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Regular use of aspirin and pancreatic cancer risk

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Abstract

Background: Regular use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been consistently associated with reduced risk of colorectal cancer and adenoma, and there is some evidence for a protective effect for other types of cancer. As experimental studies reveal a possible role for NSAIDs is reducing the risk of pancreatic cancer, epidemiological studies examining similar associations in human populations become more important.

Methods: In this hospital-based case-control study, 194 patients with pancreatic cancer were compared to 582 age and sex-matched patients with non-neoplastic conditions to examine the association between aspirin use and risk of pancreatic cancer. All participants received medical services at the Roswell Park Cancer Institute in Buffalo, NY and completed a comprehensive epidemiologic questionnaire that included information on demographics, lifestyle factors and medical history as well as frequency and duration of aspirin use. Patients using at least one tablet per week for at least six months were classified as regular aspirin users. Unconditional logistic regression was used to compute crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Pancreatic cancer risk in aspirin users was not changed relative to non-users (adjusted OR = 1.00; 95% CI 0.72–1.39). No significant change in risk was found in relation to greater frequency or prolonged duration of use, in the total sample or in either gender.

Conclusions: These data suggest that regular aspirin use may not be associated with lower risk of pancreatic cancer.

Background

Regular use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been consistently associated with reduced risk of colorectal cancer and adenoma [1–4], and there is some evidence for a protective effect for other types of cancer [5–9]. It is widely thought that the mechanism by which these drugs affect cancer risk is through the inhibition of the cyclooxygenase (COX) enzymes: the constitutively expressed COX-1 and the induced (in most tissues) COX-2 [10]. By inhibiting these enzymes, NSAIDs can inhibit prostaglandin synthesis, enhance cellular immune response, or induce of apoptosis,

all of which have been postulated to be involved in carcinogenesis [11–13].

The cyclooxygenase pathway and NSAIDs have been implicated in pancreatic carcinogenesis, as elevated levels of COX-2 mRNA and protein have been detected in pancreatic carcinomas relative to histologically normal cells [14–19]. Further, both aspirin [20–22] and other NSAIDs [19] have been shown to inhibit pancreatic cancer cell proliferation and induce apoptosis *in vitro*. Recent studies have also reported an association between oncogenic *ras* and COX-2 expression [23,24]. Since pancreatic tumors tend to exhibit a high frequency of K-*ras* mutations [25], the relationship between the K-*ras* oncogene and COX-2 should be explored further in vivo. In general, laboratory findings suggest that COX, especially COX-2, may provide a potential target for the prevention and possible treatment of pancreatic cancer.

Few studies have examined COX and pancreatic cancer in humans, whether it be in clinical or epidemiological studies. A recent study did not demonstrate an association between COX-2 expression and pathological or clinical factors, such as age, gender, survival, tumor size, stage and vascular invasion [26], confirming results reported in previous studies [14,17,22]. To our knowledge, only three population studies, with varying methodological rigor, have been published examining the relationship between NSAID use and pancreatic cancer [27–29]. Each of these studies reported a lack of association. However, a recently published report on this association, based on a prospective cohort of 28,283 post-menopausal women, described a trend of decreasing risk of pancreatic cancer with increased weekly aspirin use [30].

In light of the laboratory evidence and limited number population-based studies, we conducted a hospital-based case-control study to further investigate the association between regular aspirin use and the risk of pancreatic cancer.

Methods

The study population included men and women seen at the Roswell Park Cancer Institute (RPCI) between 1982 and 1998 who completed a comprehensive epidemiological questionnaire. Informed consent was obtained from all participants. The case group was comprised of 194 predominantly Caucasian (96.6%) patients with pancreatic cancer identified from the Roswell Park Cancer Institute tumor registry and diagnostic index, ranging in age from 30 to 84 years. Similarly, the control group included 582 men and women, mostly Caucasian (94.5%), ranging in age from 27 to 85, who received medical services at RPCI for non-neoplastic conditions. These individuals came to RPCI with a suspicion of neoplastic disease, but were not diagnosed with malignant conditions. Controls were frequency matched to cases by sex and five-year age intervals.

All participants completed the Patient Epidemiology Data System (PEDS) questionnaire, which is offered to all new patients, and returned by approximately 50% of patients. The 16-page instrument covers information on reproductive and medical histories, family history of cancer, occupational and environmental exposures, tobacco use, alcohol consumption, and diet. The instrument also assesses aspirin and other medication use prior to the onset of any current illness, with questions asking how many times per week the drug was taken, number of years taken and year of first use. For study purposes, subjects were classified as regular aspirin users if they had taken the drug at least once a week for at least one year, and non-users if they did not meet both of the conditions. Dosage of use was assessed by comparing non-users to patients reporting they had taken aspirin either one to six times per week or seven or more times per week. Duration of use was evaluated by comparing non-users to patients reporting six months to ten years of use or more than ten years. A final variable, termed "tablet-years" was created that reflected both duration and frequency of use (daily use × years of use).

Preliminary analyses were performed to examine descriptive characteristics of the pancreatic cases and hospital controls, and the association of these characteristics with risk of developing pancreatic cancer. They consisted of known and suspected risk factors for pancreatic cancer: age, education, cigarette smoking, family history of pancreatic cancer, race, sex and body mass index. Unconditional logistic regression analysis was used to compute odds ratios (ORs) with 95% confidence intervals (CIs). As packyears of cigarettes smoked smoking (packs per day × years of smoking) and family history of pancreatic cancer were found to be predictors of disease in our data, they were adjusted for in the regression models, along with age. In all analyses, non-users of aspirin represented the reference group.

Results

Descriptive characteristics of pancreatic cancer cases and hospital controls are shown in Table 1. Cases were more likely to be smokers, have a family history of pancreatic cancer, less likely to have schooling beyond high school, and have a higher BMI.

In this study population, approximately 44% of the cases and controls were classified as regular aspirin users. Risk of pancreatic cancer associated with aspirin use is shown in Table 2. Regular aspirin use was not related to pancreatic cancer risk (adjusted OR = 1.00; 95% CI 0.72–1.39). Increased weekly dosage was not associated with a modi-

Table 1: Descriptive characteristics and odds ratios of pancreatic cancer cases and hospital controls – Roswell Park Cancer Institute, Buffalo, NY 1982–1996.

	Cases (n = 194)	Controls (n = 582)	OR[1] (95% CI)
Age[2]	62.02	62.07	1.00 (0.98, 1.02)
Education[3,5]			
Up to High School	51 (26.4)	139 (24.0)	1.00
High School	67 (34.7)	182 (32.4)	0.89 (0.55, 1.42)
Some College	34 (17.6)	127 (21.9)	0.72 (0.42, 1.22)
College Graduate	41 (21.2)	132 (22.8)	0.92 (0.54, 1.56)
Cigarette Smoking (pack-years)[3,4]			
None	65 (34.0)	246 (43.6)	1.00
≤ 13.5	15 (7.9)	79 (14.0)	0.84 (0.44, 1.59)
14–30	44 (23.0)	83 (14.7)	2.12 (1.30, 3.48)
30.5–52.5	38 (19.9)	76 (13.5)	2.17 (1.32, 3.59)
≤ 53	29 (15.2)	80 (14.2)	1.41 (0.82, 2.43)
Family history of pancreatic cancer[3]			
No	183 (94.3)	570 (97.9)	1.00
Yes	11 (5.7)	12 (2.1)	2.65 (1.09, 6.45)
Race[3,5]			
Caucasian	144 (96.6)	494 (94.5)	1.00
African-American	4 (2.7)	26 (5.0)	2.38 (0.23, 24.28)
Other	1 (0.7)	3 (0.6)	0.44 (0.04, 5.53)
Sex[3]			
Female	88 (45.4)	264 (45.4)	1.00
Male	106 (54.6)	318 (54.6)	0.95 (0.65, 1.38)
Body-Mass Index[3,6]			
≤ 23	46 (24.7)	144 (25.4)	1.00
23–25.6	32 (17.2)	143 (25.3)	0.68 (0.39, 1.17)
25.7–27.9	52 (28.0)	139 (24.6)	1.20 (0.73, 1.98)
≥ 28	56 (30.1)	140 (24.7)	1.27 (0.78, 2.05)

[1]. odds ratios reported for model including age, education, cigarette smoking, relative with pancreatic cancer, race, sex and body mass index [2]. mean [3]. n (%) [4]. quartiles based on control distribution after excluding never smokers [5]. kg/m^2 [6]. quartiles based on control distribution

fication in risk (adjusted OR = 0.85; 95% CI 0.49–1.45 for seven or more tablets per week), but a non-significant increase in risk was observed for increased duration of use (adjusted OR = 1.21; 95% CI 0.81–1.82 for 11 or more years of use). Over 11 tablet-years of use was associated with a reduced risk in the overall set (adjusted OR = 0.65 95% CI 0.37–1.16), although it must be noted that the 95% confidence interval did include unity. This association was more pronounced in men than women. In general, the risk estimates and 95% confidence intervals obtained following adjustment for smoking and family history of pancreatic cancer were very similar to the unadjusted, crude results.

While stratification based on sex resulted in analysis of two smaller data sets, results and direction of point estimates were generally similar for men and women compared to each other and the total set. Analyses were also

Table 2: Risk of pancreatic cancer in association with aspirin use – Roswell Park Cancer Institute, Buffalo, NY 1982–1996.

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[1] (95% CI)
		All		
Non-Regular User	108(55.7)	327(56.2)	1.00	1.00
Regular User[2]	86 (44.3)	255(43.8)	1.02 (0.74, 1.42)	1.00 (0.72, 1.39)
Dosage Used				
1–6 tabs/wk[3]	61 (31.4)	157(26.9)	1.18 (0.82, 1.70)	1.15 (0.79, 1.67)
7+ tabs/wk[3]	25 (12.9)	98 (16.8)	0.87 (0.51, 1.48)	0.85 (0.49, 1.45)
Duration of Use				
0.5–10 years[3]	37 (19.1)	137(23.6)	0.82 (0.54, 1.25)	0.82 (0.54, 1.26)
11+ years[3]	49 (25.3)	117(20.1)	1.27 (0.85, 1.89)	1.21 (0.81, 1.82)
Tablet-years of Use[3]				
1–10 tablet years	69 (35.6)	176 (30.2)	1.19 (0.83, 1.69)	1.15 (0.80, 1.65)
11+ tablet years	17 (8.8)	79 (13.6)	0.65 (0.37, 1.15)	0.65 (0.37, 1.16)
		Men		
Non-Regular User	58 (54.7)	174 (54.7)	1.00	1.00
Regular User[2]	48 (45.3)	144 (45.2)	1.00 (0.64, 1.56)	0.99 (0.64, 1.5)
Dosage Used[3]				
1–6 tabs/wk	31 (29.2)	87 (27.4)	1.07 (0.64, 1.77)	1.05 (0.63, 1.75)
7+ tabs/wk	17 (16.0)	57 (17.9)	0.90 (0.48, 1.66)	0.91 (0.49, 1.70)
Duration of Use[3]				
0.5–10 years	27 (25.5)	81 (25.5)	1.00 (0.59, 1.69)	1.03 (0.60, 1.75)
11+ years	21 (19.8)	63 (19.8)	1.00 (0.56, 1.78)	0.95 (0.53, 1.72)
Tablet-years of Use[3]				
1–10 tablet years	43 (40.6)	113 (35.5)	1.14 (0.72, 1.81)	1.12 (0.70, 1.78)
11+ tablet years	5 (4.7)	31 (9.7)	0.48 (0.18, 1.30)	0.52 (0.19, 1.40)
		Women		
Non-Regular User	50 (56.8)	153 (59.0)	1.00	1.00
Regular User[2]	38 (43.2)	111 (42.0)	1.05 (0.64, 1.71)	1.01 (0.62, 1.67)
Dosage Used[3]				
1–6 tabs/wk	30 (34.1)	70 (26.5)	1.31 (0.77, 2.24)	1.29 (0.75, 2.23)
7+ tabs/wk	4 (9.1)	41 (15.5)	0.77 (0.24, 2.40)	0.67 (0.21, 2.14)
Duration of Use[3]				
0.5–10 years	10 (11.4)	56 (21.2)	0.55 (0.26, 1.15)	0.55 (0.26, 1.16)
11+ years	28 (31.8)	54 (20.5)	1.59 (0.91, 2.77)	1.52 (0.86, 2.69)
Tablet-years of Use[3]				
1–10 tablet years	26 (29.5)	63 (23.9)	1.26 (0.72, 2.21)	1.25 (0.70, 2.20)
11+ tablet years	12 (13.6)	48 (18.2)	0.77 (0.38, 1.55)	0.72 (0.35, 1.49)

1. Odds ratio adjusted for age, packyears of smoking and family history of pancreatic cancer. 2. Regular use defined as self-reported use for at least once a week for six consecutive months. 3. Among regular users.

performed after restricting the sample to individuals who were at least 50 years old, with similar results as those presented in Table 2 (data not shown).

Discussion

Our results do not support the notion that aspirin plays a role in the development of pancreatic cancer. Most risk estimates were close to the null. Unfortunately, the lack of a

coherent pattern or trend in the risk estimates preclude conclusions based on integrating the results.

Our results contrast with those reported by Anderson *et al.* [30], who demonstrated a significant, dose-dependent, reduced risk in a cohort of 28,283 post-menopausal women. We observed a suggestion of increased risk in women associated with duration of use, but analyses of cases by menopausal status were limited by small numbers. Further, this non-significant risk reduction is difficult to interpret, due to the inverse association with regular use and dose in women.

Three other studies have also examined NSAID use and pancreatic cancer risk [27–29]. While these studies had similar null results, they differed in their assessment of NSAID use. Langman *et al.* [29] used a general practice research database from the United Kingdom that included data on morbidity and NSAID prescriptions. For 12,174 incident cancer cases (396 pancreas) and 34,934 controls, information on NSAID prescriptions for 13–36 months prior to cancer diagnosis (equivalent information for controls) was extracted for the period of 1993–1995. Associations between risk of cancer and number of prescriptions were analyzed, with no association being found for pancreatic cancer. Gridley *et al.* [27] examined the incidence of cancer among 11,683 Swedish rheumatoid arthritis patients, testing the hypothesis that individuals who were taking regular amounts of NSAIDs would have lower cancer rates. Of the 840 cancer cases occurring from 1965 to 1983, 32 had pancreatic cancer. Using regional cancer rates, standardized incidence ratios (SIR) were calculated. There was a slightly reduced risk for pancreatic cancer, although this risk was not significant (SIR = 0.83, 95% CI 0.6–1.2). There was no information on individual doses. Finally, Coogan *et al.* [28] examined the association between NSAID use and risk of digestive cancers in a hospital-based case-control study. Included in the overall group were 504 pancreatic cancer patients and 595 controls. Defining regular NSAID use as use for at least four days per week for at least three months, initiated at least one year before hospital admission, they found a slight negative association between NSAID use and risk of pancreatic cancer (continual vs. never users OR = 0.8, 95% CI 0.5–1.1; use over 5 years vs. never users OR = 0.6, 95% CI 0.4–1.1). In general, while the methodology and exposure assessment of these three studies differed greatly, a lack of association between NSAID use and pancreatic cancer risk or incidence, as represented by risk estimates and confidence intervals, was reported.

Our null findings may be related to the possibility that, prior to cancer diagnosis or because of associated conditions or complications, cases experienced sufficient discomfort to warrant aspirin usage. Unfortunately, reasons for aspirin use were not available. Exposure misclassification of aspirin use, likely to be non-differential, may have also caused attenuation of the results, since the analyses were based on self-reported aspirin use and was based on number of pills taken, and not the actual dose of aspirin. The hospital-based design, although potentially reducing recall bias, may lessen the generalizability of our findings to the general population. However, it is unlikely that self-reported aspirin use would be different for patients treated at RPCI than for those treated at other facilities. We attempted to minimize this source of bias by randomly selecting controls from a large pool of eligible patients from a wide variety of diagnostic groups. Only about 50% of eligible cases and controls completed the PEDS questionnaire, likely to further introduce a selection bias. We had no way to ascertain whether those that refused to participate differed with respect to aspirin use. Despite these limitations, it should be pointed out that numerous previous studies that have utilized the PEDS database, and faced the same methodological issue, have consistently replicated established epidemiological associations for a variety of cancer sites [31–35]. Further, as mentioned above, smoking and family history of pancreatic cancer are two of the few established risk factors for pancreatic cancer [36], and they were found to be associated with disease risk in our data. Other limitations of this study include the potential biases inherent in case-control studies.

The primary strengths of our study are the different types of exposure variables and size. In examining general use, as well as frequency and duration, it is possible to see which measure of aspirin use, if any, is associated with pancreatic cancer risk, and not rely solely on more general categorical designations like regular vs. non-users. Further, the rareness and aggressive nature of this cancer makes it difficult to conduct large retrospective population studies. Because of the large number of patients seen at the Roswell Park Cancer Institute over the long study period (1982–1998), close to 200 pancreatic cancer patients were included in the analysis.

Conclusions

To summarize, in this hospital based case-control study of pancreatic cancer, we found no association between aspirin use and risk. Since it is widely thought that COX-2, more so than COX-1, may play a role in neoplasia, it is reasonable to think that the more effective drugs would be selective for COX-2. These agents address the different physiologic roles of the two COX enzymes as well as reduce adverse side effects of prolonged drug use [37]. Nevertheless, as discussed above, certain experimental and population studies [20–22] do indicate that drugs like aspirin, which can act on both COX-1 and 2, may play a role in prevention and therapy of pancreatic cancer. Given the biologic plausibility for a potential chemopreventive ef-

fect of aspirin and other NSAIDs on pancreatic cancer risk, additional analytic epidemiological studies are needed to further explore this risk association. These studies should incorporate more detailed information on aspirin other NSAIDs, especially selective COX-2 inhibitors, in order to allow for a more comprehensive exposure assessment.

Competing interests

None declared.

Authors' contributions

RJM and KRH participated in statistical analysis and drafting the manuscript. MCM participated in study design and manuscript preparation. KBM conceived of the study and participated in its design and manuscript preparation.

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