Use of non-steroidal anti-inflammatory drugs and survival following breast cancer diagnosis

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Abstract

Background—While there is accumulating evidence that use of non-steroidal anti-inflammatory drugs (NSAIDs) decreases breast cancer risk, little is known about the impact of NSAIDs on survival after breast cancer diagnosis.

Methods—We assessed whether recent, pre-diagnostic NSAID use and lifetime cumulative aspirin use before diagnosis were associated with survival among 1,024 women with incident, primary, invasive breast cancer.

Results—Recent, pre-diagnostic use of aspirin, ibuprofen, and acetaminophen, and lifetime use of aspirin up to diagnosis were not associated with either all-cause mortality or breast cancer specific mortality. Neither dose nor frequency of use was associated with risk. Associations were not different for pre- and post-menopausal women.

Conclusion—In our data, pre-diagnostic NSAID use and lifetime cumulative aspirin use were not associated with breast cancer survival.

Impact—Our findings do not support a role of NSAIDs prior to diagnosis in breast cancer survival.

Introduction

Identification of potential factors affecting breast cancer survival is of great public health importance, as approximately 2.6 million women previously diagnosed with breast cancer are alive in the United States today (1). Relatively consistent evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs) reduce breast cancer risk (2). Emerging evidence suggests that NSAIDs might influence cancer prognosis by inducing apoptosis and

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inhibiting angiogenesis (3). In the present study, we assessed associations of breast cancer survival with NSAID use in the period prior to breast cancer diagnosis and for aspirin use throughout the lifetime up to the time of diagnosis.

Materials and Methods

A total of 1,024 women with incident, primary, histologically confirmed, invasive breast cancer were identified as part of the Western New York Exposures and Breast Cancer (WEB) study, a population-based case-control study conducted between 1996 and 2001 in Western New York, as described in Brasky et al. (4).

Information on demographics, medication use, and breast cancer risk factors was collected through in-person interviews and self-administered questionnaires. Included were questions regarding the use of aspirin, ibuprofen, and the analgesic acetaminophen in the 12 – 24 months prior to interview. For the analysis of recent NSAID use, frequency of use was categorized as non-users (0 days/month), infrequent users (14 days/month) and regular users (>14 days/month). Intensity of use was categorized as non-users (0 pills/day), low (<2 pills/day) and high intensity (2 pills/day). Additionally, participants were asked about their average monthly frequency of aspirin use for each decade of adult life starting at age 21. Cumulative adult lifetime aspirin usage was estimated as the sum of average annual aspirin frequency for each decade of life. These data were categorized into lifetime non-users (0 days/month), irregular users (10 days/month), and regular users (>10 days/month) (4).

Vital status of the women with breast cancer was determined through a National Death Index search through December 31, 2006. Survival time was calculated as the number of months from the date of diagnosis until the date of death or December 31, 2006. All-cause mortality was defined as death from any cause, and underlying cause of death was broadly classified as breast cancer, other cancers, cardiovascular diseases and others.

Cox proportional hazards regression models, adjusted for age at diagnosis, race, education, body mass index [kg/m^2; (BMI)], menopausal status, stage of breast cancer at diagnosis, ER/PR status and use of other NSAIDs, were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause and breast cancer-specific mortality. The proportional hazards assumption was tested and found to hold in all analyses. All statistical tests were two-sided and considered statistically significant at $P < 0.05$.

Results

Descriptive characteristics of participants at the time of questionnaire completion are shown in Table 1. Up to censoring date, 160 deaths occurred with a mean survival time of 7.32 ± 1.74 years. The most frequent cause of death was breast cancer (n = 95), followed by cardiovascular disease (n = 22), and other cancers (n = 11).

Associations between NSAID use and overall and breast cancer survival are shown in Table 2. Recent use of ibuprofen was associated with reduced all-cause mortality in univariate analysis (HR 0.65, 95% CI: 0.48–0.89) and borderline significance after adjustment for potential confounders (HR 0.71, 95% CI: 0.50–1.00). None of the NSAIDs was associated with a reduction in breast cancer mortality (Table 2). Increasing frequency or intensity of use were also not associated with mortality when stratified by menopausal status (data not shown).

Discussion

Epidemiologic evidence regarding NSAID use and breast cancer survival is inconsistent. Most studies have focused on post-diagnostic use. In the Iowa Women's Health Study, ever use of any NSAID after diagnosis was associated with a statistically significant reduction in all-cause mortality and a non-significant reduction for breast cancer mortality among 591 post-menopausal women with invasive breast cancer (5). Data from the Nurses' Health Study suggested a reduced risk of breast cancer mortality and all-cause mortality for women reporting aspirin use after breast cancer (6). In contrast, post-diagnosis NSAID use was not associated with all-cause or breast cancer mortality in 3,058 breast cancer cases in Wisconsin (7).

Our study was limited to an examination of pre-diagnostic NSAID use. However examination of the association of pre-diagnosis NSAIDs use and survival after breast cancer diagnosis is also of importance due to the uncertainty about the appropriate timing of NSAIDs use to improve cancer survival (8). Information on both pre and post-diagnostic NSAIDs use is needed to address if there is a window of time when use is effective, if at all. Another limitation of this study is potential misclassification due to dependence on self-report to assess NSAIDs use. However, error in report would not be correlated with outcome in that the assessment was done prospectively. In addition, we did not have information on post-diagnosis treatment.

In conclusion, our findings do not support an association between pre-diagnostic NSAID use and breast cancer specific mortality or all-cause mortality.

Acknowledgments

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Table 1

Descriptive characteristics of breast cancer cases by vital status, Western New York Exposures and Breast Cancer (WEB) study

	Dead as of December 2006 (n = 160)	Alive as of December 2006 (n=864)
Mean (SD)		
Age (years)	59.71 (12.33)	57.79 (10.97)
Education (years)	12.80 (2.50)	13.60 (2.60) [***]
Body mass index (kg/m^2)	29.66 (6.96)	28.44 (6.35) [*]
Age at menarche (years)	12.61 (1.66)	12.56 (1.60)
Age at first birth (years)	22.78 (4.82)	23.98 (4.87) [**]
Age at menopause (years)	47.53 (6.03)	48.48 (5.34)
Number of births	2.59 (1.80)	2.31 (1.69)
Number (%)		
Race		
Caucasian	139 (86.88)	799 (92.48) [*]
Other	21 (13.13)	65 (7.52)
Menopausal status		
Premenopausal	45 (28.13)	240 (27.78)
Postmenopausal	115 (71.88)	624 (72.22)
Family history of breast cancer		
No	117 (81.25)	629 (79.22)
Yes	27 (18.75)	165 (20.78)
Estrogen receptor status		
Negative	69 (43.13)	212 (24.54) [***]
Positive	81 (50.63)	602 (69.68)
Unknown/not done	10 (6.25)	50 (5.79)
Progesterone receptor status		
Negative	78 (48.75)	277 (32.06) [***]
Positive	71 (44.38)	526 (60.88)
Unknown/not done	11 (6.88)	61 (7.06)
HER2		
Negative	87 (54.38)	540 (62.50)
Positive	14 (8.75)	48 (5.56)
Unknown/not done	59 (36.88)	276 (31.94)
Stage at diagnosis		
I	46 (28.75)	440 (50.93) [***]
IIA	25 (15.63)	187 (21.64)
IIB	30 (18.75)	74 (8.56)
IIIA	3 (1.88)	11 (1.27)
IIIB	6 (3.75)	5 (0.58)
IV	21 (13.13)	15 (1.74)

	Dead as of December 2006 (n = 160)	Alive as of December 2006 (n=864)
Stage not available	29 (18.13)	132 (15.28)
Underlying cause of death		
Breast cancer	95 (59.38)	-
Other cancer	11 (6.88)	-
Cardiovascular diseases	22 (13.75)	-
Others	32 (20.00)	-

*
p < 0.05;

**
p < 0.01;

***
p < 0.001.

Table 2

Hazard ratios (HR) and 95% confidence intervals (95% CI) for associations of NSAID intake and death from all causes and from breast cancer, WEB Study (n=1,024)[1]

	Events (n)	Crude HR (95% CI)	Adjusted HR (95% CI)[2]
All cause mortality			
Lifetime Aspirin use			
Non-users	33	1.00 (Reference)	1.00 (Reference)
Ever-users	120	0.87 (0.59–1.28)	0.82 (0.54–1.24)
Recent Aspirin use			
Non-users	90	1.00 (Reference)	1.00 (Reference)
Users	68	1.08 (0.79–1.48)	0.92 (0.65–1.29)
Recent Ibuprofen use			
Non-users	84	1.00 (Reference)	1.00 (Reference)
Users	73	**0.65 (0.48–0.89)**	0.71 (0.50–1.00)
Recent Acetaminophen use			
Non-users	63	1.00 (Reference)	1.00 (Reference)
Users	94	0.95 (0.69–1.30)	0.94 (0.67–1.32)
Breast cancer mortality			
Lifetime Aspirin use			
Non-users	21	1.00 (Reference)	1.00 (Reference)
Ever-users	71	0.81 (0.50–1.32)	0.89 (0.53–1.52)
Recent Aspirin use			
Non-users	58	1.00 (Reference)	1.00 (Reference)
Users	37	0.90 (0.60–1.37)	0.91 (0.58–1.41)
Recent Ibuprofen use			
Non-users	42	1.00 (Reference)	1.00 (Reference)
Users	53	0.96 (0.64–1.43)	0.86 (0.55–1.34)
Recent Acetaminophen use			
Non-users	36	1.00 (Reference)	1.00 (Reference)
Users	59	1.05 (0.69–1.59)	0.96 (0.62–1.49)

[1] Breast cancer cases diagnosed at stage 0 were excluded.

[2] Adjusted for age at diagnosis, race, education, BMI, menopausal status, stage of breast cancer, ER/PR status and other NSAIDs use.