

# **Nonsteroidal Anti-Inflammatory Drug Use and Breast Cancer Risk by Stage and Hormone Receptor Status**

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This study was done at the University of Southern California, Los Angeles, CA

## **FROM ABSTRACT:**

### **Background:**

Epidemiologic studies of the association between nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, and breast cancer risk have yielded inconsistent results.

We investigated the association of NSAID use with risk of breast cancer in the California Teachers Study cohort, with special attention to risk of specific breast cancer subtypes and to type of NSAID used.

### **Methods:**

We analyzed data on 114,460 women in the California Teachers Study cohort who were aged 22 to 85 years and free of breast cancer at baseline in 1995 to 1996. Information on frequency and duration of NSAID use was collected through a self-administered questionnaire. A total of 2391 women were diagnosed with breast cancer during the follow-up period from 1995 to 2001.

### **Results:**

Long-term (5 years) daily aspirin use showed a statistically significantly increased risk of [estrogen / progesterone negative sensitive] breast cancer, an 81% increased risk, with a range of 12% to 292% increase risk.

Long-term daily use of ibuprofen was also associated with an increased risk of breast cancer [51% increased risk with a range between 17% to 95% increased risk], particularly of nonlocalized tumors (92% increased risk with a range between 24% to 297% increased risk).

### **Conclusions:**

Ibuprofen use was associated with an increased risk of breast cancer, and long-term daily aspirin use was associated with an increased risk of ER/PR-negative breast cancer.

## THESE AUTHORS ALSO NOTE:

“Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for common ailments such as headaches, muscular pain, inflammation, and fever and are prescribed to alleviate chronic conditions such as arthritis.”

NSAIDs are also used prophylactically to reduce the risk of heart attack, stroke, or blood clot formation.

“Aspirin and other NSAIDs inhibit the expression of the cyclooxygenase 2 (COX-2) gene, which encodes one of two cyclooxygenase enzymes that catalyzes the synthesis of prostaglandins from the dietary fatty acid arachidonic acid.”

**[Remember, arachidonic acid is the commonly consumed omega-6 fatty acid in the American diet.]**

Given the widespread use of over-the-counter pain relievers, understanding the relationship between these drugs and breast cancer risk is of particular public health importance.

The California Teachers Study is a prospective cohort of 133,479 teachers and school administrators established from the rolls of the California State Teachers Retirement System, and was created specifically to investigate risk factors for breast cancer.

These teachers were asked, “Have you taken any of the following medications regularly (at least once a week)?”

- 1) Aspirin (Anacin, Bufferin, Excedrin)
- 2) Acetaminophen (Tylenol, Anacin-3, Panadol, Aspirin Free Excedrin, etc.)
- 3) Ibuprofen (Advil, Motrin, Nuprin)

If the answer was yes, participants were asked to indicate for how many total years (<1, 1, 2, 3–4, 5–9, or 10), and how many days per week (1–3, 4–6, or 7), on average, they took each type of medication.

“Acetaminophen is not an NSAID and does not inhibit COX-2 gene expression, but it was included in these analyses for comparison and to check that any observed associations were specific to NSAIDs and not attributable to any pain medication.”

The authors also assessed other breast cancer risk factors, including race, family history of breast cancer, body mass index, history of smoking, average alcohol consumption, physical activity, neighborhood socioeconomic status, reproductive factors, menopausal status, and use of hormone therapy.

## RESULTS

The authors analyzed 114,640 women.

40,122 (35.0%) regularly used NSAIDs **[WOW!]**

10,835 (27.0% of users) used both an NSAID and acetaminophen

8,836 (22.0% of users) used both aspirin and ibuprofen

16,895 used only aspirin

14,391 used only ibuprofen

25,731 (22.5%) were regular aspirin users (16,895 aspirin only users + 8,836 regular users of both aspirin and ibuprofen)

23,227 (20.3%) were regular ibuprofen users (14,391 ibuprofen users + 8,836 regular users of both aspirin and ibuprofen)

8,341 (7.3%) women took aspirin daily

15,590 (13.6%) women had taken aspirin for at least 5 years [14%]

7,852 (6.9%) women took ibuprofen daily for 5 or more years

Ibuprofen has been available over-the-counter in the United States since 1984.

“Regular NSAID users were more likely to be white, to be overweight or obese, to be current or former smokers, to have had a mammogram in the last 2 years, and to have used postmenopausal hormone therapy than nonregular NSAID users.” **[Interesting: maybe these factors are all inter-related]**

“During follow-up, 2,391 participants were diagnosed with invasive breast cancer.”

“Both daily and long-term uses of ibuprofen were associated with increased risk of breast cancer.”

“Compared with nonusers, women who took ibuprofen daily for 5 years or longer had a relative risk for breast cancer of 1.51.”  
**[This means a 51% increased risk]**

Daily long-term use of aspirin was associated with an 81% increased risk of breast cancer.

## DISCUSSION

These authors “observed a statistically significant increased risk of breast cancer, especially nonlocalized breast cancer, in long-term daily users of ibuprofen.”

“The results suggest that long-term daily use of ibuprofen is associated with increased breast cancer risk, particularly of nonlocalized tumors.”

“There was no association with acetaminophen [i.e.Tylenol][and breast cancer] in our study.”

In this study “daily long-term use of ibuprofen was associated with an increased risk of breast cancer, and use of aspirin and ibuprofen was associated with risks of particular tumor subtypes.”

### **USA TODAY reported the following on this study, June 1, 2005**

#### **Study Links Pain Relievers and Breast Cancer, by Rita Rubin**

“The latest study, out today in the Journal of the National Cancer Institute, is the first to suggest that long-term ibuprofen or aspirin use might actually raise the risk of breast cancer.”

“Marshall’s (Dr. Sarah Marshall from USC) study analyzed data on 114,460 women in the ongoing California Teachers Study. The women were 22 to 85 years old and free of breast cancer when they enrolled in the study a decade ago.”

“When the scientists broke their findings down by pain reliever or type of breast cancer, they found:”

- “Women who took ibuprofen daily for at least 5 years were about 50% more likely to be diagnosed with breast cancer than those who did not take the drug regularly.”
- “Women who took aspirin daily for at least 5 years were 80% more likely to develop breast cancers that were not sensitive to the hormones estrogen or progesterone than women who were not regular users of aspirin.”

#### KEY POINTS FROM DAN MURPHY

- 1) Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for common ailments such as headaches, muscular pain, inflammation, and fever and are prescribed to alleviate chronic conditions such as arthritis.
- 2) NSAIDs are also used prophylactically to reduce the risk of heart attack, stroke, or blood clot formation.

- 3) Aspirin and other NSAIDs inhibit the expression of the cyclooxygenase 2 (COX-2) gene, which encodes one of two cyclooxygenase enzymes that catalyzes the synthesis of prostaglandins from the dietary fatty acid arachidonic acid. **[Remember, arachidonic acid is the commonly consumed omega-6 fatty acid in the American diet. Maybe patients with these ailments and risks should cut down on their consumption of arachidonic acid or its precursor, or at least consume more omega-3 fatty acids to balance the omega-6 fatty acid inflammatory cascade.]**
- 4) There is widespread use of over-the-counter pain relievers in USA. Approximately 35% of adult women regularly consume NSAID pain medication, not including Tylenol. Many of these women use combinations of aspirin, Ibuprofen, and Tylenol.
- 5) Ibuprofen has been available over-the-counter in the United States since 1984.
- 6) Regular NSAID users are more likely to be overweight or obese, to be current or former smokers, and to have used postmenopausal hormone therapy than nonregular NSAID users. **[Maybe these factors are all inter-related]**
- 7) Women who took ibuprofen daily for at least 5 years were 51% more likely to be diagnosed with breast cancer than those who did not take the drug regularly.
- 8) Women who took aspirin daily for at least 5 years were 81% more likely to develop breast cancers that were not sensitive to the hormones estrogen or progesterone than women who were not regular users of aspirin.