Research Article

Cancer Epidemiology, Biomarkers & Prevention

Case–Control Study of Aspirin Use and Risk of Pancreatic Cancer

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Abstract

Background: Pancreas-cancer prognosis is dismal, with 5-year survival less than 5%. Significant relationships between aspirin use and decreased pancreas-cancer incidence and mortality have been shown in four of 13 studies.

Methods: To evaluate further a possible association between aspirin use and risk of pancreatic cancer, we used data from a population-based Connecticut study conducted from January 2005 to August 2009, of 362 pancreas-cancer cases frequency matched to 690 randomly sampled controls.

Results: Overall, regular use of aspirin was associated with reduced risk of pancreatic cancer [odds ratio (OR), 0.52; 95% confidence interval (CI), 0.39–0.69]. Increments of decreasing risk of pancreatic cancer were observed for each year of low-dose or regular-dose aspirin use (OR, 0.94; 95% CI, 0.91–0.98 and OR, 0.98; 95% CI, 0.96–1.01, respectively) and for increasing years in the past that low-dose or regular-dose aspirin use had started (OR, 0.95; 95% CI, 0.92–0.99 and OR, 0.98; 95% CI, 0.96–1.00, respectively). Reduced risk of pancreatic cancer was seen in most categories of calendar time period of aspirin use, for both low-dose aspirin and regular-dose aspirin use. Relative to continuing use at the time of interview, termination of aspirin use within 2 years of interview was associated with increased risk of pancreatic cancer (OR, 3.24; 95% CI, 1.58–6.65).

Conclusions: Our results provide some support that a daily aspirin regimen may reduce risk of developing pancreatic cancer.

Impact: Long-term aspirin use has benefits for both cardiovascular disease and cancer, but appreciable bleeding complications that necessitate risk–benefit analysis for individual applications. *Cancer Epidemiol Biomarkers Prev; 23(7); 1254–63. ©2014 AACR.*

Introduction

In the United States, pancreatic cancer is one of the most lethal cancers, with mortality rates approaching incidence rates. Pancreatic cancer ranks as the 10th highest cancer in number of new cases each year, but is 4th highest in deaths per year: 45,000 new cases diagnosed annually and 38,500 deaths annually (1). Risk factors for pancreatic cancer include cigarette smoking, family history of pancreatic cancer, family or personal history of chronic pancreatitis, history of diabetes mellitus, obesity, non-O blood group, and Jewish or African-American ethnic origin (2, 3).

Although aspirin use has been suggested to reduce the risk of pancreatic and other cancers, epidemiologic studies have been inconsistent. Over the last 2 decades, the relationship between aspirin use and pancreatic cancer has been evaluated through case–control studies, prospective cohort studies, and randomized controlled trials (RCT). Of 13 studies that have assessed the relationship, 4 have shown decreased risks of pancreatic cancer with aspirin use (4–7), 7 have shown no associations with use (8–14), and 2 studies have shown increased risks of pancreatic cancer in the highest aspirin-use categories (15, 16).

Recently, strong evidence suggesting that daily low-dose aspirin use for 5 years or more significantly reduces overall cancer incidence and mortality and notably decreases mortality from pancreatic cancer has come from secondary analyses of landmark RCTs investigating associations between daily low-dose aspirin use and vascular events (6). When the data were analyzed specifically for pancreatic cancer mortality, a significant reduction was seen in deaths occurring after the 5-year follow-up period [hazard ratio (HR), 0.43; 95% CI, 0.07–0.92]. In the posttrial 20-year follow-up period, individuals who had been scheduled to take aspirin for 7.5 to 10 years, but not those scheduled for less than 7.5 years, also had a significant reduction in mortality (HR, 0.28; 95% CI, 0.08–1.00; ref. 6). If these results are valid, reducing pancreatic cancer mortality by more than two thirds with prolonged low-dose aspirin use could dramatically decrease the burden of this cancer. To investigate further the hypothesis that aspirin use reduces the risk of pancreatic cancer, we

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evaluated the association in data from the Connecticut Pancreas Cancer Case–Control Study. We analyzed the association between risk of pancreatic cancer and regular use of aspirin, as well as examined risk relationships according to various parameters of aspirin use.

Materials and Methods

Study population

A population sample of newly diagnosed individuals with pancreatic cancer was recruited from the 30 general hospitals in the state of Connecticut between January 1, 2005 and August 31, 2009, and control subjects, randomly selected from residents of the state, were frequency matched to cases by categories of gender and age at time of recruitment, as described previously (17). Three hundred sixty-two cases and 690 controls were included in this analysis. This study was approved by the Human Investigation Committees of Yale University, the State of Connecticut Department of Public Health, and the institutional review boards of the 30 Connecticut Hospitals in which case identification occurred.

Measures

We analyzed associations between risk of pancreatic cancer and number of years in the past since aspirin use began, duration of aspirin use in years, years in the past that aspirin use ended, and calendar time periods of aspirin use. We also stratified years in the past that aspirin use began, duration of aspirin use, and time period of aspirin use, according to low-dose aspirin use versus regular-dose aspirin use.

Study subjects were interviewed in person and reported aspirin use through specific questioning. Subjects were asked, "Have you ever taken aspirin regularly, or at least once a week on average, for 3 months or more?" and if the answer to that question was yes, it was followed by "How old were you when you started, and for how many months or years did you use it?" After that, participants were shown a card with generic and brand names of various NSAIDs, including anacin, aspirin, bufferin, ecotrin, empirin, and "baby" aspirin, and asked "Have you ever taken any of the medications shown on this card regularly, at least once a week on average, for 3 months or more?" and for each positive answer, it was followed by "Which one was it? How old were you when you started, and for how many months or years did you use it? About how many days per week did you use it?" Details for each episode of use for each medication were recorded.

Potential confounding factors ascertained during interview or from laboratory analyses (and included in statistical models, chosen a priori) were: age at interview, typical adult body mass index (BMI, weight/height^2, kg/m^2), gender, race/ethnicity, smoking history, history of diabetes mellitus diagnosed more than 3 years in the past, education level, and ABO blood type. ABO type was determined by standard erythrocyte antiserum agglutination methods on fresh blood specimens, with commercial kits (17).

Statistical analyses

All statistical analyses were performed using SAS version 9.2. Descriptive distributions were examined for pancreatic cancer cases and controls: age at interview, BMI, gender, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), smoking history (never, former, current/recent), diabetes history, education level, and ABO blood group. Fact of diabetes diagnosis was only included if diagnosis was made more than 3 years in the past, as pancreatic cancer can also cause signs of diabetes (18). Former smokers were classified as smokers who had quit at least 10 years in the past, and recent/current smokers as those who quit less than 10 years in the past or were currently smoking.

Aspirin use was defined as a positive questionnaire response about regular use of any aspirin or aspirin-containing product. We created a variable for years in the past that aspirin use began, by subtracting age at the beginning of regular aspirin use from interview age. This variable was then grouped into categories of never use, start of aspirin use $\leq$3 years in the past, >3 but $\leq$5 years in the past, >5 but $\leq$7 years in the past, >7 but $\leq$10 years in the past, >10 but $\leq$20 years in the past, and more than 20 years in the past. We created an aspirin use duration variable by totaling the time periods in which aspirin use was reported. We then categorized the total duration into never use, use for 6 years or less, use for >6 but $\leq$10 years, and use for more than 10 years. We created a variable for years in the past that aspirin use ended, by adding duration of aspirin use to the age at the beginning of aspirin use. This variable was then categorized into never use, use ending more than 1 but $\leq$2 years before interview, ending >2 but $\leq$7 years before interview, and ending more than 7 years before interview, and was compared with individuals who were continuing aspirin use at the time of interview. Finally, we created a calendar time-period of aspirin use variable by considering ever-use during 7 possible periods: use (yes vs. no) of aspirin within the most recent year, use within the 2 years from >1 to $\leq$3 years in the past, use in >3 to $\leq$5 years in the past, use in >5 to $\leq$7 years in the past, use in >7 to $\leq$10 years in the past, use in >10 to $\leq$20 years in the past, and ever use at any point more than 20 years in the past. Ten individuals reported use of baby aspirin and regular aspirin at different time periods, and were therefore included in usage categories of both medications. We defined all of the various category intervals in attempt to attain roughly uniform numbers of subjects in each category, insofar as possible.

For the variables years in the past that aspirin use began, duration of use, and time period of use, aspirin use was also stratified on low-dose aspirin use and regular-dose aspirin use. Too few individuals ended aspirin use before interview to stratify the variable representing years in the past that use ended according to the 2 dose categories.

We did not have data on number of aspirin tablets taken daily, with which to calculate the exact daily dose of aspirin. We assumed that a low-dose aspirin regimen was

a dose of 75 to 325 mg aspirin per day typically taken prophylactically for heart disease prevention, and a regular-dose aspirin regimen was a dose of >325 to 1,200 mg every 4 to 6 hours taken for pain or anti-inflammation purposes (19).

Unconditional logistic regression was used to calculate odds ratios (OR) and their 95% confidence intervals (95% CI). Models were adjusted for the potential confounders age at interview, BMI, gender, race/ethnicity, smoking history, diabetes diagnosis more than 3 years in the past, education level, and ABO blood type. Regression models for low-dose aspirin were also adjusted for usage of regular-dose aspirin and vice versa. All reported *P* values are 2-sided.

Results

Case subjects were slightly older than controls, were more likely to be current/recent smokers, were more likely to have been diagnosed with diabetes at least 3 years before interview, and were less educated (Table 1). Ninety-six percent of low-dose aspirin users and 92% of regular-dose aspirin users reported daily aspirin use.

Compared with individuals who had never used aspirin, subjects who regularly used aspirin had a lower risk of pancreatic cancer: OR, 0.52 (95% CI, 0.39–0.69). For each cumulative year of any aspirin use, of low-dose aspirin use, and of regular aspirin use, decreasing risks of pancreatic cancer were observed (OR, 0.97; 95% CI, 0.95–0.99; OR, 0.94; 95% CI, 0.91–0.98; and OR, 0.98; 95% CI, 0.96–1.01, respectively, per year of use; Table 2). These dose–response trends in risk with duration of use were most apparent for users of low-dose aspirin, for whom risks declined according to increasing category of duration (Table 2). In addition, reduced risks were seen for both low-dose aspirin and regular aspirin use, for almost all categories of years in the past when the use started (Table 3). Significant differences in such risks were not observed according to the type of aspirin used (Table 3). Termination of aspirin use during 1 to 2 years before interview was associated with a substantial increased risk of pancreatic cancer (OR, 3.24; 95% CI, 1.58–6.65) compared with continuing use (Table 4). Finally, little difference in risk was seen for regular use of aspirin in various intervals of calendar time over the past (Table 5). Although a few of the reduced risks were not statistically significant, most of the risks were cut about 50% compared with nonuse, even for usage more than 20 years in the past.

Table 1. Descriptive characteristics of pancreatic cancer cases and controls

Characteristic	Controls[a] (%)	Cases[a] (%)
Age (y), mean ± SD	65.8 ± 10.4	67.4 ± 9.8
Usual adult BMI (kg/m^2) ± SD	27.3 ± 5.5	27.0 ± 5.1
Gender		
Male	390 (56.5)	206 (56.9)
Female	300 (43.5)	156 (43.1)
Race/ethnicity		
Non-Hispanic White	649 (94.1)	332 (91.7)
Non-Hispanic Black	25 (3.6)	20 (5.5)
Hispanic	7 (1.0)	4 (1.1)
Other	9 (1.3)	6 (1.7)
Smoking history		
Never	360 (52.2)	183 (50.6)
Former	279 (40.4)	130 (35.9)
Current/recent (quit <10 y in past)	51 (7.4)	49 (13.5)
Diabetes (>3 y in past)		
No	614 (89.0)	292 (80.7)
Yes	76 (11.0)	70 (19.3)
Education		
Less than high school	36 (5.2)	40 (11.1)
High school graduate	145 (21.0)	103 (28.5)
Some/all community college or technical school	86 (12.5)	47 (13.0)
Some college	67 (9.7)	33 (9.1)
Bachelor's degree	145 (21.0)	76 (21.0)
Advanced degree	211 (30.6)	63 (17.4)
ABO blood group		
A	276 (40.0)	149 (41.2)
B	81 (11.7)	44 (12.2)
AB	18 (2.6)	24 (6.6)
O	315 (45.7)	145 (40.0)

[a]Number (%) of subjects unless stated otherwise.

Discussion

To our knowledge, this is the first study to examine the association between risk of pancreatic cancer and years in the past that aspirin use began, years in the past that aspirin use ended, and the first to analyze the association between risk of pancreatic cancer and calendar time periods of aspirin use. Moreover, we specifically assessed the relationship between duration of aspirin use and risk, and observed a duration–response relationship with prolonged use of low-dose aspirin. Our results provide further evidence that a daily aspirin regimen may afford chemoprophylaxis against pancreatic cancer.

Nevertheless, limitations in our study design caused us to classify aspirin use based on reported type of aspirin, baby or regular, rather than on reason for use (cardioprophylaxis or analgesia). We did not obtain data on frequency of use beyond daily use, or on reasons for aspirin use, which might have allowed more precise classifications of use. These data limitation may have blurred the 2 types of aspirin use categories slightly. In addition, a case–control study is an efficient way to study pancreatic cancer because it is a rare disease. However, as with any case–control study, the temporal relationship between aspirin use and pancreatic cancer is difficult to establish, and case–control studies are more prone to selection and information bias. We attempted to deal with the temporal relationships between pancreatic cancer and aspirin use

Table 2. Pancreatic cancer ORs according to duration of continuing aspirin use

	Any aspirin		Low-dose aspirin		Regular aspirin	
Duration of aspirin use (y)	**No. of controls/cases**	**OR[a] (95% CI)**	**No. of controls/cases**	**OR[b] (95% CI)**	**No. of controls/cases**	**OR[c] (95% CI)**
Continuous (per year of use)[d]		0.97 (0.95–0.99)		0.94 (0.91–0.98)		0.98 (0.96–1.01)
Never used	345/218	1	345/218	1	345/218	1
≤6	204/78	0.50 (0.36–0.70)	136/63	0.63 (0.44–0.91)	75/17	0.27 (0.15–0.49)
>6, ≤10	71/33	0.50 (0.31–0.82)	46/19	0.41 (0.22–0.76)	25/14	0.61 (0.29–1.30)
>10	62/31	0.61 (0.37–1.00)	30/11	0.40 (0.18–0.87)	31/20	0.89 (0.47–1.67)

[a]Adjusted for gender, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), smoker (never compared with past and recent/current), diabetes (diagnosed more than 3 y before interview), education, age (continuous), BMI (continuous), and blood type (O vs. non-O).
[b]Adjusted as above, as well as for regular aspirin use.
[c]Adjusted as above, as well as for low-dose aspirin use.
[d]Analysis of linear trend.

as the focus of the paper, and we found evidence for both reverse causation in recent aspirin use and reduced risk with long-term aspirin use.

The present data show reduced risks with starting aspirin use, either regular-dose or low-dose, less than a decade before interview. These results do not seem consistent with an etiologic role for aspirin in preventing the initiation of pancreatic cancer, because the latency of the disease is on average apparently at least 10 years (20). Ki-67 protein labeling and sequencing of index lesions of pancreatic tumor cells have revealed that a decade or more passes between the initiating mutation of pancreatic cancer and the genesis of the parental nonmetastatic founder cell, another 5 years before the acquisition of metastatic ability, and an average of 2 more years until patient death (20). Aspirin use, within 10 years of starting, may thus slow the tumorigenesis process rather than prevent the initial tumor development.

In our data, some differences in risk were apparent for the use of low-dose versus regular-dose aspirin. The trend in risk for duration of use of low-dose aspirin revealed a significant inverse relationship, whereas such a trend for regular-dose aspirin was not observed, although some durations of use still seemed to be associated with decreased risks. Individuals who take regular-dose aspirin for pain or anti-inflammation purposes are likely taking it for reasons associated with other illnesses or in early stages of pancreatic cancer (e.g., abdominal discomfort radiating to back pain, known to be a symptom of pancreatic cancer; ref. 21). In contrast, individuals who

Table 3. Pancreatic cancer ORs according to start of continuing aspirin use

	Any aspirin		Low-dose aspirin		Regular aspirin	
Start of aspirin use (years in the past)	**No. of controls/cases**	**OR[a] (95% CI)**	**No. of controls/cases**	**OR[b] (95% CI)**	**No. of controls/cases**	**OR[c] (95% CI)**
Continuous (per year earlier started)[d]		0.98 (0.95–1.00)		0.95 (0.92–0.99)		0.98 (0.96–1.00)
Never used	345/218	1	345/218	1	345/218	1
≤3	62/19	0.41 (0.23–0.72)	42/16	0.52 (0.28–0.97)	23/4	0.21 (0.07–0.61)
>3, ≤5	48/21	0.56 (0.32–1.00)	37/18	0.63 (0.34–1.17)	12/3	0.30 (0.08–1.13)
>5, ≤7	68/27	0.52 (0.32–0.86)	45/24	0.71 (0.41–1.22)	23/4	0.18 (0.06–0.57)
>7, ≤10	39/18	0.48 (0.26–0.90)	22/11	0.48 (0.21–1.06)	18/7	0.46 (0.18–1.23)
>10, ≤20	64/35	0.69 (0.43–1.11)	43/14	0.40 (0.21–0.78)	22/21	1.21 (0.62–2.37)
>20	42/16	0.42 (0.22–0.81)	13/6	0.39 (0.13–1.17)	29/10	0.44 (0.20–0.97)

[a]Adjusted as in Table 2.
[b]Adjusted as above, as well as for regular aspirin use.
[c]Adjusted as above, as well as for low-dose aspirin use.
[d]Analysis of linear trend.

Table 4. Pancreatic cancer ORs according to end of continuing aspirin use

	Any aspirin	
End of aspirin use (years in past)	**No. of controls/cases**	**OR[a] (95% CI)**
Use continued during interview year	267/98	1
Never used	345/218	2.23 (1.62–3.06)
>1, ≤2	17/21	3.24 (1.58–6.65)
>2, ≤7	17/10	1.72 (0.75–3.98)
>7	18/6	0.92 (0.34–2.50)

[a]Adjusted as in Table 2.

take daily low-dose aspirin most likely do so for primary prevention of heart disease or secondary prevention of myocardial infarction and nonfatal stroke, conditions not associated with pancreatic cancer (22). An alternative explanation of this difference may be because of the consistency with which daily low-dose, but not necessarily regular-dose, aspirin is typically taken. It is with low-dose aspirin that our data show the strongest inverse duration–response relationship.

Interestingly, appreciably increased risk of pancreatic cancer was seen in our analysis for aspirin use ending within 2 years of interview. This elevated risk most likely reflects the increasing inability of individuals with developing pancreatic cancer to tolerate daily doses of aspirin. Dysgeusia is a feature of pancreatic cancer, similar to the fact that cigarette smokers are more likely to quit smoking within 2 to 3 years before the diagnosis of pancreatic cancer, and that diagnosis of diabetes mellitus is also more frequent during this interval, all probably reflecting physiologic changes caused by the growing cancer (18, 23).

Our findings are consistent with studies that have observed daily aspirin use to decrease the incidence or mortality of pancreatic cancer (4–7). As recognized in our discussion, analyses in other studies have involved aspirin use for less than 10 years, suggesting that use may be slowing the tumorigenesis process rather than preventing tumor development *ab initio*. Tables 6 and 7 summarize previous studies that have examined the association between pancreatic cancer and aspirin use. These tables show that practically all studies that started accruing patients in the early 1990s and published 20 years later, but not studies that started accruing patients in the 1970s and 1980s, show a reduced incidence or mortality from pancreatic cancer with aspirin use. This schism in significant and nonsignificant studies may be partially explained by the fact that use of daily low-dose aspirin for cardioprophylaxis was not introduced to the general population until 1989 (22).

Aspirin, or acetyl salicylate, is a nonsteroidal anti-inflammatory inhibitor of the cyclooxygenase (COX) enzymes, COX-1 and COX-2, that convert the long-chain polyunsaturated fatty acid, arachidonic acid, into prostaglandins, thromboxanes, and prostacyclins (24). Traditionally, COX-1 is known to be constitutively expressed in most tissues and is an important enzyme in maintaining homeostatic levels of prostaglandins for inactivated platelets and gastrointestinal protection (25), whereas COX-2 is usually absent from most tissues under physiologic conditions and is primarily induced in several important biologic and pathologic processes such as inflammation, wound healing, and neoplasia (26). Evidence accumulated in early laboratory research suggesting that COX-2 expression may be involved in cancer development (27, 28). For example, in 2 types of pancreatic cancer precursor lesions that have been examined, pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMN), COX-2 expression has been found to be upregulated (29–31). COX-2 has not yet been examined in mucinous cystic neoplasms (MCN). Furthermore, upregulated COX-2 protein and mRNA have been detected in both pancreatic carcinoma tissue and cell lines (32, 33).

Table 5. Pancreatic cancer ORs for individuals ever regularly using aspirin during specific time intervals in the past

	Any aspirin		Low-dose aspirin		Regular aspirin	
Interval during which aspirin was ever used (years in the past)	**Controls/cases**	**OR[a] (95% CI)**	**Controls/cases**	**OR[a] (95% CI)**	**Controls/cases**	**OR[a] (95% CI)**
Never used	345/218	1	345/218	1	345/218	1
Use in current year	288/128	0.51 (0.37–0.69)	189/82	0.53 (0.38–0.75)	100/39	0.46 (0.30–0.72)
>1, ≤3	252/114	0.56 (0.41–0.76)	167/78	0.57 (0.40–0.81)	88/37	0.52 (0.32–0.82)
>3, ≤5	233/105	0.54 (0.40–0.75)	152/69	0.54 (0.38–0.79)	84/37	0.56 (0.34–0.86)
>5, ≤7	190/89	0.57 (0.41–0.80)	116/53	0.55 (0.36–0.82)	74/36	0.59 (0.37–0.96)
>7, ≤10	98/51	0.62 (0.41–0.95)	75/30	0.44 (0.27–0.73)	58/34	0.74 (0.44–1.23)
>10, ≤20	101/50	0.65 (0.42–0.98)	56/21	0.44 (0.25–0.79)	45/29	0.90 (0.52–1.55)
>20	42/16	0.43 (0.22–0.83)	13/6	0.39 (0.12–1.19)	29/10	0.45 (0.20–0.99)

[a]ORs for ever having regularly used aspirin (yes/no) in the time windows shown. Adjusted as in Table 2.

Table 6. Studies showing significant decreased risks of pancreatic cancer with NSAID (specifically aspirin) use

First author	Publication year	Study design	Study subjects	Accrual period	Years of follow up	Aspirin-use definition	Strength of association (95% CI)
Rothwell	2011	RCT	Six world-wide RCTs for vascular disease[a]	1979-present	20 y	Daily low-dose aspirin use, 0–5 y of follow up	HR, 0.88 (0.44–1.77)
						≥5 y of follow up	HR, 0.25 (0.07–0.92)
						20 y follow up (low-dose aspirin treatment longer than 7.5 y)	HR, 0.28 (0.08–1.00)
Tan	2011	Case–control	Mayo Clinic, Rochester, Minnesota	2004–2010	na	Low-dose aspirin use, <1 day/month	OR, 1
						6+ days/week	OR[b], 0.71 (0.51–0.99)
						Regular aspirin use, <1 day/month	OR, 1
						6+ days/week	OR[b], 0.50 (0.31–0.81)
Bonifazi	2010	Case–control	Patients admitted to hospitals in Italy	1991–2008	na	Non regular aspirin user (<1 day/week)	OR, 1
						Current aspirin use	OR[c], 0.53 (0.24–1.17)
						Current aspirin use, ≥5 y	OR[c], 0.23 (0.06–0.90)
Anderson	2002	Cohort	Iowa Women's Health study	1992–1999	7 y	No aspirin use	RR, 1
						Aspirin use in 1992, 2–5 days/week	RR[d], 0.47 (0.22–0.98)
						Aspirin use in 1992, ≥6 days/week	RR[d], 0.40 (0.20–0.82)

Abbreviation: na, not applicable.

[a]The 6 RCTs were: Thrombosis Prevention Trial, United Kingdom Transient Ischaemic Attack Aspirin Trial, British Doctors Aspirin Trial, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial, Prevention of Progression of Arterial Disease and Diabetes Trial, and Aspirin for Asymptomatic Atherosclerosis Trial.

[b]Adjusted for age, gender, BMI, smoking status, pack-years of smoking, and history of diabetes (>3 y).

[c]Adjusted for age, gender, study center, interview year, education, BMI, smoking, and history of diabetes.

[d]Adjusted for age, smoking status, pack-years of smoking, multivitamin use, and history of diabetes.

Table 7. Studies showing nonsignificant associations between risk of pancreatic cancer and NSAID or specifically aspirin (if data available) use

First author	Publication year	Study design	Study subjects	Accrual period	Years of follow up	NSAID use definition	Strength of association (95% CI)
Jacobs	2012	Cohort	CPS II	1992–2003	17 y	No aspirin use	RR, 1
						Aspirin use in updated analysis, <5 y	RR[a], 0.89 (0.64–1.23)
						≥5 y	RR[a], 1.03 (0.73–1.46)
Bradley	2010	Case–control	United Kingdom general practice research database	1995–2006	na	No NSAID use	OR, 1
						Aspirin and derivatives use, ≤5 y before diagnosis	OR[b], 0.95 (0.81–1.13)
						High-dose aspirin use, ≤5 y before diagnosis	OR, 0.91 (0.61–1.35)
Cook	2005	RCT	Women's Health study	1993–1996	11 y	Alternate day low-dose aspirin use	RR, 1.42 (0.81, 2.49)
Ratnasinghe	2004	Cohort	NHANES I, NHANES II	1971–1975	21 y	No aspirin use	RR, 1
				1976–1980		Any aspirin use	RR[c], 0.87 (0.42, 1.77)
Schernhammer[d]	2004	Cohort	Nurses' Health Study (all female)	1980–1998	18 y	Nonregular aspirin use	RR, 1
						Regular aspirin use[e], 1–5 y	RR[f], 1.12 (0.72–1.74)
						6–10 y	RR, 1.10 (0.64–1.89)
						>10 y	RR, 1.75 (1.18–2.60)
Friis	2003	Cohort	Prescription database of North Jutland County, Denmark	1989–1995	8 y	Prescription for low-dose aspirin	SIR, 1.2 (0.8–1.6)
Menezes	2002	Case–control	Roswell Park Cancer Institute, Buffalo, New York	1982–1998	na	Nonregular aspirin use	OR, 1.00
						Regular aspirin use[g], 0.5–10 y	OR[h], 1.00 (0.59–1.69)
						11+ y	OR[h], 1.00 (0.56–1.78)
Langman[i]	2000	Case–control	United Kingdom general practice research database	1993–1995	na	No NSAID prescriptions	OR, 1
						1 NSAID prescription 13–36 months before diagnosis	OR[j], 0.94 (0.64–1.36)
						2–6 prescriptions	OR[j], 1.08 (0.75–1.54)
						≥7 prescriptions	OR[j], 1.49 (1.02–2.18)
Coogan	2000	Case–control	Hospitals in Baltimore, Boston, New York, and Philadelphia	1977–1998	na	Nonregular NSAID use	OR, 1
						Regular NSAID use, continuing into year before admission	OR[k], 0.8 (0.5–1.1)

Abbreviation: na, not applicable.

[a]Adjusted for age, gender, race, education, smoking status, physical activity level, history of heart disease, stroke, diabetes, hypertension, current cholesterol-lowering drug use, aspirin use in 1982, NSAID use, and history of colorectal endoscopy.

[b]Adjusted for smoking status, BMI, alcohol use, history of chronic pancreatitis, history of rheumatoid arthritis, use of other drugs (proton pump inhibitors, H2 antagonists, steroids, hormone replacement therapy, disease-modifying anti-rheumatic drugs), diabetes, and prior cancer.

[c]Adjusted for gender, race, BMI, poverty index, education, and smoking with age as time metric for follow up.

[d]Aspirin use for longer than 10 y shows a significant increased risk for pancreatic cancer.

[e]Regular aspirin use is defined as ≥5 aspirin tablets/week.

[f]Adjusted for age, BMI, history of diabetes, smoking status, physical activity level, and follow-up cycle.

[g]Regular aspirin use is defined as ≥1 aspirin tablet/week for at least six months.

[h]Adjusted for age, pack years of smoking, and family history of pancreatic cancer.

[i]≥Seven aspirin prescriptions showed a significant increased risk for pancreatic cancer.

[j]Individually matched for age, gender, and general practice and adjusted for age and smoking status.

[k]Adjusted for age, gender, interview year, center, race, religion, cigarettes, family history of digestive cancer, education, and alcohol consumption.

In light of such evidence, a flood of selective COX-2 inhibitors, including rofecoxib and celecoxib, were synthesized and tested for cancer prevention and recurrence inhibition in laboratory assays and clinical trials (32, 34–36). Although clinical trials showed reductions in cancer incidence and recurrence associated with selective COX-2 inhibitors, an increase in acute myocardial infarction was also observed. Selective COX-2 inhibitors suppress vascular production of prostaglandin I_2 (which inhibits platelet aggregation) with little or no inhibition of prothrombotic platelet thromboxane A_2 (TXA_2) synthesis, regulated through platelet COX-1. When TXA_2 is produced and prostaglandin I_2 is suppressed, platelet aggregation is stimulated, blood pressure is elevated, and atherogenesis is accelerated (37–39). These adverse effects seen in the selective COX-2 clinical trials suggest more of a theory of interdependence between the COX enzymes.

As discussed above in our Introduction, Rothwell and colleagues (2011) conducted a secondary analysis of low-dose aspirin use and vascular events (6). These secondary analyses provide strong evidence supporting the interplay between COX-1 and COX-2 enzymes on cancer incidence and survival outcomes. Despite strong preclinical and clinical evidence suggesting the necessity of primarily inhibiting COX-2 to impede the pathogenesis and progression of cancer, the interval (every 24 hours) and dosing (75–300 mg per day) of aspirin use in these RCTs are compatible with a direct and irreversible inhibition of platelet COX-1, but only a slight and reversible inhibition of nucleated cell COX-2. Newly formed platelets express both COX-1 and COX-2, whereas mature platelets only maintain COX-1. Mature platelets pass through the portal circulation where they encounter a higher concentration of aspirin than other cells, and they lack a nucleus, which makes them particularly susceptible to the long-lasting effects of aspirin's inhibition of platelet COX-1. Alternatively, nucleated cells encounter a lower concentration of aspirin in the systemic circulation, and they can resynthesize COX isoenzymes within a few hours, thus requiring repeated dosing of aspirin to maintain inhibition of COX-1 and COX-2 (19, 25, 40).

Both Dovizio and colleagues (2013) and Thun and colleagues (2013) proposed a novel mechanism in which COX-1 and COX-2 operate in parallel to foster tumorigenesis (19, 40). Platelet activation releases several mediators including TXA_2, Sphingosine-1-phosphate (S1P), growth and angiogenic factors, and cytokines that can upregulate COX-2 in adjacent cells of various types. In the pancreas, it is possible that activated platelets release these mediators into the thick stroma surrounding pancreatic cancer precursor lesions, which have been shown to upregulate COX-2 (30). In addition, ABO blood group antigens are expressed on the surface of platelets, which may interact with these mediators to cause the significantly increased risk of pancreatic cancer seen in non-O phenotypes compared with O phenotypes (41). When COX-1 in platelets is inhibited, these mediators are not released from platelets and COX-2 levels are suppressed.

In contrast to the daily low-dose aspirin regimen used in the Rothwell and colleagues (2011) RCT, the Cook and colleagues (2005) RCT administered low-dose aspirin on alternate days, and indicated no association between aspirin use and risk of pancreatic cancer (6, 12). It is possible that platelet COX-1 is irreversibly inhibited, but *de novo* mature platelets expressing COX-1 are synthesized within 24 to 48 hours (19). In agreement with this hypothesis, reduction of pancreatic cancer incidence with daily use of aspirin, either regular-dose or low-dose, was seen in our study, as well as in the Tan and colleagues (2011) and the Anderson and colleagues (2002) studies where significant reductions in pancreatic cancer incidence were seen in participants using aspirin at least 6 days per week (4, 5). Although reduced risk in pancreatic cancer was seen for both low- and regular dose aspirin use, use of regular-dose aspirin several times per day increases the risk of major gastrointestinal bleeding by 4- to 10-fold, whereas daily low-dose aspirin use only doubles the risk of major gastrointestinal bleeding (40).

Two of the 3 null case–control studies, Langman and colleagues (2000) and Coogan and colleagues (2000), assessed the relationship between all NSAIDs and pancreatic cancer, rather than aspirin specifically, which, in addition to the earlier accrual periods of these studies, also likely contributed to their null findings (8, 16). Observational studies that have found significant relationships between aspirin use and risk of pancreatic cancer have not shown relationships between non-aspirin NSAIDs and pancreatic cancer, possibly because only aspirin, but not non-aspirin NSAIDs, causes irreversible inactivation of COX enzymes (4, 5, 25).

One cohort study, Schernhammer and colleagues (2004), that accrued participants between 1980 and 1998, and 1 case–control study, Langman and colleagues (2000), that enrolled patients between 1993 and 1995, found significantly increased risks of pancreatic cancer for aspirin use in the highest categories of duration of aspirin use and amount of aspirin use (refs. 15 and 16 and Tables 6 and 7). It is possible that these studies identified some use of regular-dose aspirin for symptoms associated with the development or progression of pancreatic cancer.

Finally, the Jacobs and colleagues (2012) cohort study accrued participants from 1992 to 2003 and followed participants for cancer death until 2008, yet failed to see significantly reduced pancreatic cancer mortality with aspirin use (14). This apparent attenuation of the association may have occurred because of correlations between the 15 adjustment variables that were included in the analysis. In particular, cholesterol-lowering drugs are often taken in combination with aspirin for prevention of coronary artery disease, and inclusion of the variable for current cholesterol-lowering drug use could have masked the effect of reduction in pancreatic cancer mortality with current aspirin use (42).

In summary, in representative Connecticut subjects, we observed a significant inverse relationship between

aspirin use and risk of pancreatic cancer. This finding was bolstered when we assessed the relationship between the risk of pancreatic cancer and years in the past that the aspirin use began, duration of aspirin use, years in the past that aspirin use ended, and time period of aspirin use. This study is one of the largest case–control studies to examine the relationship between aspirin use and pancreatic cancer risk, second only to the study of Tan and colleagues (5). Our results are consistent with the Tan and colleagues study and a number of others and further suggest that a daily aspirin regimen may provide chemoprophylaxis against pancreatic cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of the present data. No funders of the study had any involvement in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.A. Streicher, H. Yu, L. Lu, M.S. Kidd, H.A. Risch
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.A. Risch
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