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Research Article

Cancer Prevention Research

Aspirin, Nonsteroidal Anti-inflammatory Drugs, Acetaminophen, and Pancreatic Cancer Risk: a Clinic-Based Case–Control Study

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Abstract

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) show indisputable promise as cancer chemoprevention agents. However, studies have been inconsistent as to whether aspirin has a protective effect in development of pancreatic cancer. To further evaluate the association between aspirin, NSAID, and acetaminophen use with pancreatic cancer risk, we used a clinic-based case–control study of 904 rapidly ascertained histologically or clinically documented pancreatic ductal adenocarcinoma cases, and 1,224 age- and sex-matched healthy controls evaluated at Mayo Clinic from April 2004 to September 2010. Overall, there is no relationship between non-aspirin NSAID or acetaminophen use and risk of pancreatic cancer. Aspirin use for 1 d/mo or greater was associated with a significantly decreased risk of pancreatic cancer (OR = 0.74, 95% CI: 0.60–0.91, $P = 0.005$) compared with never or less than 1 d/mo. Analysis by frequency and frequency-dosage of use categories showed reduced risk ($P = 0.007$ and 0.022, respectively). This inverse association was also found for those who took low-dose aspirin for heart disease prevention (OR = 0.67, 95% CI: 0.49–0.92, $P = 0.013$). In subgroup analyses, the association between aspirin use and pancreatic cancer was not significantly affected by pancreatic cancer stage, smoking status, or body mass index. Our data suggest that aspirin use, but not non-aspirin NSAID use, is associated with lowered risk of developing pancreatic cancer. *Cancer Prev Res; 4(11); 1835–41. ©2011 AACR.*

Introduction

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) show indisputable promise as cancer chemoprevention agents due to their antioxidant and anti-inflammatory properties (1). NSAID use, especially aspirin, has been consistently associated with reduced risk of colorectal cancer in observational epidemiologic studies (2–4) with additional support coming from clinical trials (5, 6). There is also some evidence for a protective effect for several other types of cancers such as stomach cancer (7), esophageal cancer (7), leukemia (8), breast cancer (9, 10), ovarian cancer (11), endometrial cancer (12), and prostate cancer (13, 14).

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A protective effect of aspirin and other NSAID use in pancreatic cancer is biologically plausible (15, 16); however, findings from observational epidemiologic studies of aspirin and NSAID use in relation to pancreatic cancer risk have been inconsistent. Six studies reported that aspirin and non-aspirin NSAID use are not associated with pancreatic cancer risk (17–22) whereas 2 studies reported an increased risk of pancreatic cancer (23, 24). In contrast, 2 other studies reported that aspirin or non-aspirin NSAID use is associated with a decreased risk of pancreatic cancer (25, 26). Using systematic meta-analyses, 2 studies summarized the available epidemiologic evidence on the relationship between aspirin or non-aspirin NSAID exposure and risk of pancreatic cancer, and both studies indicated null associations (27, 28). However, in a pooled analysis of 25,570 patients in 8 trials, Rothwell and colleagues recently reported that daily aspirin use reduced deaths due to several common cancers, including significant reductions in colorectal and pancreatic cancer deaths, with most benefit seen after 5 years of the scheduled trial treatment (29).

As there are limited strategies for prevention of pancreatic cancer, the potential for chemoprevention is of particular interest, and more information on the relationship between aspirin and other NSAID use with pancreatic cancer incidence is warranted. We conducted a large case–control study to further define the possible effects on pancreatic cancer risk of 3 main classes of over-the-counter analgesics: aspirin, acetaminophen, and non-aspirin NSAID, with particular

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emphasis on the effects of frequency, dosage, and stated reason for use.

Materials and Methods

Study subjects

This study was approved by the Institutional Review Boards of the Mayo Clinic and the University of Minnesota. Cases were patients who had a clinically or pathologically confirmed pancreatic ductal adenocarcinoma. From April 2004 to September 2010, using a rapid ascertainment method described elsewhere (30), a total of 1,500 of 2,284 pancreatic cancer patients (66%) consented to participate at the time of their clinical evaluation. More than 99% of the cases were confirmed by histology (>89%), medical record (9%), or death certificate (1%).

Controls were primary care clinic patients who were frequency matched to cases on age at time of recruitment (within 5-year age groups), race, sex, and region of residence [Olmsted County; 3-state (MN, WI, IA); or outside of area]. Controls with prior diagnoses of cancer except nonmelanoma skin cancer were excluded. A total of 3,278 potential controls (unrelated individuals without pancreatic cancer) were approached at the time of their visit for routine primary medical care and 2,119 (53%) consented.

Risk factor assessment

All subjects (cases and controls) in this analysis self-reported by questionnaire their use of aspirin, acetaminophen, and non-aspirin NSAID, along with extensive epidemiologic and demographic information. Eighty-seven percent of consenting participants completed questionnaires, and analyses were limited to a final total of 904 cases and 1,224 controls, who were 55 years or older. Participants responded to detailed questions on the use of these medications during different decades of their lifetime (i.e., age 20–40, 41–60, 61–70, and >70 years), which included lists of commercially available brands. The information on aspirin, NSAID, and acetaminophen use was ascertained by asking, "How many days did you use this medication" with possible responses including: never or less than 1 d/mo, 1–4 d/mo, 2–5 d/wk, or 6+ d/wk. For the question, "How many tablets did you take in a day?" possible responses included 1 to 2 tablets per day, 3 to 4 tablets per day, 5 to 6 tablets per day, or 7+ tablets per day. In addition, respondents were asked, "Why did you take this medication?" with possible responses including: headaches, body aches and pains, prevention of heart problems, menstrual cramps (women only), or other (and specify reason). Because the mean ages (SD) of controls and cases were 69.2 ± 7.6 and 69.1 ± 8.4, respectively, and the majority of subjects answered the questions about usage at ages 41 to 60 years, we focused on the information in that time period for our analyses.

Ever smoking was defined as having smoked more than 100 cigarettes during lifetime. Current smoking status, age at initiation and cessation, where relevant, were also assessed. Other data collected included age, sex, ethnicity, usual adult height and weight, level of education, level of physical activity, alcohol consumption, and multivitamin use, as well as information about diabetes, pancreatitis, gallstones, pancreatic pseudocysts, peptic ulcers, and pancreatic cancer. Usual adult height and weight were used to calculate body mass index (BMI in kg/m^2).

Statistical data analysis

Preliminary analyses were conducted to compare descriptive characteristics of pancreatic cancer cases and hospital controls, which included age, sex, cigarette smoking, alcohol consumption, mutivitamin use, history of diabetes, and BMI. The association between use of aspirin, acetaminophen, or non-aspirin NSAID and pancreatic cancer was evaluated by 3 different measures (use, frequency of usage, and typical dosage per day) using unconditional logistic regression analysis with ORs and 95% CIs. We dichotomized subjects into the groups: "ever user" (≥1 d/mo) or "never user" (<1 d/mo). Frequency of usage was categorized as "never user" (<1 d/mo), 1–4 d/mo, 2–5 d/wk, and 6+ d/wk. Dosage categories were "none," "1–2 tablets per day," and "3+ tablets per day." A combined frequency-dosage analysis was conducted by creating a variable, termed "tablets per month," which reflected both frequency and typical dosage of use (days per month × tablets per day). The "tablets per month" variable was categorized on the basis of the frequency distribution observed in the controls. After categorization, we determined that these categories appeared to coincide with use behavior and have named the categories accordingly as nonusers (0 tablet per month); light dose—infrequent use (aspirin taken <1 d/mo or 1–2 tablets taken 1–4 d/mo for a total of 1–7 tablets per month); heavy dose—infrequent use (3+ tablets taken 1–4 d/mo or 1–2 tablets taken 2–5 d/wk for a total of 8–35 tablets per month); light dose—frequent use (1–2 tablets taken 6+ d/wk for a total of 36 tablets per month); and heavy dose—frequent use (3+ tablets taken 2+ d/wk for a total of 37+ tablets per month). We also conducted a separate analysis on the patients whose primary stated reason for use of aspirin was for prevention of heart problems because this typically involves a daily intake of low-dose aspirin (81 mg). BMI, smoking status, pack-years of smoking, and diabetes mellitus as potential confounders were included in the multivariate regression models.

We evaluated whether or not reported use of aspirin, NSAID, or acetaminophen differed across strata of smoking status or by categories of BMI. A likelihood ratio test of the interaction term in a model with the main effects compared with the reduced model with main effects only was used to assess statistical significance. For each analysis, individuals missing the variables being analyzed were excluded from that particular analysis. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc.), and 2-sided values of $P < 0.05$ were considered statistically significant.

Results

As expected, cases differed from controls in smoking features, BMI, and history of diabetes (Table 1). Cases were

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Table 1. Selected characteristics of pancreatic cancer cases and controls

	Controls, *n* (%)	Cases, *n* (%)	*P*
Age at diagnosis, y, SD	69.2 ± 7.65	69.1 ± 8.41	0.41
Sex			
Female	594 (48.5)	410 (45.4)	0.15
Male	630 (51.5)	494 (54.6)	
BMI, kg/m^2			
<25	360 (33.6)	265 (30)	<0.001
≥25 and <30	496 (46.2)	367 (41.6)	
≥30	217 (20.2)	251 (28.4)	
Missing data	151	21	
Smoking status			
Never smoker	569 (52.5)	368 (40.8)	<0.001
Former smoker	484 (44.6)	408 (45.3)	
Current smoker	31 (2.9)	125 (13.9)	
Missing data	140	3	
Active smoking (lifetime pack-years)			
Never active	569 (52.5)	368 (40.8)	<0.001
<10	181 (17.0)	130 (15.0)	
10–19	104 (9.7)	86 (9.9)	
20–29	67 (6.3)	64 (7.4)	
30–39	51 (4.8)	67 (7.7)	
40+	95 (8.9)	154 (17.7)	
Missing data	157	35	
Alcohol consumption (drinks/d)			
0	213 (19.8)	175 (23.8)	0.13
1–3	792 (73.7)	514 (69.8)	
3+	69 (6.4)	47 (6.4)	
Missing data	150	168	
Multivitamin use			
Never	278 (29.4)	177 (28.8)	0.81
Ever	668 (70.6)	437 (71.2)	
Missing data	278	290	
Diabetes mellitus (>3 y)			
No	937 (91.1)	653 (80.1)	<0.001
Yes	92 (8.9)	162 (19.9)	
Missing data	195	89	
Pancreatic cancer stage			
Resected		263 (30.8)	
Locally advanced		299 (35.1)	
Metastatic		291 (34.1)	
Missing data		51	

more likely to be current smokers ($P < 0.001$) and to report significantly higher mean pack-years of smoking than controls ($P < 0.001$). Cases reported higher mean lifetime BMI than controls ($P = 0.004$), and 28.4% of cases reported BMI of 30 or greater whereas 20.2% of controls reported a BMI of 30 or greater ($P < 0.001$). A greater proportion of cases reported a history of diabetes (19.9%) than controls (8.9%; $P < 0.001$). Alcohol consumption and multivitamin use did not differ between cases and controls. More than 70% of cases had locally advanced or metastatic disease at the time of study enrollment. On the basis of smoking status, BMI, diabetes, alcohol consumption, and multivitamin use, the data appeared to be randomly missing and not following any pattern. Sensitivity analyses were conducted in which crude estimates were calculated for those who were not missing these data, and the results suggested that participants with complete data did not differ from the participants with incomplete data on the specific variable such as, age at diagnosis, BMI, smoking status, diabetes, and pancreatic cancer stage.

Overall, no significant associations were found for use of non-aspirin NSAID or acetaminophen (Table 2). Ever use of aspirin was associated with a significantly reduced parameter estimate for pancreatic cancer (unadjusted OR

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Table 2. Frequency of aspirin, acetaminophen, and non-aspirin NSAID use and ORs for pancreatic cancer

	Controls, *n* (%)	Cases, *n* (%)	OR[a] (95% CI)	*P*
Aspirin use, d/mo				
<1	493 (47.3)	393 (53.1)	1.00	0.005
≥1	550 (52.7)	347 (46.9)	0.74 (0.60–0.91)	
Aspirin: frequency of use				
<1 d/mo	493 (47.3)	393 (53.1)	1.00	0.007
1–4 d/mo	262 (25.1)	179 (24.2)	0.87 (0.67–1.12)	
2–5 d/wk	79 (7.6)	42 (5.7)	0.61 (0.38–0.96)	
6+ d/wk	209 (20.0)	126 (17.0)	0.63 (0.47–0.85)	
Aspirin: typical dosage				
None	270 (27.5)	235 (33.2)	1.00	0.125
1–2 tablets/d	576 (58.7)	388 (54.9)	0.81 (0.63–1.03)	
3+ tablets/d	136 (13.8)	84 (11.9)	0.72 (0.50–1.04)	
Acetaminophen use, d/mo				
<1	596 (65.0)	431 (65.0)	1.00	0.758
≥1	321 (35.0)	232 (35.0)	1.04 (0.82–1.32)	
Acetaminophen: frequency of use, d/wk				
<1	840 (91.6)	613 (92.5)	1.00	0.730
2–5	55 (6.0)	36 (5.4)	0.97 (0.60–1.57)	
6+	22 (2.40	14 (2.1)	0.74 (0.35–1.56)	
Acetaminophen: typical dosage				
None	319 (40.2)	249 (42.0)	1.00	0.789
1-2 tablets/d	370 (46.6)	251 (42.3)	0.98 (0.75–1.29)	
3+ tablets/d	105 (13.2)	93 (15.7)	1.11 (0.76–1.62)	
Non-aspirin NSAID use, d/mo				
<1	547 (60.5)	381 (59.2)	1.00	0.941
≥1 day per month	357 (39.5)	263 (40.8)	1.01 (0.79–1.29)	
Non-aspirin NSAID: frequency of use d/wk				
<1	759 (84.0)	554 (86.0)	1.00	0.106
2–5	77 (8.5)	52 (8.1)	0.75 (0.48–1.16)	
6+	68 (7.5)	38 (5.9)	0.66 (0.41–1.04)	
Non-aspirin NSAID: typical dosage				
None	322 (40.8)	235 (41.6)	1.00	0.943
1–2 tablets/d	338 (42.8)	232 (41.1)	0.96 (0.72–1.28)	
3+ tablets/d	129 (16.4)	98 (17.3)	0.99 (0.69–1.45)	

[a]Adjusted for age, sex, BMI (continuous), smoking status (never, former, current), pack-years of smoking, and long-standing diabetes mellitus (>3 years duration).

= 0.79; 95% CI: 0.65–0.96). This association remained significant (OR = 0.74; 95% CI: 0.60–0.91) after adjusting for the potential confounders (Table 2). Frequency of use and typical dosage per day measures also reflected reduced risk ($P = 0.007$ and 0.125, respectively), although there was no significant reduction associated with 1 to 4 d/mo of aspirin use (OR = 0.87; 95% CI: 0.67–1.12). Furthermore, the analysis by tablets per month of aspirin use showed reduced ORs for pancreatic cancer in a dose-dependent manner ($P = 0.022$; Table 3). The ORs associated with light dose-frequent use and heavy dose-frequent use of aspirin were statistically significant (OR = 0.65 and 0.52; 95% CI: 0.47–0.91 and 0.28–0.95, respectively; Table 3). In addition, aspirin use for prevention of heart problems (OR = 0.67; 95% CI: 0.49–0.92) or for other reasons (OR = 0.77; 95% CI: 0.61–0.97) showed statistically significant lower risk estimates for pancreatic cancer (Table 4).

As there was the potential for confounding and/or effect modification related to smoking and BMI, stratified analyses were conducted to examine the relationship between aspirin use and pancreatic cancer by smoking status: never smoker, former smoker, and current smoker and by BMI (<25.0, 25.0–30.0, and ≥30.0). Overall, the associations between aspirin use and pancreatic cancer were not significantly affected by smoking status (Supplementary Table S1) or BMI (Supplementary Table S2).

Discussion

In this large, clinic-based case–control study, we found that aspirin use, but not non-aspirin NSAID or acetaminophen use, appears to be protective against development of pancreatic cancer. Whether analyzed by ever/never use or frequency and dosage of use categories, the OR for aspirin

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Table 3. Frequency-dosage measure of aspirin use and ORs for pancreatic cancer

Aspirin use	Controls	Cases	OR[a] (95% CI)	*P*
Tablets/mo, mean ± SD	13.5 ± 22.1	10.9 ± 18.2	0.990 (0.985–0.996)	0.002
Frequency-dosage measure of aspirin use (counts, %)				
Nonusers	270 (27.6)	235 (33.7)	1.00	0.022
Light dose—infrequent use	350 (35.8)	242 (34.7)	0.89 (0.69–1.02)	
Heavy dose—infrequent use	123 (12.6)	75 (10.8)	0.74 (0.51–1.08)	
Light dose—frequent use	186 (19.0)	120 (17.2)	0.65 (0.47–0.91)	
Heavy dose—frequent use	49 (5.0)	25 (3.6)	0.52 (0.28–0.95)	

NOTE: The values given are number (percentage), unless otherwise indicated.
[a]Adjusted for age, sex, BMI (continuous), smoking status (never, former, current), pack-years of smoking, and long-standing diabetes mellitus (>3 years duration).

use and pancreatic cancer was statistically significantly decreased after adjustment for potential confounders. We did not find differences in association by smoking status or categories of BMI. Our results provide further evidence that aspirin may have a chemopreventive role in pancreatic cancer.

Our analysis did not permit us to draw a firm conclusion about an effective dose of aspirin in relation to prevention of pancreatic cancer. Low-dose aspirin (81 mg), commonly used for primary or secondary prevention of cardiovascular disease (31), appears relatively specific for COX-1 (32) and has been shown to permanently inhibit platelet aggregation (33). In the Aspirin/Folate Polyp Prevention Study (34), effects on risk of colorectal adenomas were observed for daily low-dose but not for daily higher dose aspirin. However, some studies found a reduction in risk of colorectal cancer only with higher doses (35-37); thus, the evidence for a dose–response effect of aspirin was inconsistent. This motivated us to investigate whether associations between aspirin use and pancreatic cancer are different when low-dose aspirin (81 mg) was used, for example, for heart disease prevention. We found that aspirin use for both heart disease prevention and for other reasons where aspirin is taken at least monthly were associated with a statistically significant decreased risk of pancreatic cancer.

To our knowledge, this is the first study to investigate the association between acetaminophen use and the risk of developing pancreatic cancer. We found no association between use of acetaminophen or non-aspirin NSAID and risk of pancreatic cancer, either overall or within subgroups defined by smoking status or BMI. Interestingly, in the prospective Iowa Women's Health Study cohort (23), investigators also found that aspirin use, but not non-aspirin NSAID, was associated with a decreased risk of pancreatic cancer (acetaminophen use was not examined

Table 4. Frequency of aspirin use stratified by reason for use and ORs for pancreatic cancer

	Aspirin use for heart disease prevention			Aspirin use for other reasons		
	Cases/controls	OR[a] (95% CI)	*P*	Cases/controls	OR[a] (95% CI)	*P*
Aspirin use, d/mo						
<1	393/493	1.00	0.013	393/493	1.00	0.026
≥1	106/180	0.67 (0.49–0.92)		241/370	0.77 (0.61–0.97)	
Aspirin: frequency of usage						
<1 d/mo	393/493	1.00	0.020	393/493	1.00	0.030
1–4 d/mo	11/19	0.93 (0.40–2.19)		168/243	0.86 (0.66–1.11)	
2–5 d/wk	4/17	0.18 (0.05–0.69)		38/62	0.74 (0.45–1.21)	
6+ d/wk	91/144	0.71 (0.51–0.99)		35/65	0.50 (0.31–0.81)	
Aspirin: typical dosage						
None	235/270	1.00	0.102	235/270	1.00	0.115
1–2 tablets/d	107/175	0.68 (0.48–0.97)		281/401	0.86 (0.66–1.11)	
3+ tablets/d	2/5	1.09 (0.18–6.78)		82/131	0.68 (0.47–0.98)	

[a]Adjusted for age, sex, BMI (continuous), smoking status (never, former, current), pack-years of smoking, and long-standing diabetes mellitus (>3 years duration).

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in that analysis). Our results are similar to previous reports that revealed different effects between these medications and cancer endpoints, that is, aspirin use, but not acetaminophen or non-aspirin NSAID use, is associated with decreased risk of breast (12) and prostate cancer (14). Acetaminophen is an analgesic that lacks a systemic anti-inflammatory effect (38), which could, in part, possibly explain these findings.

In subgroup analyses, the effects of aspirin within strata of the smoking status or categories of BMI did not differ. In the Women's Health Study, the observed reduction in cardiovascular risk associated with aspirin use was greater among never and former smokers than current smokers (39). Bardia and colleagues reported that aspirin use, but not non-aspirin NSAID use, was associated with lower risk of cancer incidence and mortality, with a more pronounced effect among former and never smokers than current smokers (40). It has been shown that cigarette smoking acts as a proinflammatory stimulus and as an oxidant and can modify the association between aspirin and non-aspirin NSAID and cancer risk (41), although data are limited.

The strengths of our study include its size, the rapid case finding, and self-completion of questionnaires by both cases and controls, which may reduce bias in the study of this lethal cancer. In addition, the questionnaire included specifically framed questions to examine use of aspirin and other non-aspirin NSAID in relation to pancreatic cancer. The study also has some limitations: First, it is a retrospective case–control study with all the inherent problems related to this study design; second, a large amount of missing data lead us to interpret our results with caution; and third, other potential selection and recall biases should be considered. Because controls in this study were drawn from subjects attending a clinic for health-related reasons, it is possible that these controls were more likely to use aspirin than population-based controls, thus leading to an overestimate of the inverse association we observed. However, the magnitude of the prevalence of aspirin use (i.e., $\geq$1 d/mo; 52.7%), observed in our controls is similar to that seen in population-based studies (14, 42). Because the cases were diagnosed at different stages of pancreatic cancer, we also evaluated the association between aspirin, acetaminophen, or NSAID use and pancreatic cancer risk by stage of pancreatic cancer. However, we did not find evidence for any differential effect of aspirin on pancreatic cancer risk by tumor stage (resectable, locally advanced, or metastatic), suggesting that the selection bias related to the cases did not play a major role in this study. Recall bias can also play a role in case–control studies; cases tend to recall past events or behaviors differently than controls. We limited our analysis to NSAID usage at ages 41 to 60. We excluded data for the age period 20 to 40 because of the greater possibility of recall bias. Furthermore, we conducted a detailed sensitivity analysis including all decades and found that potential selection bias is unlikely to have a major impact on the patterns observed in our study.

In summary, given these strengths and limitations, we observed a significant inverse association between risk of pancreatic cancer and use of aspirin, and this finding was reinforced by similar patterns with frequency and frequency-dosage of aspirin use. These data provide additional evidence that aspirin may have a chemoprevention role against pancreatic cancer. Aspirin is a widely used and inexpensive medication, and the potential public health implications of an effective chemoprevention agent for pancreatic cancer are considerable. However, long-term aspirin use has potentially serious side effects such as upper gastrointestinal bleeding. Therefore, all of the benefits and harms that can accrue from aspirin use in various population groups have to be taken into consideration, and individuals should consult with their health care professional before using this or other medications.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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