

# A Prospective Study of Aspirin Use and the Risk of Pancreatic Cancer in Women

Journal of the National Cancer Institute, Vol. 96, No. 1, 22-28, January 7, 2004

Eva S. Schernhammer, Jae-Hee Kang, Andrew T. Chan, Dominique S. Michaud, Halcyon G. Skinner, Edward Giovannucci, Graham A. Colditz, Charles S. Fuchs

## FROM ABSTRACT

**Background:** In vitro experiments and limited animal studies suggest that aspirin and nonsteroidal anti-inflammatory drugs may inhibit pancreatic carcinogenesis.

Because few studies have examined the association between aspirin use and pancreatic cancer in humans and the results have been inconsistent, we examined the relationship between aspirin use and the development of pancreatic cancer in the Nurses' Health Study.

**Methods:** Among 88,378 women without cancer at baseline, we documented 161 cases of pancreatic cancer during 18 years of follow-up.

Aspirin use was first assessed at baseline in 1980 and updated biennially thereafter.

**Results:** Participants were classified according to history of aspirin use.

The risk of pancreatic cancer was not associated with current regular aspirin use (defined as two or more standard tablets per week, compared with use of fewer than two tablets per week).

Increasing duration of regular aspirin use, compared with non-use, was associated with a statistically significant increase in risk: Women who reported more than 20 years of regular aspirin use had an increased risk of pancreatic cancer of 58%.

Among women who reported aspirin use on at least two of three consecutive biennial questionnaires compared with consistent non-users of aspirin, the risk increased with dose

(one to three tablets per week: RR = 1.11 [11% increased risk]

four to six tablets per week: RR = 1.29 [29% increased risk]

seven to 13 tablets per week RR = 1.41 [41% increased risk]

and >14 tablets per week: RR = 1.86 [86% increase]).

**Conclusion:** Extended periods of regular aspirin use appear to be associated with a statistically significantly increased risk of pancreatic cancer among women.

THESE AUTHORS ALSO NOTE:

<sup>3</sup>Pancreatic cancer, the fourth leading cause of cancer-related mortality in the United States, is a rapidly fatal malignancy with limited effective treatment.<sup>2</sup>

Aspirin should reduce the risk of neoplasms because of its anti-inflammatory actions, mediated by the inhibition of cyclooxygenase 2: NSAIDs inhibit the biosynthesis of prostaglandin E2.

This is a prospective study in a large cohort of women with 18 years of follow-up.

This is another study using the 1976 Harvard Nurses' Health Study, which enrolled 121,700 female registered nurses aged 30 to 55 years.

Women who reported taking two or more standard aspirin tablets per week were defined as regular users, whereas those who reported less aspirin use were defined as non-regular users.

The major reasons for use among women taking one to six aspirin and seven or more aspirin per week were headache, arthritis and other musculoskeletal pain, and cardiovascular disease prevention.

Smoking History and Other Risk Factors

Smoking status, history of smoking, and other risk factors for pancreatic cancer were also assessed.

During 18 years and 1,475,262 person-years of follow-up from the 88,378 women in this study, 161 women were diagnosed with pancreatic cancer.

<sup>3</sup>Participants who reported regular aspirin use at baseline, compared with those who reported using fewer than two tablets per week, experienced an increased risk of pancreatic cancer (RR = 1.43 [43% increased risk]) after adjusting for age, cigarette smoking, history of diabetes mellitus, body mass index, and nonvigorous physical activity.<sup>2</sup>

<sup>3</sup>Prolonged regular use of two or more tablets per week appeared to increase the risk of pancreatic cancer.<sup>2</sup>

<sup>3</sup>Participants who reported the use of two or more tablets per week for more than 20 years, compared with women who never regularly consumed aspirin at this dose, experienced a statistically significantly increased risk of pancreatic cancer (multivariable RR = 1.58 [58% increased risk]).<sup>2</sup>

These authors observed an increase in the risk of pancreatic cancer with increasing aspirin dose, compared with consistent non-use of aspirin.

<sup>3</sup>Women with consistent use of 14 or more tablets per week had the highest risk of pancreatic cancer (multivariable RR = 1.86 [86% increased risk]).<sup>2</sup>

<sup>3</sup>Participants who regularly consumed five or more tablets of aspirin per week for more than 10 years, compared with women who never regularly consumed five or more tablets of aspirin per week, had an increased risk of pancreatic cancer (RR = 1.75 [75% increased risk]).<sup>2</sup>

## DISCUSSION

<sup>3</sup>In this prospective cohort of women, participants who reported current use of two or more standard aspirin tablets per week experienced a modest but not statistically significantly increased risk of pancreatic cancer compared with those who reported less use.<sup>2</sup>

<sup>3</sup>Increasing duration of regular [aspirin] use was associated with a statistically significant increase in risk of [pancreatic] cancer.<sup>2</sup>

There was a statistically significant increase in the risk of pancreatic cancer with increasing aspirin dose compared with those who were non-users.

<sup>3</sup>Aspirin and NSAIDs may have several potential influences on the pancreas that could affect pancreatic carcinogenesis.<sup>2</sup>

<sup>3</sup>Case reports and cohort studies have suggested that aspirin and NSAIDs are associated with an increased risk of pancreatitis.<sup>2</sup>

<sup>3</sup>Subclinical chronic inflammation of the pancreas induced by long-term aspirin and NSAID use could elicit a modest increase in the risk of pancreatic cancer.<sup>2</sup>

Another possible explanation for the observed increase in risk after several years of aspirin use may be linked with its effect on lipoxygenases.

[Lipoxygenases are enzymes that also metabolize the omega-6 fatty acid arachidonic acid into other eicosanoids.

NSAIDs, including aspirin, primarily inhibit cyclooxygenase 2. Cyclooxygenase 2 and lipoxygenases metabolize polyunsaturated fatty acids and appear to affect carcinogenesis.

NSAIDs may alter the balance between cyclooxygenase and lipoxygenase, which could also explain the increased risk of pancreatic cancer.

Obesity may be associated with low-grade inflammation. One study suggests that inflammation precedes weight gain.

<sup>3</sup>In summary, our findings do not support a protective effect of analgesics use on the risk of pancreatic cancer.<sup>2</sup>

<sup>3</sup>Rather, aspirin appears to increase the risk of pancreatic cancer after extended periods of use.<sup>2</sup>

<sup>3</sup>Risks and benefits associated with the use of aspirin have to be weighed carefully in any recommendations made by health care providers.<sup>2</sup>

THE ABOVE ARTICLE GENERATED THE FOLLOWING EDITORIAL, in part

What Now for Aspirin and Cancer Prevention?

John A. Baron

THIS AUTHOR NOTES:

<sup>3</sup>The study is very well done: losses to follow-up are few, and detailed, high-quality data were collected.<sup>2</sup>

<sup>3</sup>The trends in relative risks over duration of aspirin use were conventionally statistically significant, and meaningful associations were present for prolonged use.<sup>2</sup>

<sup>3</sup>It is hard to think of a conventional epidemiologic bias that could explain the findings.<sup>2</sup>

<sup>3</sup>Although prostaglandins, such as prostaglandin E<sub>2</sub>, have been strongly implicated in carcinogenesis, it is likely that there are eicosanoids with anticarcinogenic properties.<sup>2</sup>

<sup>3</sup>The findings by Schernhammer et al. are provocative and force us to think carefully about the actions of aspirin and other NSAIDs and the mechanisms underlying pancreatic cancer.<sup>2</sup>

## KEY POINTS:

- 1) This is a huge study, involving 88,378 women, involving 1,475,262 person-years with an 18-year of follow-up. It showed that extended periods of regular aspirin use is associated with a statistically significantly increased risk of pancreatic cancer.
- 2) Women who reported more than 20 years of regular aspirin use had an average increased risk of pancreatic cancer of 58%.
- 3) One to three tablets per week increased the risk by 11%.
- 4) Four to six tablets per week increased the risk by 29%.
- 5) Seven to 13 tablets per week increased the risk by 41%.
- 6) Taking 5 or more tablets of aspirin per week for more than 10 years increased the risk of pancreatic cancer 75% increased risk.
- 7) Taking more than 14 tablets per week increased the risk by 86%.
- 8) Pancreatic cancer is the fourth leading cause of cancer-related death in the United States.
- 9) The major reasons these women took aspirin were for headache, arthritis and other musculoskeletal pain, and cardiovascular disease prevention. [It is often argued that aspirin is largely benign. This article would argue that aspirin is not benign, but is quite dangerous. Patients should see chiropractors to manage these complaints, and not take drugs].
- 10) Other NSAIDs and aspirin are associated with an increased risk of pancreatitis.
- 11) NSAIDs, including aspirin, primarily inhibit cyclooxygenase-2 (Cox-2), but they also affect lipoygenases. Both lipoygenases and cyclooxygenase-2 metabolize the omega-6 fatty acid arachidonic acid into eicosanoids, which appear to affect carcinogenesis. NSAIDs may alter the balance between cyclooxygenase and lipoygenase, which could also explain the increased risk of pancreatic cancer. This altered balance is bad because some eicosanoids have anti-carcinogenic properties.