Research Article

Aspirin Use and Reduced Risk of Pancreatic Cancer

Harvey A. Risch[1], Lingeng Lu[1], Samantha A. Streicher[1], Jing Wang[2], Wei Zhang[2], Quanxing Ni[3], Mark S. Kidd[4], Herbert Yu[5], and Yu-Tang Gao[2]

Abstract

Background: Few options besides the avoidance of smoking and obesity are available to prevent pancreatic cancer. The association between aspirin use and risk of pancreatic cancer has been inconsistent across studies.

Methods: We performed a population-based study of 761 case and 794 control subjects frequency matched on sex and age during 2006 to 2011 in Shanghai, China. Participants were asked about episodes of regular use of aspirin, tablets per day or week, and ages that the use started and stopped. Data were analyzed by unconditional logistic regression, with adjustments for age, sex, education, body mass index, years of cigarette smoking, cigarettes smoked per day, *Helicobacter pylori* CagA seropositivity, ABO blood group, and history of diabetes mellitus. Meta-regression was carried out to summarize the literature.

Results: Ever-regular use of aspirin was associated with lowered risk of pancreatic cancer: OR = 0.54; 95% confidence interval (CI), 0.40–0.73; $P = 10^{-4.2}$. Risk decreased 8% per each cumulative year of use: $OR_{trend} = 0.92$; 95% CI, 0.87–0.97; $P = 0.0034$. Across this and 18 published studies of this association, the OR for ever-regular use decreased with increasingly more recent mid-study year, for any aspirin type ($P_{trend} = 10^{-5.1}$), and for low-dose aspirin ($P_{trend} = 0.0014$).

Conclusions: Regular use of aspirin thus appears to reduce risk of pancreatic cancer by almost half.

Impact: People who take aspirin for prevention of other diseases likely also reduce their risk of pancreatic cancer. Aside from benefits for both cardiovascular disease and certain cancers, long-term aspirin use entails some risks of bleeding complications, which necessitates risk–benefit analysis for individual decisions about use. *Cancer Epidemiol Biomarkers Prev; 26(1); 68–74. ©2016 AACR.*

Introduction

Pancreatic cancer is among the most fatal of all cancer types. By 2022, in the United States, deaths from pancreatic cancer are expected to exceed all other cancer types except lung (1). Although cigarette smoking and long-term obesity/diabetes mellitus are two avoidable causes of pancreatic cancer, most cases of the disease are apparently not preventable. Some conflicting evidence suggests that aspirin use may lower risk, and in fact, our study in Connecticut found approximately 50% reduced risk with regular use of either low-dose or regular-dose aspirin (2). During 2006 to 2011, we carried out a second population-based case–control study of pancreatic cancer in Shanghai, China, and thus sought to examine whether or not aspirin use was associated with risk in that population.

Materials and Methods

Our Shanghai study has been described in detail elsewhere (3). In brief, from December 2006 to January 2011, in 37 Shanghai hospitals, we identified 1,241 newly diagnosed patients with pancreatic cancer and recruited 1,092 (88%), of whom 892 were confirmed to be eligible by review of pathology and clinical records. Patients were identified in each hospital by active, real-time surveillance of admissions for workup of possible pancreatic cancer, and were interviewed in-hospital, generally within 1 to 2 days of admission. Over the same years, we attempted to contact 1,529 age and sex frequency-matched potentially eligible control subjects randomly selected from the Shanghai Residents Registry and interviewed 1,067 (70%) at home. At the in-person questionnaire interviews, after receiving signed informed consent, we obtained venipuncture blood samples from 761 cases and 794 controls. Study subjects were questioned about various standard demographic, lifestyle, and medical history factors, as well as specifically asked about all episodes of regular use of aspirin and other NSAIDs. A show-card listing names of medications of current and past availability was used to promote recall of dates, durations, and frequencies of use. Regular use was considered to be use of at least one tablet per week for 3 months or longer. We did not distinguish regular-dose from low-dose aspirin preparations in recording subject responses. For laboratory analyses, we used commercial ELISA Kits to determine plasma seropositivity for CagA-positive *Helicobacter pylori* (*H. pylori*) strain (Ravo

[1]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut. [2]Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. [3]Department of Pancreatic and Hepatobiliary Surgery, Fudan University Shanghai Cancer Center, Shanghai, China. [4]Wren Laboratories LLC, Branford, Connecticut. [5]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii.

Corresponding Author: Harvey A. Risch, Department of Chronic Disease Epidemiology, Yale School of Public Health, 60 College Street, New Haven, CT 06520-8034. Phone: 203-785-2848; Fax: 203-785-4497; E-mail: harvey.risch@yale.edu

AACR

Table 1. Characteristics of pancreatic cancer case patients and population control subjects in urban Shanghai, China, 2006–2011

Characteristics	No. of cases (%)[a]	No. of controls (%)[a]	P[b]
Total number	761	794	
Age at interview, y			
Mean (SD)	64.9 (9.6)	64.9 (9.9)	0.99
35–49	59 (7.8)	63 (7.9)	
50–59	183 (24.0)	193 (24.3)	
60–69	231 (30.4)	232 (29.2)	
70–79	288 (37.8)	306 (38.5)	
Sex			
Male	435 (57.2)	460 (57.9)	0.74
Female	326 (42.8)	334 (42.1)	
Education			
Primary school or lower	146 (19.2)	142 (17.9)	0.21[c]
Middle or high school	445 (58.5)	498 (62.7)	
College or higher	170 (22.3)	154 (19.4)	
BMI at age 21 years, mean (SD)			
Males	20.6 (2.30)	20.2 (2.02)	$10^{-4.4}$[d]
Females	20.5 (2.50)	19.9 (2.34)	
History of diabetes mellitus			
Never	581 (76.3)	693 (87.3)	
Within previous 3 years	80 (10.5)	22 (2.8)	$10^{-10.1}$[c]
More than 3 years in the past	100 (13.1)	79 (9.9)	
H. pylori CagA seropositivity			
No	319 (41.9)	257 (32.4)	$10^{-4.0}$
Yes	442 (58.1)	537 (67.6)	
ABO blood group[e]			
O	200 (26.3)	250 (31.5)	
A	289 (38.0)	225 (28.3)	$10^{-3.6}$
B	193 (25.4)	229 (28.8)	0.70
AB	79 (10.4)	90 (11.3)	0.61
Tobacco use			
Never smoker	428 (56.3)	458 (57.7)	0.55[c]
Former smoker	97 (12.7)	109 (13.7)	
Current smoker	236 (31.0)	227 (28.6)	
Cigarettes, years of smoking, mean (SD)			
Among former smokers	29.2 (14.5)	30.2 (12.5)	0.76[d]
Among current smokers	36.5 (10.5)	36.0 (10.5)	
Cigarettes, frequency per day, mean (SD)			
Among former smokers	16.7 (10.2)	14.9 (9.3)	0.029[d]
Among current smokers	17.8 (9.2)	16.1 (9.3)	

Abbreviation: BMI, body mass index, weight/height^2 (kg/m^2).

[a]Values in the table are numbers (percentages) of participants unless indicated otherwise.

[b]P values calculated by χ^2 distribution for categorical variables (sex, education, H. pylori CagA seropositivity, ABO blood group, each group vs. group O) and as trends by unconditional logistic regression for continuous variables (age at interview, BMI at age 21 years, years of smoking, and cigarette frequency per day).

[c]P value based on 2 degrees of freedom for homogeneity of risk across three categories.

[d]P value based on 2 degrees of freedom for simultaneous continuous trends in both strata.

[e]For ABO group A vs. non-A, the P value is $10^{-4.2}$.

Diagnostika p120, Alere GmbH; ref. 4). ABO blood group was determined by custom TaqMan genotyping (Applied Biosystems, Inc.) of two functional SNPs, rs8176719 and rs8176746 (3). The study was approved by the human subjects review boards of the Shanghai Cancer Institute (Shanghai, China) and Yale University (New Haven, CT).

We used unconditional logistic regression methods to estimate ORs and their 95% confidence intervals (CI). All analyses were adjusted for the continuous terms age at interview, education category, age 21 body mass index (BMI), years of cigarette smoking and number of cigarettes smoked per day, and indicator terms for sex, H. pylori CagA seropositivity, ABO blood group A versus non-A, and history of diabetes mellitus more than 3 years in the past. All P values are two-sided. For the calculation of trends in published ORs over calendar time, we used meta-regression of the log ORs (5, 6). We generally followed the MOOSE guidelines (7) in searching the PubMed, Ovid, and EMBASE databases for articles and abstracts on aspirin and cancer in any language published or in-press from the database start through July 25, 2016, as well as in reviewing the reference lists of the obtained articles for additional papers. We did not weight individual studies for quality. We evaluated the adequacy of the time–trend models by calculating, using the method-of-moments variance estimator, the adjusted R^2, the proportion of between-study variance explained by the linear covariate (8).

Results

Various demographic and risk factor characteristics of the cases and controls are presented in Table 1. The subjects were well matched on age at interview and sex. Cases on average had slightly

Risch et al.

Table 2. Associations between regular use of aspirin and risk of pancreatic cancer[a]

Aspirin use	No. of case patients[b] $n = 761$	No. of control subjects[b] $n = 794$	OR (95% CI)	P
Ever use				
No	674	651	Ref.	
Yes	87	143	0.54 (0.40–0.73)	$10^{-4.2}$
Duration of use, y	3.59	4.06	0.92 (0.87–0.97)	0.0034
Categories of use duration, y				
Never use	674	651	Ref.	
>0, <2	34	47	0.69 (0.43–1.10)	0.12
≥2, <4	23	45	0.41 (0.24–0.69)	$10^{-3.0}$
≥4	30	51	0.53 (0.33–0.86)	0.0099
Time in past since starting use, y	5.41	4.96	0.96 (0.92–1.00)	0.034
Categories of starting time in past, y				
Never use	674	651	Ref.	
>0, <2	23	37	0.58 (0.34–1.00)	0.051
≥2, <4	22	43	0.44 (0.26–0.75)	0.0027
≥4	42	63	0.59 (0.39–0.90)	0.014
Categories of ending time in past, y				
Never used	674	651	2.30 (1.62–3.26)	$10^{-5.5}$
Continuing current use	57	113	Ref.	
>0, <2	15	15	2.36 (1.06–5.25)	0.035
≥2	15	15	2.06 (0.92–4.60)	0.077
Age at start of use, y	62.7	64.4	0.90 (0.86–0.95)[c]	$10^{-4.5}$
Categories of age at start of use, y				
Never used	674	651	Ref.	
>0, <60	33	43	0.68 (0.42–1.09)	0.11
≥60, <70	32	52	0.55 (0.34–0.88)	0.012
≥70	22	48	0.39 (0.23–0.68)	$10^{-3.1}$
Age at end of use, y	66.3	68.4	0.91 (0.87–0.95)[c]	$10^{-4.6}$
Categories of age at end of use, y				
Never used	674	651	Ref.	
>0, <60	19	31	0.53 (0.29–0.97)	0.039
≥60, <70	33	42	0.69 (0.42–1.11)	0.13
≥70	35	70	0.45 (0.29–0.70)	$10^{-3.3}$

[a]Unconditional logistic regression models were used to obtain the ORs and 95% CIs. All models were adjusted for age at interview (continuous), sex, education category (continuous), BMI at age 21 (continuous), years of cigarette smoking (continuous), number of cigarettes per day (continuous), *H. pylori* CagA seropositivity, ABO blood group A vs. non-A, and history of diabetes mellitus more than 3 years in the past. Each row in the table is a separate adjusted model.
[b]Numbers of subjects for the category variables. For the duration variables, these columns give the mean durations among aspirin ever users; the ORs are per one year of duration, and the *P* values represent trend associations.
[c]OR and confidence limits per a 10-year difference in age among aspirin ever users.

but significantly higher age 21 BMI than controls, were more likely to carry blood group A and less likely to be *H. pylori* CagA seropositive, and smoked more cigarettes per day. Cases had a higher frequency of past diagnosis of diabetes mellitus, especially within 3 years before interview, during which time such diagnoses are considered more likely than not to arise from the developing pancreatic cancers.

Results for aspirin use among study subjects are given in Table 2. All but six of the 230 ever-users used aspirin at least daily. Ever-regular use was associated with approximately 50% reduced risk of pancreatic cancer ($P = 10^{-4.2}$). A trend in decreasing risk with duration of use was evident ($P = 0.0034$). More than half of all use started within 4 years of interview. Compared with continuing use, quitting use of aspirin within the recent 2 years was associated with more than doubled risk of pancreatic cancer, comparable with the risk of never having used it. Magnitudes of associations among case subjects limited to local, regional, or distant tumor stages at diagnosis were similar (Table 3). Ever regular use of aspirin was associated with lower risk in women (OR = 0.42; 95% CI, 0.26–0.67) than in men (OR = 0.64; 95% CI, 0.44–0.94); both associations were significant, but not significantly different from each other ($P = 0.16$). Analyses of all interviewed subjects, not just those who provided blood samples,

yielded similar results (data not shown). Regular non-aspirin NSAID use was reported by only 12 subjects and was not analyzed.

Discussion

The pattern of risk associations in Chinese subjects in Shanghai as seen here is remarkably similar to that in our Connecticut study (2). Both studies demonstrated about 50% reduced risk with ever use of aspirin, as well as some evidence of trends of decreasing risk with increasing durations of use. Typical durations of use were shorter in Shanghai than Connecticut; nevertheless, the relative reductions in risk were comparable. Both studies also showed that people who quit using aspirin in the recent 2 years had about 2- to 3-fold higher risks compared with individuals continuing on the medication and that never-users had about double the risk of current users. These observations suggest that aspirin use may be associated with decreased risk of pancreatic cancer, as well as that individuals with developing pancreatic cancer may become increasingly less tolerant of aspirin and thus more likely to terminate use a little before diagnosis. In spite of this possible dual relationship, long-term aspirin use or use of 5 to 10 years or more in the past has been associated with reduced risk (2). Because most observed associations with reduced risk have been

Table 3. Associations between regular use of aspirin and risk of pancreatic cancer, according to stage of disease and gender[a]

Aspirin use	No. of case patients[b] $n = 761$	No. of control subjects[b] $n = 794$	OR (95% CI)	P
Local stage case patients vs. controls:				
Ever use				
No	90	651	Ref.	
Yes	13	143	0.61 (0.33–1.15)	0.13
Duration of use, y	2.04	4.06	0.81 (0.67–0.98)	0.031
Regional stage case patients vs. controls:				
Ever use				
No	386	651	Ref.	
Yes	52	143	0.56 (0.39–0.80)	0.0013
Duration of use, y	3.65	4.06	0.92 (0.86–0.99)	0.019
Distant stage case patients vs. controls:				
Ever use				
No	198	651	Ref.	
Yes	22	143	0.46 (0.28–0.75)	0.0020
Duration of use, y	4.36	4.06	0.93 (0.85–1.02)	0.11
Male subjects:				
Ever use				
No	378	377	Ref.	
Yes	57	83	0.64 (0.44–0.94)	0.023
Duration of use, y	3.68	4.23	0.93 (0.87–1.00)	0.045
Female subjects:				
Ever use				
No	296	274	Ref.	
Yes	30	60	0.42 (0.26–0.67)	$10^{-3.5}$
Duration of use, y	3.41	3.82	0.89 (0.80–0.99)	0.028

[a]Unconditional logistic regression models were used to obtain the ORs and 95% CIs. All models were adjusted for age at interview (continuous), sex, education category (continuous), BMII at age 21 (continuous), years of cigarette smoking (continuous), number of cigarettes per day (continuous), *H. pylori* CagA seropositivity, ABO blood group A vs. non-A, and history of diabetes mellitus more than 3 years in the past. Each row in the table is a separate adjusted model.
[b]Numbers of subjects for the category variables. For the duration variables, these columns give the mean durations among aspirin ever users; the ORs are per one year of duration, and the P values represent trend associations.

for use within a decade of diagnosis, aspirin use may be inferred to slow tumor development rather than prevent initial tumor occurrence (9).

In examining the literature to calculate meta-analysis, we found 18 other studies that have investigated aspirin use and risk of pancreatic cancer (Supplementary Table S1; plotted in Fig. 1; refs. 2, 10–26). The summary association (OR = 0.83; 95% CI, 0.78–0.89) was not substantially different for the five studies having data for males (OR = 0.78; 95% CI, 0.67–0.90; refs. 2, 17, 18, 23, and the current study) or the eight with data for females (OR = 0.84; 95% CI, 0.73–0.97; refs, 2, 10, 17, 18, 20, 23, 25, and the current study). Among all of the published studies, six have shown significantly reduced risk with use (2, 10–14). Of the 12 others (15–26), many of those that began accruing patients in the 1990s or later (and thus that were conducted after the general population introduction of aspirin for cardioprophylaxis) show nonsignificant reduced risk with use. In Fig. 1, a trend in the OR for ever-regular use of aspirin is evident according to increasingly more recent midpoint of when the aspirin exposures were ascertained in the study, with decline in OR of 2.3% per year (95% CI, 1.3%–3.3%; $P = 10^{-5.1}$; adjusted $R^2 = 91\%$). For a recent study conducted with midpoint in 2011, the predicted OR = 0.64 (95% CI, 0.57–0.74; $P = 10^{-10.2}$). A similar trend in OR is seen for the six studies specifically examining ever-regular use of low-dose aspirin (Fig. 2; refs. 2, 11, 12, 18, 20, 21), with decline in OR of 3.6% per year (95% CI, 1.4%–5.8%; $P = 0.0014$; adjusted $R^2 = 84\%$). The predicted OR for a recent study conducted with exposure midpoint in 2011 would be 0.59 (95% CI, 0.45–0.76; $P = 10^{-4.3}$). On average, ORs for regular use of aspirin and risk of pancreatic cancer

have been declining over the past two decades as the general population use of aspirin has increased. We also examined trends in ORs according to year of study publication, and the results were stronger and more significant, but we felt that mid-year of study accrual better represented the time period of aspirin exposure. Finally, we found similar significant decreasing trends in the ORs over time for both ever use of any aspirin and ever use of low-dose aspirin when analyses were limited to case–control studies and to case–control studies involving aspirin information obtained from clinical records rather than subject interviews (data not shown).

Although our study results and the declining OR trends in the literature provide evidence for a beneficial effect of aspirin use on risk of pancreatic cancer, some limitations of this work should be considered. In our Shanghai study, we ascertained aspirin use by self-report, which could have inherent differences between cases and controls, both in our study and in other similar ones. In case–control studies, given that cases generally tend to overreport past exposures relative to controls (27), such differential reporting would not be likely to explain the reduced risks seen here. Evidence of benefit from cohort (10, 18, 19, 22, 23, 25), randomized trial (12, 20), and case–control (13, 21, 24) studies in which aspirin use information was obtained from clinical databases is weaker but still suggestive, although these studies are mostly older, and the cohort and case–control studies do not reflect more current population frequencies of aspirin use, in which lower ORs are seen. Aspirin is an over-the-counter medication for which use may not be well characterized by standard clinical database information. Analyses of more recent follow-up periods in the cohort studies will be helpful in determining the

Risch et al.

Figure 1.
Adjusted OR of pancreatic cancer according to ever-regular use of aspirin. Squares are plotted descending in order of increasing mid-years of study subject aspirin-use ascertainment. Black squares, case–control studies; gray squares, cohort studies; white squares, randomized controlled trials or their extensions; diamonds, summary estimates. Risch et al., 2008 refers to the current study. Horizontal lines in each square represent the 95% CI, and the area of each square is proportional to its weight in the analyses. The diagonal dotted line is the regression line of the log OR according to study mid-year, calculated by inverse variance-weighted linear regression of the log ORs (8). The current regression estimate is the regression OR predicted at the midpoint of the most recent study (2011).

Author, study mid-year	OR (95% CI)
Ratnasinghe et al., 1976	0.87 (0.42–1.77)
Coogan et al., 1988	0.75 (0.50–1.10)
Menezes et al., 1990	1.00 (0.72–1.39)
Rothwell et al., 1991	0.25 (0.07–0.92)
Langman et al., 1992	1.26 (0.97–1.63)
Friis et al., 1992	1.07 (0.82–1.40)
Anderson et al., 1995	0.43 (0.26–0.72)
Cao et al., 1996 (NHS)	1.04 (0.81–1.32)
Cao et al., 1998 (HPFS)	0.87 (0.69–1.09)
Cook et al., 1998	1.42 (0.81–2.49)
Jacobs et al., 2000	0.95 (0.72–1.25)
Bonifazi et al., 2001	0.87 (0.47–1.61)
Bradley et al., 2001	0.95 (0.81–1.13)
Brasky et al., 2002	0.69 (0.45–1.06)
Pugh et al., 2006	0.49 (0.29–0.84)
Tan et al., 2007	0.73 (0.61–0.88)
Streicher et al., 2007	0.52 (0.39–0.69)
Kollárová et al., 2007	0.33 (0.17–0.62)
Risch et al., 2008	0.54 (0.40–0.73)
Archibugi et al., 2011	0.77 (0.58–1.04)
Total pooled	0.83 (0.78–0.89)
Current regression estimate	0.64 (0.57–0.74)

Adjusted OR of pancreatic cancer according to ever-regular use of aspirin

Figure 2.
Adjusted OR of pancreatic cancer according to ever-regular use of low-dose aspirin. Squares are plotted descending in order of increasing mid-years of study subject aspirin-use ascertainment. Black squares, case–control studies; gray squares, cohort studies; white squares, randomized controlled trials or their extensions; diamonds, summary estimates. Horizontal lines in each square represent the 95% CI, and the area of each square is proportional to its weight in the analyses. The diagonal dotted line is the regression line of the log OR according to study mid-year, calculated by inverse variance-weighted linear regression of the log ORs (8). The current regression estimate is the regression odds ratio predicted at the midpoint of what would be a recent study as in Fig. 1 (2011).
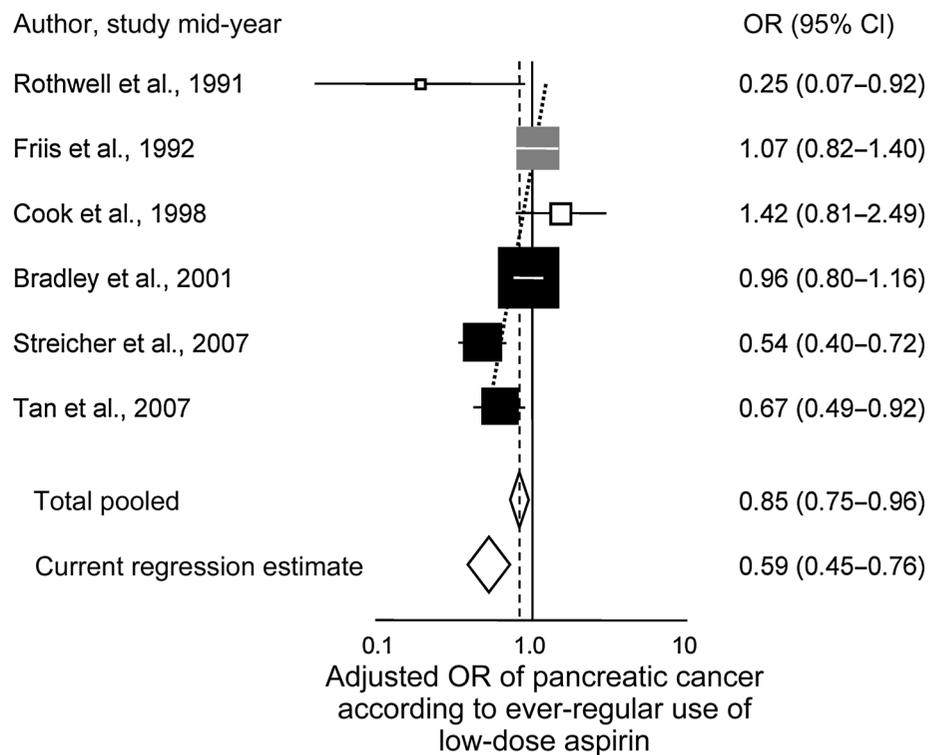
magnitude of benefit of aspirin use. Finally, various physiologic mechanisms for risk reduction with aspirin use have been suggested, and although a number of these mechanisms are plausible, none has yet been convincingly established. We have discussed these mechanisms at length elsewhere (2).

In conclusion, we observed a significant inverse relationship between aspirin use and risk of pancreatic cancer in a large representative sample of Chinese individuals. The pattern of risk reduction was very similar to that seen in other recent studies in the United States and elsewhere. Although the choice to use aspirin for disease prophylaxis generally depends upon evaluated risks of cardiovascular disease, colorectal cancer, etc., it is likely that such use at least does not increase risk of pancreatic cancer and very probably appreciably lowers it.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for the analyses and the interpretation of the study 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.

Authors' Contributions

Conception and design: H.A. Risch, W. Zhang, M.S. Kidd, H. Yu, Y.-T. Gao
Development of methodology: H.A. Risch, H. Yu

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.A. Risch, L. Lu, J. Wang, W. Zhang, H. Yu, Y.-T. Gao
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.A. Risch, M.S. Kidd
Writing, review, and/or revision of the manuscript: H.A. Risch, L. Lu, S.A. Streicher, M.S. Kidd, H. Yu, Y.-T. Gao
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.A. Risch, W. Zhang, Q. Ni, Y.-T. Gao
Study supervision: H.A. Risch, Y.-T. Gao

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913–21.

2. Streicher SA, Yu H, Lu L, Kidd MS, Risch HA. Case-control study of aspirin use and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2014;23:1254–63.

3. Risch HA, Lu L, Wang J, Zhang W, Ni Q-X, Gao Y-T, et al. ABO blood group and risk of pancreatic cancer: a study in Shanghai and meta-analysis. Am J Epidemiol 2013;177:1326–37.

4. Risch HA, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, et al. *Helicobacter pylori* seropositivities and risk of pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev 2014;23:172–8.

5. Baker WL, White CM, Cappelleri JC, Kluger J, Coleman CI; Health Outcomes, Policy, and Economics (HOPE) Collaborative Group. Understanding heterogeneity in meta-analysis: the role of meta-regression. Int J Clin Pract 2009;63:1426–34.

6. Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23:1663–82.

7. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

8. Harbord RM, Higgins JPT. Meta-regression in Stata. Stata J 2008; 8:493–519.

9. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467:1114–7.

10. 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.

11. Tan XL, Reid Lombardo KM, Bamlet WR, Oberg AL, Robinson DP, Anderson KE, et al. Aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen, and pancreatic cancer risk: a clinic-based case-control study. Cancer Prev Res 2011;4:1835–41.

12. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377: 31–41.

13. Pugh TFG, Little M, Carey F, Metcalfe M, Robinson R, Clark A, et al. Aspirin, NSAIDS, calcium-channel blockers and statins in the aetiology of pancreatic cancer: preliminary results from a case-control study in two centres in the UK. Gut 2011;60Suppl 1:A81.

14. Kollárová H, Azeem K, Tomášková H, Procházka V, Martínek A, Shonová O, et al. Zdravotní stav a karcinom pankreatu. [Health status and pancreatic cancer]. Gastroenterologie et Hepatologie (Prague) 2013;67:154–61.

15. Bonifazi M, Gallus S, Bosetti C, Polesel J, Serraino D, Talamini R, et al. Aspirin use and pancreatic cancer risk. Eur J Cancer Prev 2010;19:352–4.

16. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD, 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.

17. Menezes RJ, Huber KR, Mahoney MC, Moysich KB. Regular use of aspirin and pancreatic cancer risk. BMC Public Health 2002;2:18.

18. Friis S, Sorensen 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.

19. 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.

20. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, 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.

21. Bradley MC, Hughes CM, Cantwell MM, Napolitano G, Murray LJ. Nonsteroidal anti-inflammatory drugs and pancreatic cancer risk: a nested case-control study. Br J Cancer 2010;102:1415–21.

22. Jacobs EJ, Newton CC, Gapstur SM, Thun MJ. Daily aspirin use and cancer mortality in a large US cohort. J Natl Cancer Inst 2012;104:1208–17.

23. Cao Y, Nishihara R, Wu K, Wang M, Ogino S, Willett WC, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. JAMA Oncol 2016;2:762–9.

24. 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.

25. Brasky TM, Liu J, White E, Peters U, Potter JD, Walter RB, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. Int J Cancer 2014;135:1869–83.

26. Archibugi L, Maisonneuve P, Piciucchi M, Valente R, Delle Fave G, Capurso G. Statins but not aspirin nor their combination have a chemopreventive effect on pancreatic cancer occurrence. Pancreas 2015;44:1359.

27. Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE. Recall (report) bias and reliability in the retrospective assessment of melanoma risk. Am J Epidemiol 1991;133:240–5.

Cancer Epidemiology, Biomarkers & Prevention

Aspirin Use and Reduced Risk of Pancreatic Cancer

Harvey A. Risch, Lingeng Lu, Samantha A. Streicher, et al.

Updated version	Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-16-0508
Supplementary Material	Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2016/10/20/1055-9965.EPI-16-0508.DC1

Cited articles	This article cites 27 articles, 8 of which you can access for free at: http://cebp.aacrjournals.org/content/26/1/68.full#ref-list-1
Citing articles	This article has been cited by 11 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/26/1/68.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/26/1/68. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.