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Use of nonsteroidal anti-inflammatory drugs and reduced breast cancer risk among overweight women

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Abstract

Purpose—Chronic inflammation is associated with increased risk of multiple cancers, including breast cancer. Adipose tissues produce pro-inflammatory cytokines, and obesity is a risk factor for postmenopausal breast cancer. We evaluated the association of regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) with breast cancer risk, overall and by body mass index (BMI) and tumor subtypes defined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status.

Methods—We conducted a population-based, case-control study involving 5,078 women aged 25–75 years who were recruited primarily from the Nashville metropolitan area of Tennessee. Multivariate unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk after adjusting for multiple potential confounding factors.

Results—Regular use of any NSAID was associated with significantly reduced breast cancer risk (OR=0.78; 95% CI=0.69–0.89). This association was observed for regular use of baby aspirin only (OR=0.82, 95% CI=0.69–0.99), other NSAIDs only (OR=0.81, 95% CI=0.69–0.95), and both baby aspirin and other NSAIDs (OR=0.52, 95% CI=0.40–0.69). These significant inverse associations were found among overweight women (BMI≥25 kg/m^2) overall and by subtypes of breast cancer, but not among women with BMI<25 kg/m^2 (*P* for interaction=0.023).

Conclusions—Regular use of NSAIDs was inversely associated with breast cancer risk, particularly among overweight women. Overweight women may benefit more from the protective effects of NSAIDs use than normal-weight women.

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Conflicts of interest
The authors declare no conflicts of interest.

Keywords

NSAIDs; obesity; breast cancer; epidemiology

Introduction

It is well recognized that chronic inflammation is involved in the etiology of multiple cancers, including breast cancer [1–3]. Cumulative evidence suggests that regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with a reduced risk of cancer [4–6]. NSAIDs inhibit cyclooxygenase-2 (COX2), the rate-limiting enzyme of prostaglandin synthesis [6, 7]. COX2 overexpression is observed in approximately 40% of breast cancers, but not in normal breast tissue [8], and COX2 positivity is correlated with several parameters related to the aggressiveness of breast cancer, such as large tumor size, presence of axillary node metastases, high histologic grade, negative hormone receptor status, high proliferative rate, high p53 expression, and human epidermal growth factor receptor 2 (HER2) amplification [9]. It is generally believed that most COX2 effects on carcinogenesis are mediated through overproduction of prostaglandin E (PGE_2). PGE_2 is a key mediator of inflammation and plays an important role in carcinogenesis by inducing epithelial cell proliferation and angiogenesis and inhibiting immunosurveillance and cell apoptosis [10]. Prior epidemiologic studies have suggested that regular use of aspirin and/or other NSAIDs may be inversely associated with breast cancer risk (11–13].

Obesity is a known risk factor for postmenopausal breast cancer and is also considered a chronic inflammatory condition, characterized by increased circulating levels of proinflammatory cytokines and chemokines [14–16]. *In vitro* experiments and human studies have shown that excessive fat accumulation in breast adipose tissues may activate PGE_2-mediated aromatase and increase estrogen biosynthesis [14–18]. It is unclear whether body weight interacts with NSAIDs, thus modifying the association between NSAIDs and breast cancer risk. Furthermore, COX2-derived PGE_2 also mediates multiple cellular pathways that are independent of estrogen signaling [10]. It is unclear whether the effects of NSAIDs on tumors are mediated through estrogen receptors or through cellular pathways independent of estrogen signaling. To date, no human study has comprehensively investigated the possible interaction of body mass index (BMI) and NSAIDs use in relation to risk of breast cancer subtypes as characterized by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. Herein, using data from the Nashville Breast Health Study (NBHS), a large population-based, case-control study of breast cancer, we evaluate associations of regular use of NSAIDs with risk of breast cancer, overall and by subtype defined by ER, PR, and HER2 status, and further examine whether BMI modifies these associations.

Materials and Methods

Study participants

The NBHS is a population-based, case-control study of incident breast cancer conducted primarily in the Nashville metropolitan area of Tennessee. Eligible cases were women newly

diagnosed with primary breast cancer, aged 25–75 years, and had no prior history of cancer other than nonmelanoma skin cancer. From February 1, 2001 through December 31, 2011, through a rapid case-ascertainment system established for this study across the major hospitals in Nashville and the Tennessee Cancer Registry, the study identified and recruited 2,694 women with breast cancer. Most participants (92%) were residents of the eight-county Nashville metropolitan area. Controls (n=2,384) were identified primarily via random-digit dialing (RDD) of households in the same eight-county Nashville metropolitan area, and were frequency-matched to cases on five-year age groups, race, and county of residence. Among the cases, the median interval from time of breast cancer diagnosis to study enrollment was 10.4 months. Participation rates were approximately 58% for cases and 48% for controls. Among cases, reasons for nonparticipation included refusal (n=1,554), not completing the interview (n=220), death (n=206), illness (n=13), and inability to be reached (n=1). Among controls, reasons for nonparticipation included refusal (n = 614), illness (n=7), and death (n=5), and others (*n*=124). All participants provided written informed consent prior to study enrollment. The study was approved by the Institutional Review Boards of Vanderbilt University Medical Center and all other collaborating institutions. Of the 5,078 NBHS participants, 44 had missing data on aspirin and/or other NSAID use; thus the total number of participants included in this analysis was 5,034.

A telephone interview using a structured questionnaire was conducted by a trained interviewer using a reference date, defined as the date of breast cancer diagnosis for cases or the date of interview for controls. During the interview, information was collected regarding socio-demographics, medical history, medication use, personal history of breast diseases, family history of breast cancer among first-degree relatives, menstrual and reproductive history, current weight and height, diet, and various lifestyle factors. Participants were asked to report both prescription and over-the-counter use of all NSAIDs, including aspirin. Specifically, participants were first asked to report whether they had ever used baby aspirin (81 mg/tablet) or any aspirin at least three days a week over a duration of at least two months in the past 15 years. Participants were then asked to report whether they had ever used any NSAID at least three days a week over a duration of at least two months in the past 15 years. Individuals responding “yes” to these questions were asked to report NSAID brands, duration of use, and frequency. For this analysis, we defined regular users as individuals taking any NSAID three or more times a week for a minimum duration of one year. NSAID users were categorized into subgroups based on reported use patterns, including users of baby aspirin only, users of other NSAIDs only, such as ibuprofen, naproxen, indomethacin, as well as regular strength aspirin (325mg), and those reporting the use of both baby aspirin and other NSAIDs. All NSAID users were categorized into duration groups (< 5 years, 5–9 years, and 10 or more years of continuous use).

Information on the ER, PR, and HER2 status of breast cancer tumors was obtained from pathology records. Among breast-cancer cases, data on ER, PR, and HER2 status were available for 76.0%, 75.2%, and 61.3% of tumors, respectively. Prevalence rates for ER, PR, and HER2 positivity in our study sample were 77.4%, 62.6%, and 23.8%, respectively. In this analysis, breast cancer subtypes were classified by hormone receptor (ER and PR) and HER2 status into the following groups and subgroups: ER status (ER+ or ER−); PR status

(PR+ or PR−); combined ER/PR status (ER+/PR+ or ER−/PR−); and combined ER/PR/HER2 status including luminal A (ER+ and/or PR+ and HER2−), luminal B (ER+ and/or PR + and HER2+) or HER2 overexpressing (ER−, PR−, HER2+), and triple-negative (ER−, PR −, HER2-).

Statistical methods

We used the *t*-test (for continuous variables) or the χ^2 test (for categorical variables) to examine differences in demographic characteristics and major risk factors for breast cancer between cases and controls and between NSAID users and nonusers. Unconditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association between NSAID use and risk of breast cancer. Multivariable unconditional polytomous logistic regression models were used to estimate ORs and 95% CIs simultaneously for breast cancer subtypes, defined by ER, PR, and HER2 status. All OR estimates were adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, other), educational attainment (high school or lower, college, above college), annual household income (US <$20,000, $20,000-$40,000, $40,001-$60,000, >$60,000), cigarette use (ever use/never use), regular alcohol consumption (yes/no), regular exercise (yes/no), personal history of benign breast disease (yes/no), family history of breast cancer among first-degree relatives (yes/no), age at menarche (years, ≤11, 12, 13, and ≥14), age at first live birth (years, <20, 20–25, 26–30, and >30), parity (0, 1, 2, and ≥3), age at menopause (years), and ever-use of hormone replacement therapy (yes/no). To examine the potential modifying effects of BMI on the association between NSAID use and breast cancer risk, we categorized women into two groups: underweight or normal weight (BMI<25 kg/m^2) and overweight (BMI≥25 kg/ m^2) based on WHO criteria. Tests for linear trends across categories of exposure were performed by including the categorical variables as continuous variables in the model. Interaction terms were included in regression models; likelihood ratio tests were used to test for an interaction between NSAID use and BMI. All *P*-values reported are two-sided. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Table 1 presents the distribution of demographic and major risk factors for breast cancer among cases and controls and by NSAID use. Breast cancer cases were more likely to have lower educational attainment, have lower family income, be less physically active, be overweight (BMI≥25 kg/m^2), and have a personal history of benign breast disease and/or family history of breast cancer when compared with controls. Compared with nonusers of NSAIDs, ever-users tended to be older, have lower educational attainment, and have lower family income. Also, they were more likely to have breast cancer risk factors, including being less physically active, overweight, ever-cigarette smokers, older age at first live birth, or ever-users of hormone replacement therapy, and to have a personal history of benign breast disease.

Regular use of any NSAID was associated with a significantly reduced breast cancer risk compared with nonusers (OR=0.78; 95% CI=0.69–0.89) (Table 2). An inverse association

was also seen for use of baby aspirin only (OR=0.82, 95% CI=0.69–0.99), use of other NSAIDs only (OR=0.81, 95% CI=0.69–0.95), and use of both baby aspirin and other NSAIDs (OR=0.52, 95% CI=0.40–0.69). However, we did not find a significant trend for decreasing risk with increasing duration of NSAID use of any type (Table 2).

A significant inverse association was found between ever-NSAIDs use and breast cancer risk among women who were overweight (BMI≥25 kg/m^2) (OR=0.71, 95% CI=0.60–0.83), but not among normal-weight women (BMI<25 kg/m^2; OR=0.95, 95% CI=0.77–1.17) (*P* for interaction=0.023, Table 3). A similar pattern of association was seen in each subgroup of NSAID users (baby aspirin only, other NSAIDs only, and both baby aspirin and other NSAIDs). Similar results were seen when analyses were conducted among postmenopausal women. Again, no dose-response relationship was observed between duration of NSAID use and breast cancer risk, regardless of BMI.

We further examined associations between use of any NSAID and risk of breast cancer by breast cancer subtype among women with BMI<25 kg/m^2 and ≥25 kg/m^2. Among overweight women, use of any NSAID was associated with reduced risk for all subtypes of breast cancer, including ER+, ER−, PR+, PR−, ER+/PR+, ER−/PR−, HER2+, HER2-, luminal A, luminal B and HER2 overexpressing, and triple-negative breast cancer tumors (Table 4). No association, however, was seen among women with BMI<25 kg/m^2.

Discussion

In this large-scale, population-based, case-control study, we evaluated the association of regular use of NSAIDs with risk of breast cancer, overall and stratified by BMI and by tumor subtype according to ER, PR, and HER2 status. We confirmed that regular use of any NSAID, including baby aspirin (81mg), was associated with an overall reduced risk of breast cancer (OR=0.78; 95% CI=0.69–0.89), consistent with the majority of previous studies reporting an approximate 20% reduction in risk with aspirin/other NSAIDs use [11–13]. We further found that the protective association with NSAIDs exists for all subtypes of breast cancer, regardless of ER, PR, or HER2 receptor status, and these inverse associations are evident primarily among overweight women. Our findings suggest that body weight may modify the effect of NSAIDs on breast cancer risk, and overweight women may benefit more from NSAIDs use than normal-weight women.

Although most epidemiologic studies that examined the association between NSAIDs use and breast cancer support a moderate reduction in risk, few studies have evaluated whether the protective association of NSAIDs varies by hormone receptor (ER and PR) status. Findings from previous studies have been inconsistent, with reports including reduced risk of hormone-receptor-positive tumors only [11, 19, 20], reduced risk of both hormone-receptor-positive and - negative tumors [21–24], increased risk of hormone-receptor-negative tumors [25], and no association [26]. Moreover, only a few studies have examined the association of aspirin and/or other NSAID use with breast cancer characterized by joint ER/PR status, HER2 expression, and combinations of ER/PR status and HER2 expression [27, 28]. In a population-based, case-control study conducted in western New York, Brasky et al. found that recent and lifetime aspirin use was associated with reduced breast cancer

risk, however, no differences by breast cancer subtype were observed [27]. They also reported that recent use of ibuprofen was associated with increased risk of ER+/PR+ and HER2-breast cancers, as well as luminal A and B breast cancers [27]. In contrast, a recent analysis from the Nurses' Health Study (NHS) reported no consistent significant associations of use of aspirin, other NSAIDs, or total NSAIDs with breast cancer incidence, either overall or by molecular subtype [28]. In our study population, regular use of aspirin and/or other NSAIDs showed an association with reduced breast cancer risk, regardless of ER, PR, or HER2 status or breast cancer subtype. Reasons for the inconsistent findings between studies are unclear. It is possible that differences in study design, assessment of aspirin/NSAID exposure, or underlying exposure to other risk factors may have contributed to differences in findings. Our findings, however, are in line with results from *in vitro* and *in vivo* experiments showing that COX2-derived PGE_2 promotes tumor growth, and NSAID use may reduce cancer risk by inhibiting PGE_2 production and other pathways [10].

We found that the protective association for NSAIDs was primarily restricted to overweight women. This finding is in line with the fact that obesity is a well established risk factor for breast cancer among postmenopausal women and is also associated with low-grade chronic inflammation, characterized by increased circulating chemoattraction of immune cells that contribute to the inflammatory condition [14–16]. Increasing adiposity may lead to the recruitment of macrophages that produce and release proinflammatory cytokines, therefore upregulating cyclooxygenase *COX-2* expression which, in turn, increases PGE_2 production [1, 29]. PGE_2 plays an important role in carcinogenesis by inducing epithelial cell proliferation and angiogenesis and inhibiting immunosurveillance and cell apoptosis [10, 29]. It also acts as a potent activator of aromatase *CYP19* gene expression via the c-AMP-dependent pathway, thereby increasing estrogen production [10, 29]. Thus, our finding supports the notion that NSAID use may reduce the inflammatory status induced by obesity and thus reduce the risk of breast cancer. Only a few studies have examined the potential modifying effect of BMI on the association between NSAIDs and breast cancer [19, 28, 30]. The Women's Health Initiative Study (WHIS) reported a 21% decrease in breast cancer risk among women who used any NSAIDs for five or more years, compared with those who reported no use or minimal use, and this protective effect was more evident among women with BMI≥27 kg/m^2 [30]. Such an association, however, was not observed in two other studies [19, 28]. More studies with larger sample sizes, data on breast cancer subtypes, and better measurement of NSAID use and BMI are warranted.

Several limitations of our study should be acknowledged. First, approximately 30% of breast cancer cases in our study did not have information available for ER, PR, or HER2 status, which might introduce selection bias. However, the prevalence rates for ER, PR, and HER2 positivity in our study are consistent with many large-scale studies [31, 32]. Second, as with any case-control study, our study is subject to recall bias, especially because we relied on self-reported information about NSAID use. Multiple studies, however, have shown high agreement between self-reports and medical records regarding medication use among women with breast cancer [33–36]. Third, although we carefully adjusted for a wide range of potential confounding factors, we could not rule out the possible effects of residual confounding on our results. In addition, in our study population, the vast majority of regular

NSAID users (89%) reported that they took aspirin/NSAIDs once a day, limiting our ability to examine the association between frequency of use and breast cancer risk.

In summary, our study shows that regular use of NSAIDs was inversely associated with breast cancer risk. This inverse association was seen for all types of breast cancer, as defined by ER, PR, and HER2 status, suggesting that the protective effects of NSAIDs may be mediated through cellular pathways, both dependent and independent of estrogen signaling. Our finding of a modifying effect of BMI on the association between NSAIDs and breast cancer risk suggests that overweight women may benefit more from NSAID use than normal weight women.

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All experiments comply with the current laws of the United States of America.

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Table 1

Distribution of demographic and major risk factors for breast cancer among cases and controls and by user/nonuser of any NSAID, the Nashville Breast Health Study, 2001–2010

Participant Characteristics	Cases N (%)	Controls N (%)	*P*-value	Users among controls, N (%)	Nonusers among controls, N (%)	*P*-value
Demographics						
Age (mean ± SD)	52.7±10.9	54.4±10.5	<0.001	56.8±10.2	50.4±10.7	<0.001
Race						
Non-Hispanic white	1951 (72.5)	1961 (82.2)		690 (84.2)	1251 (81.1)	
Non-Hispanic black	663 (24.6)	345 (14.5)	<0.001	108 (13.2)	234 (15.2)	0.124
Other	79 (2.9)	78 (3.3)		21 (2.6)	57 (3.7)	
Education						
≤High school	988 (36.7)	756 (31.7)		289 (35.3)	459 (29.8)	
Some college	705 (26.2)	649 (27.3)	<0.001	233 (28.4)	409 (26.5)	0.001
≥College	998 (37.1)	978 (41.0)		297 (36.3)	674 (43.7)	
Income per annum (US$)						
≤20,000	380 (14.1)	195 (8.2)		96 (11.7)	98 (6.4)	
20,001–40,000	513 (19.0)	388 (16.3)		147 (18.2)	236 (15.3)	
40,001–60,000	542 (20.1)	553 (23.2)	<0.001	194 (23.7)	351 (22.8)	<0.001
>60,000	1159 (43.0)	1183 (49.6)		354 (43.2)	822 (53.3)	
Missing data	100 (3.71)	65 (2.7)		26 (3.2)	35 (2.3)	
Postmenopausal	1751 (65.3)	1477 (62.1)	0.019	645 (79.0)	814 (52.9)	<0.001
Major risk factors						
Age at menarche (yrs, mean ± SD)	12.6±1.6	12.5±1.6	0.181	12.5±1.6	12.7±1.6	0.007
Parity						
0	421 (15.7)	380 (16.0)		121 (14.5)	252 (16.3)	
1	489 (18.2)	431 (18.1)		140 (17.1)	289 (18.7)	
2	988 (36.7)	886 (37.2)	0.958	284 (34.7)	594 (38.5)	0.005
≥3	791 (29.4)	686 (28.8)		274 (33.5)	407 (26.4)	
Age at first live birth (yrs) [a]						

Participant Characteristics	Cases N (%)	Controls N (%)	*P*-value	Users among controls, N (%)	Nonusers among controls, N (%)	*P*-value
≤20	766 (33.8)	561 (28.0)		246 (35.2)	313 (24.3)	
21–25	743 (32.8)	721 (36.0)		254 (36.4)	460 (35.7)	
26–30	486 (21.4)	482 (24.1)	<0.001	139 (19.9)	338 (26.2)	<0.001
>30	273 (12.0)	239 (11.9)		59 (8.5)	179 (13.9)	
Ever use of hormone replacement therapy	1134 (42.2)	946 (39.7)	0.076	442 (54.0)	493 (32.0)	<0.001
BMI (kg/m^2)						
<25	967 (36.0)	999 (42.0)		265 (32.4)	722 (46.9)	
≥25	1718 (64.0)	1380 (58.0)	<0.001	553 (67.6)	817 (53.1)	<0.001
Regular exercise	1365 (50.8)	1343 (56.4)	<0.001	451 (55.1)	883 (57.3)	0.298
Regular alcohol consumption	479 (17.8)	471 (19.8)	0.071	176 (21.5)	292 (19.0)	0.149
Ever cigarette smoking	1117 (41.5)	975 (40.9)	0.668	381 (46.5)	585 (37.9)	<0.001
Family history of breast cancer	541 (20.1)	332 (13.9)	<0.001	106 (12.9)	224 (14.5)	0.291
Personal history of benign breast disease	1186 (44.1)	775 (32.5)	<0.001	298 (36.4)	468 (30.4)	0.003

[a] Among parous women.

Table 2

Associations of breast cancer risk with ever NSAID use and duration of NSAID use, the Nashville Breast Health Study, 2001–2010

	Cases (n)	Controls (n)	OR (95% CI)[a]	OR (95% CI)[b]
Regular use of any NSAIDs				
Non-users	1,818	1,542	1.00 (ref.)	1.00 (ref.)
Ever-users	856	819	0.81 (0.71–0.91)	0.78 (0.69–0.89)
Baby aspirin only	336	289	0.82 (0.69–0.99)	0.82 (0.69–0.99)
Other NSAIDs only	407	380	0.86 (0.73–1.01)	0.81 (0.69–0.95)
Both	113	147	0.57 (0.44–0.74)	0.52 (0.40–0.69)
Duration of any NSAIDs use (yrs)				
Non-users	1,818	1,542	1.00 (ref.)	1.00 (ref.)
Ever-users				
≤4	315	337	0.72 (0.61–0.86)	0.71 (0.60–0.85)
5–9	249	234	0.84 (0.69–1.02)	0.80 (0.66–0.98)
≥10	292	248	0.90 (0.74–1.08)	0.86 (0.71–1.05)

[a] Adjusted for age, race, education, and household income.

[b] Additionally adjusted for personal history of benign breast disease, first-degree family history of breast cancer, menopausal status, history of live birth, age at first live birth, use of hormone replacement therapy, regular exercise, alcohol consumption, and cigarette smoking status.

Table 3

Associations of breast cancer risk with ever NSAID use and duration of use according to BMI, the Nashville Breast Health Study, 2001–2010

All women	BMI < 25 kg/m^2		BMI ≥ 25 kg/m^2	
	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI[a])
Regular use of any NSAIDs[b]				
Non-users	698/722	1.00 (ref.)	1117/817	1.00 (ref.)
Ever-users	262/265	0.95 (0.77–1.17)	593/553	0.71 (0.60–0.83)
Baby aspirin only	116/105	0.99 (0.73–1.34)	219/184	0.74 (0.59–0.94)
Other NSAIDs only	120/128	0.93 (0.70–1.23)	287/255	0.75 (0.61–0.92)
Both	26/32	0.73 (0.42–1.26)	87/114	0.45 (0.33–0.62)
Duration of any NSAIDs use (yrs)				
Non-users	698/722	1.00 (ref.)	1117/817	1.00 (ref.)
Ever-users				
≤4	106/110	0.92 (0.68–1.23)	208/227	0.62 (0.50–0.78)
5–9	83/83	0.97 (0.70–1.36)	166/151	0.72 (0.56–0.92)
≥10	73/72	0.98 (0.68–1.40)	219/175	0.81 (0.64–1.02)
Postmenopausal women	**BMI < 25 kg/m^2**		**BMI ≥ 25 kg/m^2**	
	Cases/controls	**OR (95% CI)[a]**	**Cases/controls**	**OR (95% CI)[a]**
Regular use of any NSAIDs				
Non-users	382/340	1.00 (ref.)	685/472	1.00 (ref.)
Ever-users	191/196	0.89 (0.69–1.15)	475/449	0.67 (0.56–0.81)
Baby aspirin only	99/88	1.01 (0.72–1.42)	184/165	0.68 (0.52–0.87)
Other NSAIDs only	69/78	0.81 (0.58–1.18)	209/179	0.75 (0.59–0.96)
Both	23/30	0.68 (0.38–1.21)	82/105	0.47 (0.33–0.65)
Duration of regular use (yrs)				
Non-users	382/340	1.00 (ref.)	685/472	1.00 (ref.)
Ever-users				
≤4	72/80	0.79 (0.55–1.14)	164/171	0.61 (0.47–0.79)
5–9	64/65	0.94 (0.63–1.38)	128/125	0.64 (0.47–0.84)
≥10	55/51	1.00 (0.65–1.53)	183/153	0.77 (0.59–0.99)

[a] Adjusted for age, race, education, household income, personal history of benign breast disease, first-degree family history of breast cancer, menopausal status, history of live birth, age at first live birth, use of hormone replacement therapy, regular exercise, alcohol consumption, and cigarette smoking status.

[b] Test for interaction between regular use of any NSAIDs (non-users and ever-users) and BMI (< 25 kg/m^2 and ≥ 25 kg/ m^2); P=0.023.

Table 4

Associations between NSAID use and risk of breast cancer by subtype, the Nashville Breast Health Study, 2001–2010

All women	BMI <25 kg/m^2			BMI ≥25 kg/m ^{2}		
	Users	Nonusers	OR (95% CI)[a]	Users	Nonusers	OR (95% CI)[a]
Controls	265	722		553	817	
Cases by receptor status						
ER status						
ER+	164	386	1.06 (0.83–1.36)	313	551	0.72 (0.60–0.87)
ER−	47	118	1.13 (0.77–1.67)	110	217	0.72 (0.55–0.94)
PR status						
PR+	133	309	1.07 (0.80–1.40)	252	462	0.69 (0.57–0.85)
PR−	74	188	1.07 (0.78–1.48)	168	300	0.77 (0.61–0.97)
ER/PR status						
ER+/PR+	130	303	1.07 (0.82–1.39)	247	455	0.69 (0.56–0.84)
ER−/PR−	43	112	1.08 (0.73–1.62)	103	210	0.69 (0.53–0.91)
HER2 status						
HER2+	31	98	0.95 (0.61–1.50)	76	144	0.73 (0.53–1.00)
HER2−	130	309	1.06 (0.81–1.38)	249	464	0.69 (0.56–0.85)
ER/PR/HER2 status						
Luminal A	101	237	1.02 (0.76–1.37)	189	331	0.71 (0.56–0.88)
Luminal B/HER2 overexpressing	31	95	0.98 (0.62–1.55)	72	139	0.72 (0.52–0.99)
Triple Negative	26	67	1.15 (0.70–1.90)	59	122	0.71 (0.50–1.01)

[a]Adjusted for age, race, education, household income, personal history of benign breast disease, first-degree family history of breast cancer, menopausal status, history of live birth, age at first live birth, use of hormone replacement therapy, regular exercise, alcohol consumption, and cigarette smoking status.