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Aspirin Use and Reduced Risk of Pancreatic Cancer

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Abstract

Background—Few options beside 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 2006–2011 in Shanghai, China. Participants were asked about episodes of regular use of aspirin, tablets per day or week, and ages that 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: odds ratio [OR] = 0.54; 95% 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=.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).

Conclusion—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-

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term aspirin use entails some risks of bleeding complications which necessitates risk-benefit analysis for individual decisions about use.

Keywords

Aspirin; Case-control Studies; Pancreatic Cancer

Introduction

Pancreatic cancer is among the most fatal of all cancer types. By 2022, in the U.S., deaths from pancreatic cancer are expected to exceed all other cancer types except lung (1). While 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 2006–2011, 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–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 1–2 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 non-steroidal anti-inflammation medications (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 three months or longer. We did not distinguish regular-dose from low-dose aspirin preparations in recording subject responses. For laboratory analyses, we used commercial enzyme-linked immunosorbent assay kits to determine plasma seropositivity for CagA-positive *Helicobacter pylori* strain (Ravo Diagnostika p120, Alere GmbH, Köln, Germany) (4). ABO blood group was determined by custom TaqMan genotyping (Applied Biosystems, Inc., Foster City, California) of two functional SNPs, rs8176719 and rs8176746 (3). The study was approved by the human subjects review boards of the Shanghai Cancer Institute and Yale University.

We used unconditional logistic regression methods to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). All analyses were adjusted for the continuous terms age at interview, education category, age-21 body mass index, years of cigarette smoking and number of cigarettes smoked per day, and indicator terms for sex, *H. pylori* CagA seropositivity, ABO blood group A vs 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 odds ratios over calendar time, we used meta-regression of the log odds ratios (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 but significantly higher age-21 body mass index 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 three 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 ($P=.0034$). More than half of all use started within four years of interview. Compared to continuing use, quitting use of aspirin within the recent two years was associated with more than doubled risk of pancreatic cancer, comparable to 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 to 0.67) than in men (OR=0.64, 95% CI 0.44 to 0.94); both associations were significant, but not significantly different from each other ($P=.16$). 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 two years had about 2–3 fold higher risks compared to 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 5–10 years or more in the past has been associated with reduced risk (2). Because most observed associations with reduced risk have been 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 in order to calculate meta-analysis, we found eighteen other studies that have investigated aspirin use and risk of pancreatic cancer (Supplementary Table 1; plotted in Figure 1) (2,10–26). The summary association (OR=0.83; 95% CI 0.78 to 0.89) was not substantially different for the five studies having data for males (OR=0.78; 95% CI 0.67 to 0.90) (2,17,18,23 and the present study) or the eight with data for females (OR=0.84; 95% CI 0.73 to 0.97) (2,10,17,18,20,23,25 and the present study). Among all of the published studies, six have shown significantly reduced risk with use (2,10–14). Of the twelve 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 Figure 1, a trend in the odds ratio for ever regular use of aspirin is evident according to increasingly more recent mid-point of when the aspirin exposures were ascertained in the study, with decline in odds ratio of 2.3% per year (95% CI 1.3% to 3.3%, $P=10^{-5.1}$; adjusted $R^2=91\%$). For a recent study conducted with mid-point in 2011, the predicted odds ratio = 0.64 (95% CI 0.57 to 0.74, $P=10^{-10.2}$). A similar trend in odds ratio is seen for the six studies specifically examining ever regular use of low-dose aspirin (Figure 2) (2,11,12,18,20,21), with decline in odds ratio of 3.6% per year (95% CI 1.4% to 5.8%, $P=0.0014$; adjusted $R^2=84\%$). The predicted odds ratio for a recent study conducted with exposure mid-point in 2011 would be 0.59 (95% CI 0.45 to 0.76, $P=10^{-4.3}$). On average, odds ratios 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 odds ratios 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 odds ratios 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).

While our study results and the declining odds ratio 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, though 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 odds ratios 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 magnitude of benefit of aspirin use. Finally, various physiological mechanisms for risk reduction with aspirin use have been suggested, and while 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 US and elsewhere. While 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index (weight/height^2, kg/m^2)
CagA	*Helicobacter pylori* cytotoxin-associated gene A
CI	confidence interval
NSAID	non-steroidal anti-inflammation medication
OR	odds ratio

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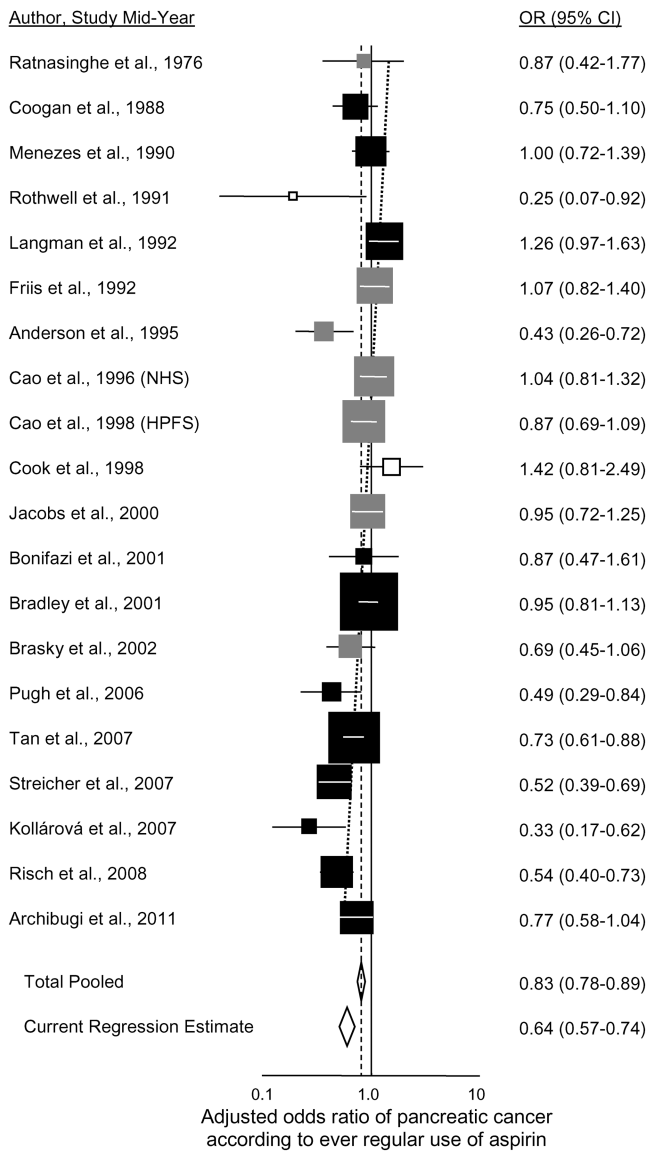

Figure 1.

Adjusted odds ratio 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 denote case-control studies; gray squares cohort studies; white squares randomized controlled trials or their extensions; diamonds denote 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 odds ratio according to study mid-year, calculated by inverse variance-weighted linear regression of the log odds ratios (8). The Current Regression Estimate is the regression odds ratio predicted at the mid-point of the most recent study (2011).

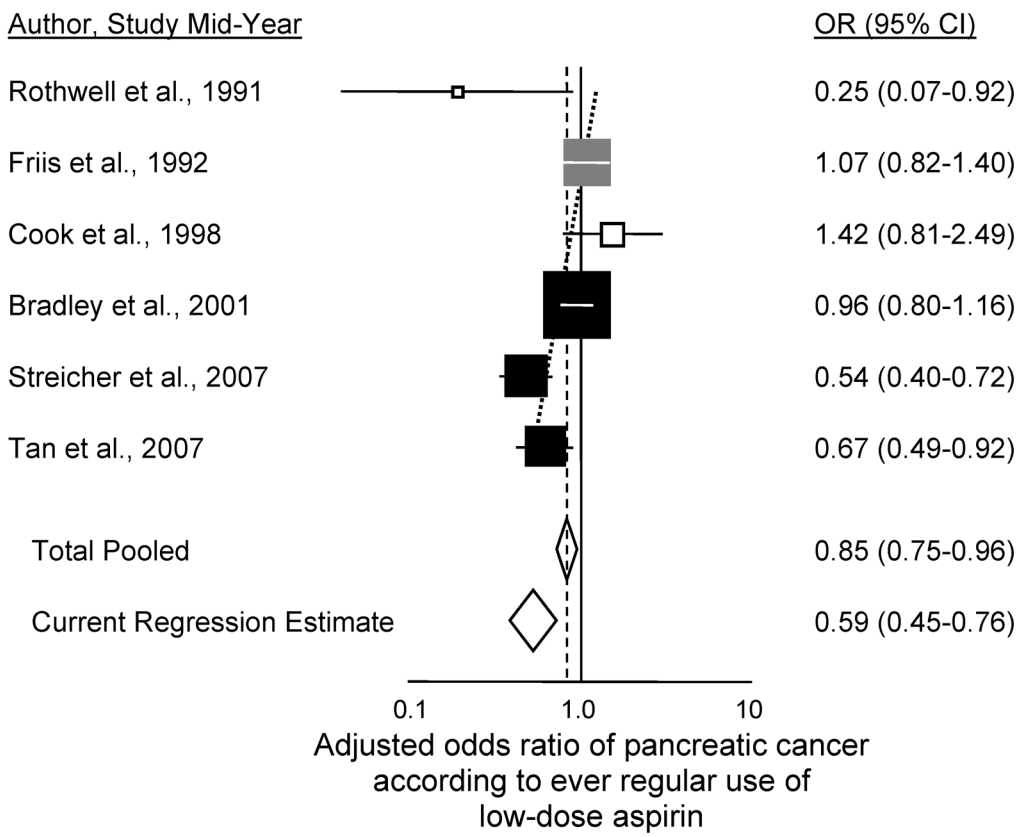

Figure 2.

Adjusted odds ratio 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 denote case-control studies; gray squares cohort studies; white squares randomized controlled trials or their extensions; diamonds denote 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 odds ratio according to study mid-year, calculated by inverse variance-weighted linear regression of the log odds ratios (8). The Current Regression Estimate is the regression odds ratio predicted at the mid-point of what would be a recent study as in Figure 1 (2011).

Table 1

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

Characteristic	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)	
Helicobacter 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)			

Characteristic	No. of cases (%)[a]	No. of controls (%)[a]	P[b]
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)	

Abbreviations: BMI, body mass index, weight/height^2 (kg/m^2); SD, standard deviation.

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

[b] *P* values calculated by chi-square distribution for categorical variables (sex, education, *Helicobacter pylori* CagA seropositivity, ABO blood group—each group vs group O) and as trends by unconditional logistic regression for continuous variables (age at interview, body mass index at age 21 years, years of smoking, 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 $10^{-4.2}$.

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)	.0034
Categories of use duration, y				
Never use	674	651	Ref.	
>0, <2	34	47	0.69 (0.43–1.10)	.12
≥2, <4	23	45	0.41 (0.24–0.69)	$10^{-3.0}$
≥4	30	51	0.53 (0.33–0.86)	.0099
Time in past since starting use, y	5.41	4.96	0.96 (0.92–1.00)	.034
Categories of starting time in past, y				
Never use	674	651	Ref.	
>0, <2	23	37	0.58 (0.34–1.00)	.051
≥2, <4	22	43	0.44 (0.26–0.75)	.0027
≥4	42	63	0.59 (0.39–0.90)	.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)	.035
≥2	15	15	2.06 (0.92–4.60)	.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)	.11
≥60, <70	32	52	0.55 (0.34–0.88)	.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)	.039
≥60, <70	33	42	0.69 (0.42–1.11)	.13
≥70	35	70	0.45 (0.29–0.70)	$10^{3.3}$

[a] Unconditional logistic regression models were used to obtain the odds ratios (ORs) and 95% confidence intervals (CIs). All models were adjusted for age at interview (continuous), sex, education category (continuous), body mass index 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]Odds ratio and confidence limits per a 10-year difference in age among aspirin ever users.

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)	.13
Duration of use, y	2.04	4.06	0.81 (0.67–0.98)	.031
Regional stage case patients vs controls:				
Ever use				
No	386	651	Ref.	
Yes	52	143	0.56 (0.39–0.80)	.0013
Duration of use, y	3.65	4.06	0.92 (0.86–0.99)	.019
Distant stage case patients vs controls:				
Ever use				
No	198	651	Ref.	
Yes	22	143	0.46 (0.28–0.75)	.0020
Duration of use, y	4.36	4.06	0.93 (0.85–1.02)	.11
Male subjects:				
Ever use				
No	378	377	Ref.	
Yes	57	83	0.64 (0.44–0.94)	.023
Duration of use, y	3.68	4.23	0.93 (0.87–1.00)	.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)	.028

[a]Unconditional logistic regression models were used to obtain the odds ratios (ORs) and 95% confidence intervals (CIs). All models were adjusted for age at interview (continuous), sex, education category (continuous), body mass index 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.