

## Short Communication

# Aspirin and Nonsteroidal Anti-inflammatory Drug Use and Risk of Pancreatic Cancer: A Meta-analysis

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## Abstract

**Background:** The association between use of nonsteroidal anti-inflammatory drugs (NSAID), including aspirin, and risk of pancreatic cancer is controversial. We did a meta-analysis to summarize available evidence from epidemiologic studies investigating the relation between use of aspirin or other NSAIDs and the risk of pancreatic cancer.

**Methods:** We identified potential studies by searching the MEDLINE database (from 1966 to October 2006) and by reviewing the reference lists of pertinent publications. Studies were eligible for inclusion if they met the following criteria: (a) had a case-control or prospective design, (b) examined exposure to aspirin or NSAIDs, (c) the outcome was pancreatic cancer incidence or mortality, and (d) they provided a relative risk (RR) estimate with corresponding confidence interval or sufficient information to permit their calculation. Study-specific RR estimates were pooled using a random effects model.

**Results:** A total of 11 studies (3 case-control studies, 7 cohort studies, and 1 randomized trial), involving 6,386 pancreatic cancer cases, was included in the meta-analysis. The summary RR estimate did not indicate any association between aspirin/NSAID use and risk of pancreatic cancer [any/regular use versus nonregular/never use: RR, 1.01; 95% confidence interval (95% CI), 0.91-1.11;  $P_{\text{heterogeneity}} = 0.09$ ]. Neither use of aspirin, nonaspirin NSAIDs, nor overall NSAIDs were associated with pancreatic cancer risk. There was also no overall association with frequent (six or more tablets/times per week versus none: RR, 0.86; 95% CI, 0.61-1.23) or long-term ( $\geq 20$  years) use of aspirin (RR, 1.21; 95% CI, 0.74-1.96).

**Conclusions:** Current epidemiologic evidence does not indicate that use of aspirin or NSAIDs is associated with the risk of pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2561-4)

## Introduction

Pancreatic cancer is the most fatal cancer in adults, ranking eight for cancer mortality in the World (1) and fourth in the United States (2). Survival with pancreatic cancer is dismal; the 5-year survival rate is  $<4\%$  (2). Therefore, identification of potential chemoprevention agents is highly desirable.

Considerable evidence from experimental, epidemiologic, and clinical studies indicates that nonsteroidal anti-inflammatory drugs (NSAID) have promise as chemopreventive agents (3). Most epidemiologic studies have found an inverse relationship between use of NSAIDs, particularly aspirin, and risk of colorectal (3), gastric (4), and esophageal cancer (5). However, whether NSAID use may reduce the risk of pancreatic cancer remains controversial. Although data from animal and laboratory studies have shown that aspirin and other NSAIDs may inhibit pancreatic carcinogenesis (6-11), findings from observational epidemiologic studies of aspirin (12-18) and NSAID use (13, 19-21) in relation to pancreatic cancer risk have been inconsistent. In the Women's Health Initiative trial, the number of incident cases of pancreatic cancer during an average follow-up of 10 years was nonsignificantly higher

among women receiving 100 mg aspirin on every other day than among women receiving placebo (22).

We used meta-analysis as a systematic approach to summarize all available epidemiologic evidence about the relation between aspirin and NSAID use and risk of pancreatic cancer.

## Materials and Methods

**Study Selection.** Studies were identified by searching MEDLINE using the search terms "aspirin," "NSAIDs," or "nonsteroidal anti-inflammatory drugs" combined with "pancreatic cancer" or "pancreatic neoplasm." The search covered the period from 1966 to October 2006. We also manually searched the reference lists of the retrieved articles to identify additional studies. No language restrictions were imposed. Studies were eligible for inclusion if they fulfilled the following criteria: (a) had a case-control or prospective study design, (b) evaluated exposure to aspirin or NSAIDs, (c) the outcome was pancreatic cancer incidence or mortality, and (d) they reported a relative risk (RR) estimate (rate ratio, hazard ratio, or odds ratio) with corresponding confidence interval or sufficient information to permit their calculation.

**Statistical Analysis.** RR was used as a measure of the association between use of aspirin/NSAIDs and risk of pancreatic cancer. Because pancreatic cancer is rare, odds ratio in case-control studies and rate ratio in cohort studies yield similar estimates of RR (23). Summary RR estimates and 95% confidence intervals (95% CI) were calculated with the method of DerSimonian and Laird (24) by use of the assumption

Received 7/13/06; revised 8/24/06; accepted 9/18/06.

**Grant support:** Swedish Cancer Society and Swedish Foundation for International Cooperation in Research and Higher Education.

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doi:10.1158/1055-9965.EPI-06-0574

of a random effects model, which considers both within-study and between-study variation. One study reported results separately for aspirin and nonaspirin NSAIDs (13). To avoid double counting of the cases, we included only the results for aspirin in the overall summary estimate. Statistical heterogeneity among studies was assessed with the  $Q$  and  $I^2$  statistics (25). For the  $Q$  statistic,  $P < 0.1$  was considered representative of statistically significant heterogeneity.  $I^2$  is the proportion of total variation contributed by between-study variation (25). Publication bias was evaluated with the Egger's regression asymmetry test (26);  $P < 0.1$  was considered representative of statistically significant publication bias. All analyses were carried out using Stata software version 9.1 (StataCorp, College Station, Texas), and all statistical tests were two sided.

## Results

We identified three case-control studies (14, 19, 20), seven prospective cohort studies (12, 13, 15-18, 21), and one randomized trial (22) of aspirin and/or NSAID use in relation to risk of pancreatic cancer (Table 1). Nine studies were

conducted in the United States (12-14, 16, 17, 19, 20, 22) and two in Denmark (15, 21). The outcome was pancreatic cancer mortality in two studies (17, 18) and pancreatic cancer incidence in the remaining nine studies.

The 11 studies included in the meta-analysis involved 6,386 cases. The overall summary estimate did not reveal any association between use of aspirin/NSAIDs and risk of pancreatic cancer (any/regular use versus nonregular/never use: RR, 1.01; 95% CI, 0.91-1.11), but there was evidence of heterogeneity among studies ( $Q = 16.34$ ;  $P = 0.09$ ;  $I^2 = 38.8\%$ ). There was no indication of publication bias ( $P = 0.78$ , Egger's test). The summary estimate did not change materially when excluding the clinical trial (RR, 1.00; 95% CI, 0.91-1.10; ref. 22) or the three studies based on aspirin/NSAID prescriptions (RR, 0.94; 95% CI, 0.81-1.09; refs. 15, 20, 21). The summary estimates were similar for case-control (RR, 1.01; 95% CI, 0.83-1.23) and cohort studies (RR, 0.99; 95% CI, 0.88-1.13). Neither use of aspirin, nonaspirin NSAIDs, nor overall NSAIDs were associated with risk of pancreatic cancer (Fig. 1).

Overall, frequent aspirin use (six or more tablets/times per week) was not associated with pancreatic cancer risk, but there was statistically significant heterogeneity among the results

**Table 1. Characteristics of studies included in the meta-analysis of aspirin and NSAIDs and risk of pancreatic cancer, ordered by exposure and year of publication**

Study and country	Study design	Cases	Controls or cohort size	Exposure	Exposure definition	RR (95% CI)	Adjustments
Schreinemachers and Everson (12); United States	Cohort	30	12,668	Aspirin	Any use of aspirin in the last 30 days	0.67 (0.33-1.36)	Age, sex
Anderson et al. (13); United States	Cohort	80	28,283	Aspirin	Any use vs no use	0.58 (0.36-0.90)	Age, smoking, diabetes, multivitamin use
Menezes et al. (14); United States	Hospital-based case-control	194	582	Aspirin	≥6 times/wk ≥1 tablet/wk for >6 mo	0.40 (0.20-0.82) 1.00 (0.72-1.39)	Age, smoking, family history of pancreatic cancer
Friis et al. (15); Denmark	Cohort	62	29,470	Aspirin	Prescriptions of low-dose (75-150 mg) aspirin >10 y	1.21 (0.81-1.82)	Age, sex
Schernhammer et al. (16); United States	Cohort	161	88,378	Aspirin	≥2 tablets/wk ≥7 tablets/wk >20 y and ≥2 tablets/wk	1.20 (0.87-1.65) 1.30 (0.70-2.40)* 1.58 (1.03-2.43)	Age, smoking, BMI, physical activity, diabetes
Jacobs et al. (17); United States	Cohort	4,577 (deaths)	987,590	Aspirin	Any use vs no use >7 times/wk ≥20 y and >7 times/wk	0.96 (0.92-1.01) 0.97 (0.86-1.09) 0.96 (0.69-1.33)	Age, sex, race, smoking, BMI, diabetes
Ratnasinghe et al. (18); United States	Cohort	78 (deaths)	22,834	Aspirin	Any use vs no use	0.87 (0.42-1.77)	Age, sex, race, poverty index, education, BMI
Cook et al. (22); United States	Randomized trial <sup>†</sup>	51	39,876	Aspirin	Low-dose (100 mg) aspirin every other day for 10 y vs placebo	1.42 (0.81-2.49)	None
Anderson et al. (13); United States	Cohort	80	28,283	NA-NSAIDs	Any use vs no use ≥6 times/wk	1.19 (0.76-1.88) 1.28 (0.68-2.43)	Age, smoking, diabetes, multivitamin use
Sørensen et al. (21); Denmark	Cohort	149	172,057	NA-NSAIDs	Any prescription ≥10 prescriptions	1.10 (0.90-1.20) 0.90 (0.60-1.30)	Age, sex
Coogan et al. (19); United States	Hospital-based case-control	491	5,833	NSAIDs	≥4 d/wk for ≥3 mo	0.80 (0.50-1.10)	Age, sex, education, smoking, family history of digestive cancer, other
Langman et al. (20); United States	Population-based case-control	513	1,535	NSAIDs	Any prescription ≥7 prescriptions during mo 13-36 before index date	1.15 (0.88-1.49) <sup>‡</sup> 1.49 (1.02-2.18)	Age, smoking

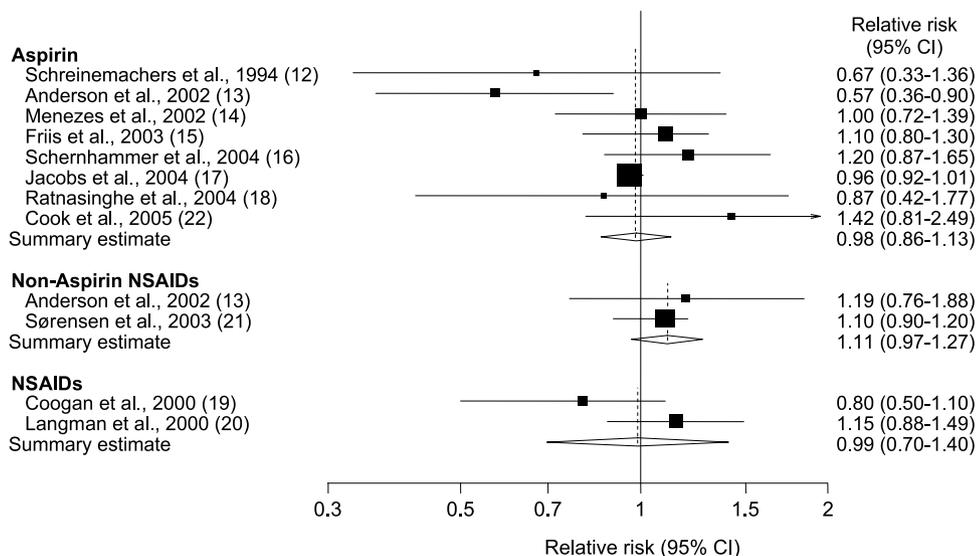
Abbreviations: NA-NSAIDs, nonaspirin NSAIDs; BMI, body mass index.

\*The RR (and its 95% CI) was derived by pooling the RRs for categories 7 to 13 and ≥14 tablets per week.

<sup>†</sup>Randomized 2 × 2 factorial trial evaluating the effects of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer.

<sup>‡</sup>The RR (and its 95% CI) was derived by pooling the RRs for 1, 1 to 6, and ≥7 prescriptions during months 13 to 36 before index date.

**Figure 1.** RRs of pancreatic cancer associated with regular/any use of aspirin, nonaspirin NSAIDs, and overall NSAIDs. *Squares*, study-specific RRs (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); *horizontal lines*, 95% CIs; *diamonds*, summary RR estimates with corresponding 95% CIs. Test for heterogeneity: aspirin,  $Q = 10.98$ ,  $P = 0.14$ ,  $I^2 = 36.3\%$ ; nonaspirin NSAIDs,  $Q = 0.11$ ,  $P = 0.75$ ,  $I^2 = 0\%$ ; NSAIDs,  $Q = 2.25$ ,  $P = 0.13$ ,  $I^2 = 55.6\%$ .



from the four studies (Fig. 2). The summary estimate based on data from two cohort studies showed no significant association between long duration ( $\geq 20$  years) of aspirin use and risk of pancreatic cancer (Fig. 2).

## Discussion

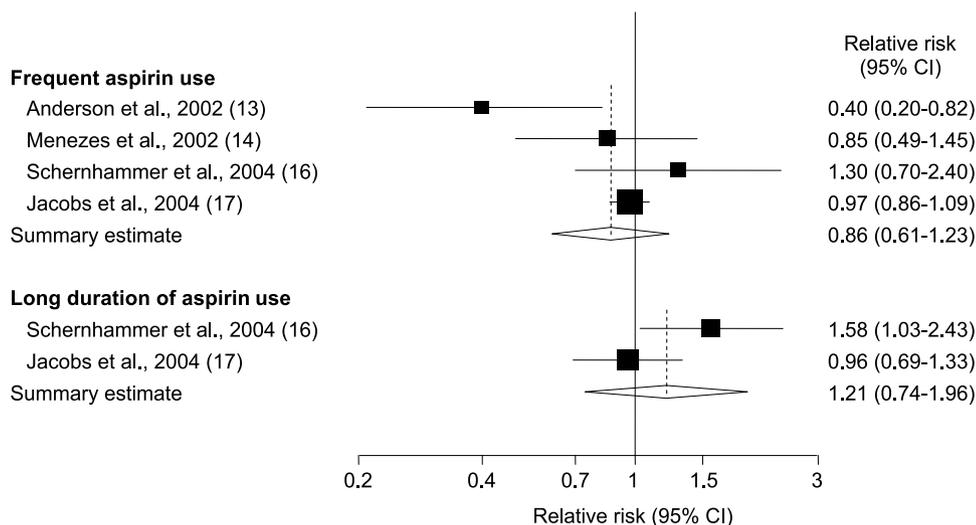
Long-term use of aspirin and other NSAIDs has almost consistently been associated with a reduced risk of colorectal cancer (3, 27), and there is some evidence, although more limited and mainly from case-control studies, that aspirin may have a favorable effect on gastric (4) and esophageal cancer (5). In the present meta-analysis, however, we found no evidence that use of aspirin, nonaspirin NSAIDs, or overall NSAIDs may lower pancreatic cancer risk.

The majority of the studies included in this meta-analysis showed no significant association between use of aspirin or NSAIDs and pancreatic cancer incidence or mortality. However, one prospective cohort of 28,283 U.S. postmenopausal women found a statistically significant 60% reduction in risk of pancreatic cancer associated with use of six or more aspirin tablets per week (13). This cohort study was based on a relatively small number of cases ( $n = 80$ ) and indicated no association with NSAID use. In contrast, in the Nurses' Health Study, women who reported  $>20$  years of regular use of aspirin

(two or more tablets per week) had a statistically significant 58% increase in pancreatic cancer risk compared with nonusers (16). Similarly, in the randomized trial involving  $\sim 40,000$  women, slightly more cases of pancreatic cancer were diagnosed among women who received low-dose aspirin (100 mg on alternate days) than among women who received placebo (30 versus 21 cases), but this difference was not statistically significant (RR, 1.42; 95% CI, 0.81-2.49; ref. 22).

There are some potential limitations that should be considered when interpreting the results from this meta-analysis. First, as the meta-analysis is based on observational studies, we cannot rule out the possibility that the lack of association between aspirin/NSAID use and pancreatic cancer risk is due to bias or confounding inherent in the original studies. Recall and selection bias could be a problem in case-control studies and could result in an underestimation or an overestimation of the true exposure effect. However, summary estimates were very similar for case-control and cohort studies, suggesting that this aspect of study design was not important. Confounding is an important consideration when evaluating results from both case-control and cohort studies. Individual studies may have failed to control for potential confounders, which could have concealed a possible association with aspirin/NSAIDs. Second, misclassification of exposure to aspirin/NSAIDs is likely to be present. If exposure is measured on a dichotomous scale (exposed

**Figure 2.** RRs of pancreatic cancer associated with frequent (six or more tablets/times per week) and long duration ( $\geq 20$  years) of aspirin use. *Squares*, study-specific RRs (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); *horizontal lines*, 95% CIs; *diamonds*, summary RR estimates with corresponding 95% CIs. Test for heterogeneity: frequent use,  $Q = 7.05$ ,  $P = 0.07$ ,  $I^2 = 57.4\%$ ; long duration of use,  $Q = 3.27$ ,  $P = 0.07$ ,  $I^2 = 69.4\%$ .



versus nonexposed), the consequence of nondifferential misclassification would be to bias the findings toward the null, potentially obscuring a true decrease or increase in risk of pancreatic cancer associated with use of aspirin/NSAIDs. Finally, the possibility of publication bias is always a concern in meta-analyses of published studies. In this meta-analysis, we found no evidence for such bias.

In summary, current epidemiologic evidence does not indicate that use of aspirin or NSAIDs lowers the risk of pancreatic cancer. Whether regular use of aspirin for long duration increases the risk of pancreatic cancer remains unclear and warrants further study.

## References

- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
- Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK, editors. SEER cancer statistics review, 1975-2002, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2002/](http://seer.cancer.gov/csr/1975_2002/), based on November 2004 SEER data submission, posted to the SEER Web site 2005.
- Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 2002;94:252–66.
- Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC. Nonsteroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003;95:1784–91.
- Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003;124:47–56.
- Kokawa A, Kondo H, Gotoda T, et al. Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors. *Cancer* 2001;91:333–8.
- Yip-Schneider MT, Sweeney CJ, Jung SH, Crowell PL, Marshall MS. Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells. *J Pharmacol Exp Ther* 2001;298:976–85.
- McDade TP, Perugini RA, Vittimberga FJ, Jr., Carrigan RC, Callery MP. Salicylates inhibit NF- $\kappa$ B activation and enhance TNF- $\alpha$ -induced apoptosis in human pancreatic cancer cells. *J Surg Res* 1999;83:56–61.
- Takahashi M, Furukawa F, Toyoda K, et al. Effects of various prostaglandin synthesis inhibitors on pancreatic carcinogenesis in hamsters after initiation with *N*-nitrosobis(2-oxopropyl)amine. *Carcinogenesis* 1990;11:393–5.
- Schuller HM, Zhang L, Weddle DL, Castonguay A, Walker K, Miller MS. The cyclooxygenase inhibitor ibuprofen and the FLAP inhibitor MK886 inhibit pancreatic carcinogenesis induced in hamsters by transplacental exposure to ethanol and the tobacco carcinogen NNK. *J Cancer Res Clin Oncol* 2002;128:525–32.
- Perugini RA, McDade TP, Vittimberga FJ, Jr., Duffy AJ, Callery MP. Sodium salicylate inhibits proliferation and induces G<sub>1</sub> cell cycle arrest in human pancreatic cancer cell lines. *J Gastrointest Surg* 2000;4:24–32, discussion 32–3.
- Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology* 1994;5:138–46.
- Anderson KE, Johnson TW, Lazovich D, Folsom AR. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. *J Natl Cancer Inst* 2002;94:1168–71.
- Menezes RJ, Huber KR, Mahoney MC, Moysich KB. Regular use of aspirin and pancreatic cancer risk. *BMC Public Health* 2002;2:18.
- Friis S, Sørensen HT, McLaughlin JK, Johnsen SP, Blot WJ, Olsen JH. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. *Br J Cancer* 2003;88:684–8.
- Schernhammer ES, Kang JH, Chan AT, et al. A prospective study of aspirin use and the risk of pancreatic cancer in women. *J Natl Cancer Inst* 2004;96:22–8.
- Jacobs EJ, Connell CJ, Rodriguez C, Patel AV, Calle EE, Thun MJ. Aspirin use and pancreatic cancer mortality in a large United States cohort. *J Natl Cancer Inst* 2004;96:524–8.
- Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawk E. Aspirin use and mortality from cancer in a prospective cohort study. *Anticancer Res* 2004;24:3177–84.
- Coogan PF, Rosenberg L, Palmer JR, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. *Cancer Epidemiol Biomarkers Prev* 2000;9:119–23.
- Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ* 2000;320:1642–6.
- Sørensen HT, Friis S, Norgard B, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. *Br J Cancer* 2003;88:1687–92.
- Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294:47–55.
- Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987;9:1–30.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005;294:914–23.

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*Cancer Epidemiol Biomarkers Prev* 2006;15:2561-2564.

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