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NSAID use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project

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Abstract

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Chronic inflammation plays a pivotal role in the pathogenesis of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), the two most common types of liver cancer. A number of prior experimental studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen, may potentially protect against liver cancer. However, no observational study has examined the association between aspirin duration and dose or other over-the-counter non-aspirin NSAIDs, such as ibuprofen, and liver cancer incidence. Furthermore, the association between NSAID use and risk of ICC is unclear. As part of the Liver Cancer Pooling Project, we harmonized data on 1,084,133 individuals (HCC=679, ICC=225) from ten US-based prospective cohort studies. Cox proportional hazards regression models were used to evaluate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Current aspirin use, versus nonuse, was inversely associated with HCC (HR=0.68, 95% CI=0.57-0.81), which persisted when restricted to individuals not using non-aspirin NSAIDs and in a 5 and 10-year lag analysis. The association between aspirin use and HCC risk was stronger for users who reported daily use, longer duration use, and lower dosage. Ibuprofen use was not associated with HCC risk. Aspirin use was associated with a reduced ICC risk in men (HR=0.64, 95% CI=0.42-0.98) but not women (HR=1.34, 95% CI=0.89-2.01, $p_{interaction}$=0.01). The observed inverse association between aspirin use and liver cancer in our study, together with previous data, suggest the merit of future intervention studies of aspirin and other agents that affect chronic inflammatory pathways for HCC and possibly ICC.

Introduction

Primary liver cancer has a 5-year survival of approximately 17% (1). This malignancy is the second leading cause of cancer death worldwide (2) and the seventh leading cause in the United States (U.S.) (3). Since 1980, primary liver cancer rates have been rising (4, 5) and have been among the most rapidly increasing cancer types in the U.S. and other Western countries (6). In addition to poor survival and increasing incidence, primary liver cancer is characterized by aggressive growth, lack of effective screening or early detection methods, and high rates of metastases. Thus, developing preventive strategies for reducing the substantial disease burden associated with primary liver cancers is of considerable clinical and public health importance (5, 7, 8).

There are two major histologic types of primary liver cancer: hepatocellular carcinoma (HCC), which is the dominant histologic type of liver cancer in the U.S. and accounts for approximately 75% of cases, and intrahepatic cholangiocarcinoma (ICC), which is the second most common histologic type and accounts for approximately 12% of cases. The other 13% of cases are rare tumor types (e.g., hepatoblastoma and sarcoma) or poorly specified (9). Risk factors for HCC include chronic hepatitis B or C virus (HBV or HCV) infection, excessive levels of alcohol consumption, aflatoxin exposure, obesity, and diabetes (10). While ICC is commonly associated with primary sclerosing cholangitis and inflammatory bowel diseases, a recent meta-analysis identified potential common risk factors for HCC and ICC, such as chronic HBV and HCV infection, excessive alcohol consumption, diabetes, and obesity (11).

Chronic inflammation is a common feature underlying the etiology of both HCC and ICC (12, 13). Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are potential chemopreventive agents for primary liver cancer. Observational studies and clinical trials have reported inverse associations between aspirin use and incidence of gastrointestinal tract cancers (14-19). *In vivo* and *in vitro* studies (20-22) and two observational studies (23, 24) suggest similar inverse associations for primary liver cancer. However, associations between duration or dosage of aspirin use and liver cancer risk, or with commonly used 'over-the-counter' (OTC) non-aspirin NSAIDs (e.g., ibuprofen) have not been previously described. Furthermore, possible associations between NSAIDs and ICC have not been studied. Therefore, we conducted a study of pooled data from ten U.S.-based prospective cohort studies in order to examine associations of aspirin and OTC non-aspirin NSAIDs (i.e., ibuprofen) with HCC and ICC.

Materials and Methods

Study Population

The Liver Cancer Pooling Project (LCPP) has been described previously (25). Briefly, all U.S.-based cohort studies that are members of the National Cancer Institute (NCI) Cohort Consortium were invited to participate in the LCPP. Of the 14 studies that agreed to participate, ten studies contributed data on both NSAID use and liver cancer histology (Supplementary Table S1).

Outcomes

While follow-up times varied by parent study, participants in the LCPP were followed-up for outcomes for an average of 11.9 years. Incident primary liver cancer cases (defined as International Classification of Diseases, 10th edition [ICD-10] diagnostic code C22) among LCPP cohort participants were ascertained by various methods, depending on the parent cohort: linkage to state cancer registries, medical record review, National Death Index linkage, or a self-report to the parent cohort study. Cases missing histology information were excluded (n=840). Cases were then classified as HCC (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] histology codes of 8170-8175) or ICC (ICD-O-3 histology codes of 8032-8033, 8041, 8050, 8070-8071, 8140-8141, 8160, 8260, 8480, 8481, 8490, and 8560). Cases with all other histology codes were excluded from the primary analysis (n=225). Finally, individuals with missing aspirin information were excluded from the analytic cohort (HCC n=285, ICC n=71, non-case n=303,119). Thus, the current study included 679 HCC cases, 225 ICC cases, and 1,083,229 non-cases.

Exposure assessment

With the exception of BWHS, self-reported questionnaires collected information on use of both aspirin and non-aspirin NSAIDs, either currently or during the previous year (Supplementary Table S2). Four studies (AHS, USRT, PLCO, and CPSII) specifically asked about ibuprofen use. Five studies (NIH-AARP, BCDDP, PLCO, CPSII, WHI) asked about frequency of aspirin use (categorized as non-user, less than daily, daily, and more than daily), and five studies (AHS, BCDDP, CPSII, BWHS, WHI) also asked about duration (categorized as non-user, <5, and ≥5 years of aspirin use). Two studies (CPSII and WHI) ascertained absolute dose (categorized as non-user, <163, and ≥163 mg). NSAID use was ascertained at baseline or first follow-up questionnaire for all cohorts.

Statistical Analysis

Cox proportional hazard regression analysis was used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the associations of aspirin or ibuprofen use with HCC and ICC risk, utilizing follow-up time as the underlying time metric. The proportional hazards assumption was tested using an interaction term between aspirin or ibuprofen (defined as current use versus non-users) and log(time) in models that included confounders. The proportional hazards assumption was not observed to be violated ($p \geq 0.05$).

Effect measure modification by sex, cigarette smoking (evaluated as never/former/current and cigarettes/day [continuous]), alcohol consumption (evaluated as ever/never and drinks/day [continuous]), self-reported history of diabetes, and ibuprofen use was assessed using likelihood ratio tests comparing regression models with and without a multiplicative term (26).

Potential confounders (27) were examined to determine if they were associated with 1) the exposure in the general population (i.e., entire cohort), utilizing a logistic regression model and 2) the outcome among the unexposed (i.e., non-NSAID users), utilizing a Cox proportional hazards regression, by examining the magnitude of association (28). If a potential confounder was associated with the exposure and outcome, then the full model was then evaluated both with and without the covariate of interest. If the covariate significantly contributed to the full model ($p<0.05$), it was retained for the final model (29, 30); age at questionnaire administration (years, continuous), sex (male [referent]/female), race (Caucasian [referent], African American, Asian/Pacific Islander, American Indian/Alaskan Native, Other), smoking (never/current/former), alcohol consumption (categorized drinks/day [0, >0-<1, 1-3, >3]), self-reported history of diabetes (yes/no), and self-reported or directly measured body mass index (BMI, kg/m^2, continuous) met this criterion and were included in all final models. We adjusted for parent study in all models using fixed study effects. We also used fixed-effects meta-analysis to estimate a summary HR and assess heterogeneity using I^2. An I^2 of 0% indicates no heterogeneity, whereas larger values indicate increasing heterogeneity between studies (31). Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and STATA version 13 (StataCorp LP, College Station, TX). All p-values are two-sided.

Nested Case-Control Study of HBV/HCV

As individuals with HBV/HCV infection are at the highest risk of developing chronic liver disease, they are often advised to stop taking NSAIDs. Thus, we wanted to examine if our results could further be confounded by HBV/HCV status. However, serum samples were not available from all persons, so a nested case-control analysis was conducted. At time of diagnosis, all cases with serum were matched to non-cases (controls) with serum on age, race/ethnicity, sex, date of baseline blood collection and parent study. Age and date-of-blood draw were matched within 2 months. Within this nested case-control study, conditional logistic regression was utilized to examine potential confounding by HBV and HCV, adjusting for BMI, smoking, alcohol, and history of diabetes.

To determine HBV status, hepatitis B surface antigen (HBsAg) was assayed using the Bio-Rad GS HBsAg 3.0 enzyme immunoassay (Bio-Rad Laboratories, Redmond, WA, USA). HBsAg is a marker of active HBV infection and the marker on which HBV carrier status is based. To determine HCV status, antibody to hepatitis C virus (anti-HCV) was assessed using the Ortho HCV Version 3.0 ELISA test system (Ortho-Clinical Diagnostics, Inc.). A positive anti-HBV test indicates that the person is, or was, infected with HCV. Current HCV infection can be confirmed via determination of HCV RNA. As the correlation between anti-HCV positivity and HCV RNA positivity is high, the current study elected not to incur the additional costs of running the confirmatory tests.

Sensitivity Analyses

To reduce the potential influence of concurrent exposure to non-aspirin NSAIDs, we examined aspirin use among individuals who did not use ibuprofen or other non-aspirin NSAIDs. Next, to evaluate whether the associations were entirely driven by the inverse associations previously reported in the NIH-AARP cohort (24), we repeated analyses after excluding this study. As a sensitivity analysis for duration of aspirin use, we conducted a lag analysis, excluding cases that developed within the first 5 or 10-years of follow-up by delaying the start of follow-up for all participants. Finally, we analyzed all confirmed or suspected HCC cases, which included HCC cases (ICD-O-3 histology codes of 8170-8175) and additional suspected HCC cases defined as ICD-O-3 histology codes of 8000, 8010, or missing.

Results

Demographic characteristics of aspirin users and non-users at baseline are shown in Table 1. Forty-four percent of the participants reported current aspirin use. Compared to non-users of aspirin, aspirin users were more likely to be men, white, overweight (BMI>25), heavy drinkers (>3 drinks/day), non-smokers, and report a history of diabetes.

Current aspirin use was associated with a 32% reduction in risk of HCC, compared to participants who did not use aspirin (HR=0.68, 95% CI=0.57-0.81) (Table 2), and studies were homogeneous (I^2=0%, p=0.8). Results were similar when restricted to people who did not use other non-aspirin NSAIDs (HR=0.63, 95% CI=0.50-0.78). Less than once daily or once daily aspirin use was associated with an approximately 35% and 32% reduction of HCC risk (HR=0.65, 95% CI=0.51-0.82 and HR=0.68, 95% CI=0.53-0.87, respectively). However, no association was observed among participants who used aspirin more than once a day. Longer duration of aspirin use (≥ 5 years) was associated with a nonsignificantly greater decreased HR of HCC than shorter duration (<5 years) (HR=0.70, 95% CI=0.42-1.16 and HR=0.84, 95% CI=0.49-1.44). Associations were stronger among those taking low-dose aspirin (<163 mg; HR=0.39, 95% CI=0.17-0.91) compared to higher-dose aspirin (≥163 mg; HR=0.67, 95% CI=0.42-1.08), although we had small case numbers for these analyses. In contrast to aspirin, ibuprofen use was not associated with HCC risk (HR=1.01, 95% CI=0.72-1.42). However, when ibuprofen use was restricted to non-users of aspirin and other NSAIDs, a nonsignificant decreased risk of HCC was noted (HR=0.78, 95% CI=0.45-1.38). For overall ICC, no association was observed for either aspirin or ibuprofen use (HR=0.94, 95% CI=0.70-1.27 and HR=1.17, 95% CI=0.64-2.15, respectively).

Table 3 shows sensitivity analyses after excluding the NIH-AARP cohort, for which an association between aspirin and liver cancer was previously shown, and a 5 and 10-year lag-analysis. When then NIH-AARP cohort was excluded from the analysis, current aspirin remained inversely associated with HCC risk – both overall (HR=0.72, 95% CI=0.57-0.90) and when restricted to non-users of other NSAIDs (HR=0.66, 95% CI=0.50-0.86). Similar results were found in the 5-year lag analysis (overall HR=0.75, 95% CI=0.60-0.94 and non-user of other NSAIDs HR=0.62, 95% CI=0.46-0.82). Results were consistent in the 10-year lag analysis, but sample size was small.

As shown in Supplementary Table S3, there was some evidence of a multiplicative interaction between aspirin use and sex and history of diabetes for ICC (p=0.01 and p=0.01, respectively) but not for HCC (p=0.9 and p=0.1, respectively). Among men, current aspirin users had 36% lower risk of ICC (HR=0.64; 95% CI=0.0.42-0.98) than non-users. Whereas, no association was observed in women (HR=1.34; 95% CI=0.89-2.01). There was also some evidence of a multiplicative interaction between aspirin use and ibuprofen use for HCC (p=0.09) but not ICC (p=0.7). However, sample size was limited. We also observed generally similar findings when we expanded our HCC case definition to include suspected but not histologically confirmed HCC cases (Supplementary Table S4).

Among the HCC cases tested (n=158), 42 (26.6%) were positive for anti-HCV and 5 (3.2%) were positive for HBsAg. Among the matched controls (n=397), 10 (2.5%) were positive for anti-HCV and 3 (0.8%) were positive for HBsAg. In this nested-case control study, current aspirin use was associated with a 42% reduction in risk of HCC, compared to participants who did not use aspirin (HR=0.58, 95% CI=0.36-0.93). When further adjusted for HBsAg and anti-HCV status, the results were not substantially altered (HR=0.60, 95% CI=0.35-1.04).

Discussion

In the current study, we examined the association between aspirin and ibuprofen use and risk of HCC and ICC, stratified by dose, frequency, and duration of use. In our analyses, current aspirin use was associated with 32% lower risk of HCC. The inverse associations were robust in sensitivity analyses that excluded ibuprofen and other non-aspirin NSAID users and after excluding the NIH-AARP cohort, which made up about half of our cases. Among aspirin users who reported taking aspirin once daily, we found risk reductions for HCC of 32%. Additionally in our study, aspirin use was associated with a 36% reduced risk of ICC in men but not women.

Three previous studies have reported an association between NSAID use and risk of liver cancer (23, 24, 32). In a previous study from the NIH-AARP cohort, any reported aspirin use in the 12 months prior to baseline was associated with a 41% decreased risk of HCC incidence and a 45% decreased risk of liver disease mortality (24). Across varying frequencies of aspirin use, risk reductions for HCC incidence were similar (24). In another US-based, case-control study, regular NSAID use (at least 4 days/week for 3 months) was associated with a non-significant 10% reduction in liver cancer. However, this study was limited by a small number of cases (n=49) (23). Finally, a Canadian, population-based study of rheumatoid arthritis patients treated with long-term NSAID therapy reported nearly twice the expected rate of liver or gallbladder cancer. However, this results were non-significant and based on only 5 observed cases (32). Additionally, this study was focused on rheumatoid arthritis patients that were actively being treated for their disease, which is very different population than individuals taking a daily aspirin for prevention purposes.

Similar to the previous study from the NIH-AARP cohort (24), we report homogeneous associations between aspirin use and HCC risk by sex. However, aspirin use among men, and not women, was associated with a reduced risk of ICC that was similar in magnitude to the association between aspirin use and HCC risk. Although the explanation of this is unclear, it could reflect etiological differences between HCC and ICC or it could be a chance finding. Additionally, we report that taking aspirin, on average, more than once daily or higher dosage aspirin (≥163 mg) was not associated with a decreased risk of HCC. Thus, individuals who chronically use high-dose aspirin may differ in important ways from those who use lower dose aspirin for cardiovascular benefits. Finally, in the group of participants reporting both ibuprofen use, the possible converse association between aspirin use and HCC risk is potentially due to ibuprofen use interfering with the antiplatelet effects of aspirin (33).

Chronic inflammation is thought to contribute to the pathogenesis of both HCC and ICC (12, 13). COX-2, an enzyme that mediates inflammation and is usually expressed only at low levels in normal tissue, is overexpressed in response to a broad spectrum of pro-inflammatory stimuli, including those that mediate hepatic carcinogenesis (34). Overexpression of COX-2 has been reported in premalignant, malignant, and metastatic HCC tissues, suggesting COX-2 may be involved several stages of hepatocarcinogenesis, beginning with the earliest stages of initiation. Similarly, COX-1, an enzyme that is expressed in most normal tissue, has been reported to be more highly expressed in cirrhotic tissue compared to surrounding tissue and in well-differentiated HCC compared to poorly-differentiated HCC (34). Such a result suggests that COX-1 may also be involved in the early stages of tumor growth. In tumors, COX-2 and possibly COX-1 overexpression leads to increased prostaglandin levels, which can increase angiogenesis, cellular proliferation, and cell invasiveness and inhibit apoptosis (34). Aspirin and ibuprofen inhibit and modify both COX enzymatic pathways necessary for prostaglandin synthesis, thus inhibiting HCC cellular growth through cell cycle arrest and induction of apoptosis (34). However, when aspirin and ibuprofen are taken concomitantly, ibuprofen interferes with the aspirin binding of platelet COX-1 via competitive inhibition or by inducing conformational changes in the COX-1 enzyme that slows down the rate of acetylation by aspirin (35, 36). Aspirin and ibuprofen may also modulate hepatocarcinogenesis through non-COX pathways, such as mitogen-activated protein kinase and PI3K/Akt pathways (21, 37), or down regulation of pro-inflammatory cytokines (38). While aspirin and ibuprofen are thought to act through similar mechanistic pathways, we may not see an association between ibuprofen use and HCC risk due to the fact that ibuprofen has a much shorter antiplatelet effect duration (a few hours) compared to aspirin (7-10 days) (39). Low-dose aspirin does not work through the conventional COX pathways or downregulation of pro-inflammatory cytokines. However, research suggests that low-dose aspirin has anti-inflammatory properties in humans, through triggering 15-epi-lipoxin A_4 synthesis and ALX expression (40).

In an experimental study, aspirin decreased inflammation, fibrosis severity, and HCC progression in a mouse model of chronic HBV immune-mediated HCC but not when HCC was nonimmunologically induced (41). Thus, NSAIDs may differentially impact risk for viral and non-viral hepatocarcinogenesis. While the current study was adjusted for several major confounders, including alcohol consumption, obesity, and diabetes, we were unable to assess HBV and HCV status of all individuals. However, within the nested case-control study with information on HBsAg and anti-HCV status, results were not altered.

This study is susceptible to residual confounding for several reasons. We considered the possibility of a healthy-user bias, whereby individuals that consistently engage in beneficial behaviors (e.g., daily aspirin use to reduce risk of cardiovascular disease) may be fundamentally different from individuals that do not (42). Thus, aspirin use may reflect a healthier lifestyle in general. However, when results were stratified by smoking or alcohol consumption, we did not observe any notable differences. Further, the use of other concomitant medications (e.g., statins), which may confound the association between aspirin use and liver cancer (43, 44), were also not assessed in this analysis. Confounding by indication is also a concern in the present study, as patients at highest HCC risk (e.g., those with cirrhosis and portal hypertension with thrombocytopaenia) may be advised to avoid aspirin use due to risk of gastrointestinal bleeding and renal failure (45). However, we did not have information on preexisting liver disease. Thus, additional research is needed to examine whether aspirin use is inversely associated with risk among individuals without preexisting liver disease.

Several additional limitations should also be noted. All data on aspirin and non-aspirin NSAIDs were based on self-report at baseline interview and are subject to measurement error. Additionally, data on dosage, duration, frequency, and time-varying change in use was not captured consistently in the questionnaires of the contributing studies. As aspirin use for the prevention of colorectal cancer is subject to duration (46), further research is needed to determine if liver cancer has a similar necessary lag time before observing beneficial effects. Our lag analysis did not note any differences for when outcomes in the first 5 and 10-years were excluded, but for the studies with duration information, there was a non-significant decreased risk for more than 5 years of aspirin use. More research is also needed on the time-varying change in aspirin use. Participants may also alter their aspirin use during follow-up. Thus, the parent studies may have introduced measurement error by not assessing aspirin use repeatedly. Finally, these results may not be generalizable to non-white, younger, or Hispanic populations, as the cohorts included in our analysis were primarily composed of white, older age, non-Hispanic participants.

This study had a large sample size to evaluate the association between aspirin and ibuprofen use and liver cancer incidence by the two major subtypes, HCC and ICC. Although the case numbers for ICC in this pooled analysis were limited. The large sample size of the LCPP, compared to previous studies, also allowed us to investigate potential effect modification by sex, smoking, and alcohol consumption; however, the number of cases for the stratified analyses is still relatively small. Finally, questionnaires utilized in these studies allowed participants' to self-report use of OTC products like aspirin and ibuprofen that are likely to be incompletely ascertained in studies based on medical records or prescription databases.

In conclusion, our finding of an inverse association between aspirin use and HCC, and possibly ICC among men, suggests that aspirin may reduce the risk of HCC and ICC in the U.S. Further research is needed to elucidate the role of aspirin use, specifically frequency, duration, dosage, and combinations of these factors, in relation to HCC and ICC in the U.S. In particular, our results suggest the need for intervention trials which assess the potential role of aspirin and other agents in the modulation of HCC, ICC, and related endpoints.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of participants in the Liver Cancer Pooling Project by current aspirin use.

	Aspirin Non-Users (N=606,663)		Aspirin Users (N=477,470)	
	N	**(%)**	**N**	**(%)**
Outcome				
Non-Cases	606,179	(99.92)	477,050	(99.91)
HCC	364	(0.06)	315	(0.07)
ICC	120	(0.02)	105	(0.02)
Age at Entry				
<50	124,428	(20.51)	55,624	(11.65)
50-59	178,233	(29.38)	141,274	(29.59)
60-69	228,897	(37.73)	224,413	(47.00)
≥70	75,076	(12.38)	56,152	(11.76)
Missing	29		7	
Sex				
Male	161,777	(26.67)	227,231	(47.59)
Female	444,886	(73.33)	250,239	(52.41)
Race				
White	500,570	(83.10)	441,925	(93.06)
Black	73,601	(12.22)	18,198	(3.83)
Asian/Pacific Islander	11,780	(1.96)	4,034	(0.85)
American Indian/Alaskan Native	1,266	(0.21)	881	(0.19)
Other	15,129	(2.51)	9,847	(2.07)
Missing	4,317		2,585	
Body Mass Index (kg/m^2)				
<18.5	7,502	(1.28)	4,530	(0.97)
18.5-24.9	251,394	(42.77)	183,585	(39.17)
25-29.9	208,682	(35.50)	187,999	(40.12)
≥30	120,262	(20.46)	92,516	(19.74)
Missing	18,823		8,840	
Diabetes				
No	568,533	(94.72)	440,926	(92.70)
Yes	31,674	(5.28)	34,697	(7.30)
Missing	6,456		1,847	
Alcohol (drinks/day)				
Non-Drinker	161,511	(28.27)	97,688	(21.69)
>0-<1 drink	322,465	(56.44)	253,415	(56.27)
1-3 drinks	68,445	(11.98)	72,060	(16.00)
>3 drinks	18,957	(3.32)	27,228	(6.05)
Missing	35,285		27,079	
Cigarette Smoking Status				
Never Smoker	300,077	(50.32)	192,369	(40.97)

	Aspirin Non-Users (N=606,663)		Aspirin Users (N=477,470)	
	N	**(%)**	**N**	**(%)**
Former Smoker	205,550	(34.47)	197,922	(42.15)
Current Smoker	90,668	(15.21)	79,251	(16.88)
Missing	10,368		7,928	

Table 2

Adjusted* Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations Between NSAID Use and Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Incidence, Liver Cancer Pooling Project.

	Hepatocellular Carcinoma				Intrahepatic Cholangiocarcinoma			
	Cases	**Person-years**	**HR**	**(95% CI)**	**Cases**	**Person-years**	**HR**	**(95% CI)**
Aspirin Use								
Non-user	313	6,686,327	1.0	–	105	6,684,656	1.0	–
Any current use	368	5,037,223	0.68	(0.57 - 0.81)	95	5,035,905	0.94	(0.70 - 1.27)
Frequency of use, average times per day								
Non-user	196	2,335,809	1.0	–	54	2,334,914	1.0	–
Less than Once Daily	112	1,658,658	0.65	(0.51 - 0.82)	38	1,658,171	0.82	(0.53 - 1.27)
Once Daily	92	951,535	0.68	(0.53 - 0.87)	24	951,104	0.80	(0.49 - 1.31)
More than Once Daily	20	249,938	0.92	(0.58 - 1.46)	9	249,869	1.59	(0.78 - 3.23)
Duration of use, years								
Non-user	56	1,164,323	1.0	–	15	1,163,940	1.0	–
<5	18	341,066	0.84	(0.49 - 1.44)	5	340,939	0.84	(0.30 - 2.41)
≥5	21	497,395	0.70	(0.42 - 1.16)	10	497,284	1.27	(0.56 - 2.89)
Dosage of aspirin, mg								
Non-user	89	1,887,651	1.0	–	42	1,887,342	1.0	–
<163	6	197,820	0.39	(0.17 - 0.91)	4	197,816	0.95	(0.33 - 2.70)
≥163	23	518,242	0.67	(0.42 - 1.08)	12	518,168	1.08	(0.56 - 2.08)
Aspirin Use, restricted to non-users of other NSAIDs								
Non-user	223	4,743,276	1.0	–	70	4,741,957	1.0	–
Any current use	142	3,236,674	0.63	(0.50 - 0.78)	56	3,235,969	1.08	(0.74 - 1.57)
Ibuprofen Use								
Non-user	150	2,534,499	1.0	–	42	2,533,705	1.0	–
Any current use	46	1,092,098	1.01	(0.72 - 1.42)	15	1,091,857	1.17	(0.64 - 2.15)
Ibuprofen Use, restricted to non-users of aspirin and other NSAIDs								
Non-user	87	1,411,196	1.0	–	21	1,410,729	1.0	–
Any current use	15	485,570	0.78	(0.45 - 1.38)	7	485,522	1.51	(0.63 - 3.64)

* Adjusted for: sex, age (continuous), race (white, black, Asian/Pacific Islander, American Indian/Alaskan Native, other), cohort (AARP, AHS, USRT, PLCO, HPFS, CPSII, IWHS, BWHS, WHI, NHS), BMI (continuous), smoking status (non-smoker, former smoker, current smoker), alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day), and history of diabetes (yes/no).

Table 3

Adjusted* Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations Between Aspirin Use and Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Incidence; Sensitivity Analysis Excluding the NIH-AARP Cohort and Lag-Analysis, Liver Cancer Pooling Project.

	Hepatocellular Carcinoma				Intrahepatic Cholangiocarcinoma			
	Cases	**Person-years**	**HR**	**(95% CI)**	**Cases**	**Person-years**	**HR**	**(95% CI)**
Excluding the NIH-AARP Cohort								
Aspirin Use								
Non-user	220	5,977,872	1.0	–	81	5,976,554	1.0	–
Any current use	126	3,492,787	0.72	(0.57 - 0.90)	49	3,492,031	0.98	(0.68 - 1.42)
Aspirin Use, restricted to non-users of other NSAIDs								
Non-user	173	4,392,942	1.0	–	60	4,391,840	1.0	–
Any current use	86	2,584,988	0.66	(0.50 - 0.86)	37	2,584,482	1.08	(0.71 - 1.66)
Lag-analysis, excluding the first five years of follow-up								
Aspirin Use								
Non-user	163	3,293,179	1.0	–	50	3,292,426	1.0	–
Any current use	172	2,783,718	0.75	(0.60 - 0.94)	51	2,783,146	0.82	(0.54 - 1.23)
Aspirin Use, restricted to non-users of other NSAIDs								
Non-user	119	2,350,842	1.0	–	31	2,350,219	1.0	–
Any current use	84	1,879,068	0.62	(0.46 - 0.82)	31	1,878,714	1.03	(0.62 - 1.73)
Lag-analysis, excluding the first ten years of follow-up								
Aspirin Use								
Non-user	66	1,596,930	1.0	–	20	1,596,605	1.0	–
Any current use	47	1,120,116	0.74	(0.50 - 1.08)	16	1,119,940	0.95	(0.48 - 1.85)
Aspirin Use, restricted to non-users of non-aspirin NSAIDs								
Non-user	54	1,287,268	1.0	–	17	1,286,985	1.0	–
Any current use	34	932,565	0.70	(0.45 - 1.08)	13	932,410	0.98	(0.47 - 2.04)

*Adjusted for: sex, age (continuous), race (white, black, Asian/Pacific Islander, American Indian/Alaskan Native, other), cohort (AARP, AHS, USRT, PLCO, HPFS, CPSII, IWHS, BWHS, WHI, NHS), BMI (continuous), smoking status (non-smoker, former smoker, current smoker), alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day), and history of diabetes (yes/no).