		**ER-negative cases *n*, cases (deaths) HR* (95 % CI)**	
NSAID use				
No use	64 (16)	1.00 (ref)	39 (8)	1.00 (ref)
Use	426 (76)	0.63 (0.37-1.09)	354 (100)	1.46 (0.71-3.01)
NSAID regularity and duration of use				
No use	64 (16)	1.00 (ref)	39 (8)	1.00 (ref)
Occasional	251 (52)	0.73 (0.41–1.29)	222 (65)	1.56 (0.74–3.28)
Regular <3 years	63 (10)	0.57 (0.26–1.25)	68 (20)	1.47 (0.65–3.34)
Regular ≥3 years	112 (14)	0.48 (0.23–0.98)	64 (15)	1.19 (0.50–2.81)
p-trend		0.036		0.891

*HRs adjusted for age and race