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ARTICLE

Nonsteroidal Anti-inflammatory Drug Use, Chronic Liver Disease, and Hepatocellular Carcinoma

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Background Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce chronic inflammation and risk of many cancers, but their effect on risk of hepatocellular carcinoma (HCC) and death due to chronic liver disease (CLD) has not been investigated.

Methods We analyzed prospective data on 300 504 men and women aged 50 to 71 years in the National Institutes of Health–AARP Diet and Health Study cohort and linked self-reported aspirin and nonaspirin NSAID use with registry-confirmed diagnoses of HCC (n=250) and death due to CLD (n=428, excluding HCC). We calculated hazard rate ratios (RRs) and their two-sided 95% confidence intervals (CIs) using Cox proportional hazard regression models with adjustment for age, sex, race/ethnicity, cigarette smoking, alcohol consumption, diabetes, and body mass index. All tests of statistical significance were two-sided.

Results Aspirin users had statistically significant reduced risks of incidence of HCC (RR = 0.59; 95% CI = 0.45 to 0.77) and mortality due to CLD (RR = 0.55; 95% CI = 0.45 to 0.67) compared to those who did not use aspirin. In contrast, users of nonaspirin NSAIDs had a reduced risk of mortality due to CLD (RR = 0.74; 95% CI= 0.61 to 0.90) but did not have lower risk of incidence of HCC (RR = 1.08; 95% CI = 0.84 to 1.39) compared to those who did not use nonaspirin NSAIDs. The risk estimates did not vary in statistical significance by frequency (monthly, weekly, daily) of aspirin use, but the reduced risk of mortality due to CLD was statistically significant only among monthly users of nonaspirin NSAIDs compared to non-users.

Conclusions Aspirin use was associated with reduced risk of developing HCC and of death due to CLD whereas nonaspirin NSAID use was only associated with reduced risk of death due to CLD.

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Liver cancer, particularly hepatocellular carcinoma (HCC), is the fifth most frequently occurring cancer worldwide and the third most common cause of cancer mortality (1). Although liver cancer is more common in developing countries, incidence and mortality rates have been rapidly rising in the United States since the 1980s (2,3). HCC, especially with late presentation, is characterized by aggressive growth, frequent metastases, and poor survival rates, which demands intensive research on prevention of HCC to reduce the substantial disease burden (3–5). Major risk factors for HCC include chronic infections with hepatitis B and hepatitis C viruses, excessive alcohol consumption, certain rare metabolic disorders, and consumption of food contaminated with aflatoxin. In recent years, HCC has also been associated with obesity, diabetes, and the metabolic syndrome (6).

Almost all HCCs occur in persons with preexisting chronic liver disease (CLD) (2). Chronic hepatic inflammation, secondary to CLD, represents an early stage in the carcinogenesis process. In general, chronic inflammation is associated with persistent cell damage and consecutive regeneration, potentially leading to changes such as fibrosis and cirrhosis and eventual hepatocellular carcinoma (7). Inflammation-mediated events, such as the production of cytokines, reactive oxygen species, and mediators of the inflammatory pathways, such as cyclooxygenase (COX), may contribute to tumor formation (8). It is also hypothesized that the existence of an inflammatory microenvironment increases the stochastic likelihood of neoplastic progression in a nonspecific manner, synergistically with other host and environmental risk factors (9).

Investigating the cancer chemopreventive role of modifiable anti-inflammatory agents, especially the widely used nonsteroidal anti-inflammatory drugs (NSAIDs), is an important prevention research area (10,11). NSAIDs, including aspirin and nonaspirin NSAIDs, are widely used as analgesic drugs, and aspirin is widely used in the chemoprevention of cardiovascular and cerebrovascular disease (12). Observational studies and clinical trials point to the substantial

protective effects of aspirin on colorectal cancer and other digestive tract cancers, and modest risk reductions for breast and prostate cancers (10,13–18).

In vitro studies and animal experiments suggest that NSAIDs have preventive and therapeutic benefit for HCC (19–21). However, only a few human studies have investigated the association of NSAID use with liver cancer (22, 23). Results in these studies are inconsistent, likely due to a limited number of cancer endpoints. Further, whether reduction of inflammation via NSAID use decreases the risk of developing HCC or death due to CLD is not known. To examine this question, we conducted an analysis among participants in the National Institutes of Health (NIH)–AARP (formerly the American Association of Retired Persons) Diet and Health Study, a large prospective study with comprehensive data on NSAID use.

Methods

Study Population

The NIH–AARP Diet and Health study cohort included men and women, aged 50 to 71 years at recruitment, from six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). The study has been described in detail elsewhere (24). Briefly, a self-administered questionnaire to assess demographic, diet, and lifestyle characteristics was satisfactorily completed at baseline in 1995–1996 by 566 309 participants. Subsequently, a risk factor questionnaire was mailed 6 months after completion of the baseline questionnaire to living participants who did not have self-reported colon, breast, or prostate cancer at baseline. The risk factor questionnaire collected additional information, including information on the use of NSAIDs, and was completed by 334 906 individuals. For our analyses, we excluded individuals for whom either the baseline (n = 6959) or the risk factor questionnaire (n = 3424) was completed by proxy; those with registry-linkage–confirmed prevalent cancers (n = 2781); those with self-reported prevalent cancers at the administration of the baseline questionnaire (n = 14 565) and risk factor questionnaire (n = 1517); those who were caloric-intake outliers (ie, those with total energy intake more than twice the interquartile range of log-transformed energy intake) (n = 2503); those who died before their questionnaires were scanned (n = 11); and those with missing data on use of both aspirin and nonaspirin NSAIDs (n = 2642). The resulting analytic cohort for our primary analysis included 300 504 participants (n = 175 366 men and n = 125 138 women). The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, NIH. All participants gave informed consent by virtue of completing and returning the questionnaire. For information on cohort follow-up and identification of outcomes (deaths due to CLD and incident HCC), please see the Supplementary Methods (available online).

Assessment of NSAIDs Use

The risk factor questionnaire assessed NSAIDs use (yes or no) during the previous 12 months. Aspirin products were ascertained as generic aspirin or by name brand (Bayer, Bufferin, Anacin, Ecotrin, Excedrin). Nonaspirin NSAIDs were identified by 19 generic and trade names that represented seven drugs: ibuprofen (generic ibuprofen, Advil, Nuprin, Motrin), naproxen (Aleve, Naprosyn, Anaprox), ketoprofen (Orudis, Ketoprofen), piroxicam (Feldene, Piroxicam), sulindac (Clinoril, Sulindac), indomethacin (Indocin, Indomethacin), and nambumetone (Relafen). The questionnaire specifically asked respondents to exclude from consideration any nonNSAIDs analgesics such as acetaminophen (Tylenol) and other pain relievers. Selective COX2 inhibitors (eg, Celecoxib, Rofecoxib) were not marketed at the time of questionnaire administration. Participants were asked, in separate questions, how frequently they took aspirin and/or nonaspirin NSAIDs: less than 2 times per month, 2 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, 5 to 6 times per week, 1 time per day, or 2 or more times per day. Because of small numbers in some of the categories, we collapsed these responses into three categories of frequency of use: monthly (≤2–3 times per month), weekly (1–2 times to 5–6 times per week), or daily use (≥1 times per day).

Statistical Analysis

Hazard rate ratios (RRs) and 95% confidence intervals (95% CIs) were estimated for NSAIDs exposure (aspirin and nonaspirin NSAIDs; individually and in combination) and HCC incidence and CLD mortality outcomes using Cox proportional hazards regression models, with follow-up time as the underlying time metric. The proportional hazard assumption was verified using a time-by-exposure interaction model. Several sensitivity analyses to assess the relationship between NSAID use and CLD and HCC were also conducted. All tests were two-sided, and *P* values less than .05 were considered to denote statistical significance. Statistical analysis was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC). For more details on the statistical analysis, please see the Supplementary Methods (available online).

Results

The total analytic cohort of 300 504 that included 175 366 (58.4%) men and 125 138 (41.6%) women had an overall mean age of 62.8 (standard deviation = ±5.3) years at baseline (Table 1). Most participants were non-Hispanic white (92.6%). Slightly more than one-third (35.9%) of participants were "never smokers," whereas the rest included former smokers (48.2%) and current smokers (12.7%). One-fourth of the participants (23%) reported never drinking alcohol, whereas more than half (53.4%) reported drinking one drink per day. Less than one-tenth (8.5%) of participants reported being diabetic, and a vast majority (87.7%) reported that they were in good or excellent health.

Almost three-fourth of the participants (219 291; 73%) reported using aspirin, whereas more than half of the participants (168 499; 56.1%) reported using nonaspirin NSAIDs (Table 1). Males constituted a greater proportion of aspirin users (62.6%) than nonaspirin NSAIDs users (55.6%). There were no statistically significant differences between aspirin and nonaspirin NSAIDs users in age, race/ethnicity, body mass index levels, smoking, alcohol use, or self-reported diabetes. The distribution of covariates among aspirin-only users, nonaspirin NSAIDs only users, users of both, and users of either is also shown in Table 1. The distribution of covariates by frequency (monthly, weekly, daily) of any aspirin and any nonaspirin NSAID use is shown in Supplementary Table 1 (available online).

Table 1. Distribution of variables by type and combination of aspirin and nonaspirin NSAIDs in the National Institutes of Health (NIH)–AARP Diet and Health Study cohort*

Characteristic	Total cohort, %, N = 300504	Any aspirin users, %, n = 219291	Any nonaspirin NSAIDs users, %, n = 168499	Neither, %, n = 39949	Aspirin only, %, n = 89585	Nonaspirin NSAIDs only, %, n = 39726	Both aspirin and nonaspirin NSAIDs, %, n = 127969	Either aspirin, nonaspirin NSAIDs, or both, %, n = 257280
Age, mean (SD), y	62.8 (5.3)	62.8 (5.3)	62.2 (5.4)	63.7 (5.1)	63.6 (5.1)	62.1 (5.4)	62.3 (5.4)	62.7 (5.3)
Sex								
Male	58.4	62.6	55.6	53.4	65.8	40.4	60.5	59.2
Female	41.6	37.4	44.4	46.7	34.2	59.6	39.5	40.8
Race and/or ethnicity								
Non-Hispanic white	92.6	93.5	93.1	89.1	93.4	91.6	93.6	93.3
Non-Hispanic black	3.3	2.6	3.1	5.3	2.6	4.3	2.6	2.9
Hispanic	1.6	1.5	1.6	2.0	1.5	1.7	1.5	1.5
Asian/Pacific Islander /Native American	1.4	1.3	1.2	2.3	1.4	1.3	1.2	1.3
Missing	1.1	1.0	1.0	1.3	1.1	1.1	1.0	1.0
Body mass index								
<18.5, kg/m^2	1.0	0.9	0.8	1.4	1.0	1.0	0.8	0.9
18.5 to <25, kg/m^2	35.2	34.6	33.7	38.1	36.9	35.7	33.1	34.8
25 to <30, kg/m^2	41.2	42.4	41.3	38.3	42.4	37.5	42.5	41.7
30 to <35, kg/m^2	14.8	14.8	15.7	13.6	13.4	15.6	15.7	14.9
≥35, kg/m^2	5.8	5.3	6.5	5.9	4.3	8.0	6.0	5.7
Missing	2.1	2.0	2.0	2.8	2.0	2.1	1.9	2.0
Cigarette smoking								
Never	35.9	35.0	35.5	39.0	35.4	38.0	34.7	35.4
Quit, ≤20 cigs/day	27.1	27.3	27.6	26.1	26.6	27.0	27.8	27.2
Quit, >20 cigs/day	21.1	22.0	21.5	18.7	21.7	18.9	22.3	21.6
Current, ≤20 cigs/day	8.2	8.0	8.0	8.7	8.2	8.9	7.7	8.1
Current, >20 cigs/day	4.5	4.5	4.2	4.3	4.9	4.2	4.3	4.5
Missing	3.3	3.3	3.3	3.3	3.3	3.0	3.3	3.3
Alcohol consumption								
None	23.0	20.8	21.1	31.9	22.4	26.3	19.5	21.6
1 drink/day	53.4	54.2	55.3	48.5	52.3	54.3	55.6	54.3
2–3 drinks/day	15.7	16.8	16.0	12.5	16.7	13.1	16.9	16.3
>3 drinks/day	7.5	8.0	7.3	6.7	8.3	6.0	7.7	7.7
Missing	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3
Diabetes								
Yes	8.5	8.4	8.1	9.4	8.6	7.8	8.2	8.3
No	91.5	91.6	91.9	90.6	91.4	92.2	91.8	91.7

* NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.

Of the total of 250 individuals with HCC (ascertained through December 31, 2006) and the total of 428 deaths due to CLD (excluding HCC; ascertained through December 31, 2008), datasets for various regression models used available information on baseline self-reported NSAID use (marked as "yes," "no," or missing responses) in relation to the specific analyses (Supplementary Table 2, available online).

Users of any NSAIDs (either aspirin or nonaspirin NSAIDs or both) had a reduced risk of developing HCC (RR = 0.63; 95% CI = 0.46 to 0.87) and a reduced risk of death due to CLD (RR = 0.49; 95% CI = 0.39 to 0.61) compared to users of neither NSAIDs (Table 2). Any aspirin use (regardless of concurrent nonaspirin NSAIDs use) was statistically significantly associated with reduced risks of both HCC development (RR = 0.59; 95% CI = 0.45 to 0.77) and CLD mortality (RR = 0.55; 95% CI = 0.45 to 0.67) in comparison with non-use. The statistical significance of risk estimates did not vary by frequency (monthly, weekly, daily) of aspirin use compared to non-use. The risks for HCC incidence (RR = 0.51; 95% CI = 0.35 to 0.75) and for CLD mortality (RR = 0.50; 95% CI = 0.38 to 0.65) were even lower when restricted to aspirin-only users (ie, those who did not report concurrent nonaspirin NSAID use), overall (Table 2) and across all frequencies of use (data not shown) as compared to users of neither NSAIDs.

Nonaspirin NSAID users (regardless of concurrent aspirin use) were not at reduced risk of developing HCC (RR = 1.08; 95% CI = 0.84 to 1.39) but were at reduced risk of death due to CLD (RR = 0.74, 95% CI = 0.61 to 0.90) as compared to nonusers (Table 2). The reduced risk of CLD mortality with nonaspirin NSAIDs use, was, however, statistically significant only in monthly users (RR = 0.60; 95% CI = 0.47 to 0.76), not in daily or weekly users. Users of nonaspirin NSAIDs-only (ie, those who did not report concurrent aspirin use) did not have reduced risk for HCC incidence [RR = 0.96; 95% CI = 0.63 to 1.47] but were at reduced risk of CLD mortality [RR = 0.66; 95% CI = 0.48 to 0.91] as compared to users of neither NSAIDs. However, the reduced risk of CLD mortality was not statistically significant individually for any of the categories of frequency of use among nonaspirin NSAIDs-only users since the case count was reduced in this subgroup analysis (data not shown).

In the regression models for any NSAID use (either aspirin or nonaspirin NSAIDs or both), other measured factors associated with increased risk for both HCC and CLD outcomes were higher age (vs lower age; yearly increments), being obese (body mass index between 30 and 35) (vs body mass index between 18.5 and 25), current smoking (vs never smoking), and diabetes (vs no diabetes). Women had lower risk of HCC compared with men, and participants consuming low (1 drink per day) amount of alcohol had reduced risk for both HCC and CLD outcomes in comparison with those who reported never drinking alcohol. In comparison with non-Hispanic whites, persons of Hispanic ethnicity and Asian/Pacific Islanders/Native Americans had a higher risk of HCC, whereas non-Hispanic blacks were at lower risk of death due to CLD (P <.05 for all aforementioned statistically significant risk factors) (Supplementary Table 3, available online).

In the sensitivity analyses (data not shown), the aforementioned patterns of risk did not change when the users who reported a history of cardiovascular disease or hypertension at baseline were excluded. The patterns of risk also did not change when the outcomes in the first 5 years of follow-up were excluded (lag analysis).

Discussion

In this large, prospective study with substantial follow-up time (2 750 319 person-years for HCC incidence and 3 365 907 person-years for CLD mortality), we found evidence of risk reductions with the use of NSAIDs for both carcinogenic (incident HCC) and noncarcinogenic (death due to CLD, excluding HCC) liver disease outcomes. The use of NSAIDs among men and women aged 50 to 71 years in our cohort was associated with a 37% reduced risk of HCC incidence and 51% reduced risk of mortality due to CLD as compared to non-use. Aspirin-only users had a 49% reduced risk of HCC and a 50% reduced risk of death from CLD, whereas non-aspirin NSAIDs-only users experienced a 34% reduced risk of CLD mortality but no reduced risk of HCC in comparison with users of neither aspirin nor nonaspirin NSAIDs. Participants who reported using both aspirin and nonaspirin NSAIDs in the past 12 months had a 36% reduced risk of HCC and a 57% reduced risk of death due to CLD in comparison with users of neither NSAIDs. The reduced risk of HCC incidence and CLD mortality associated with any aspirin use was consistent across frequency (daily, monthly, and weekly) of use, whereas the reduced risk of mortality due to CLD was observed only among monthly users of any nonaspirin NSAIDs. These reductions were apparent after controlling for potential confounders, including age, sex, race/ethnicity, body mass index, smoking, alcohol, and diabetes.

Aspirin, in particular, when used exclusively or with other nonaspirin NSAIDs showed a consistent protective effect related to both HCC incidence and CLD mortality, regardless of the frequency or exclusivity of use. In several observational studies and in a few randomized clinical trials, aspirin has been shown to have a chemopreventive effect on several cancers (10,13–18). Although liver cancer has not been extensively studied, experimental and in vivo evidence for a protective effect against liver cancer and liver disease offers biological plausibility for this association. NSAIDs modulate the risk of inflammation by inhibiting the COX enzymatic pathways necessary for synthesis of prostaglandins (25). This inhibition of prostaglandins, as well as decreases in epithelial proliferation and angiogenesis, coupled with increased apoptosis, results in the reduction in the inflammatory response, which has implications for cancer prevention (26). It has also been suggested that aspirin and NSAIDs in general might play a protective role in hepatic carcinogenesis through other non-COX inhibitory pathways (20,27) and downregulation of proinflammatory cytokines (28).

The finding that use of nonaspirin NSAIDs was associated with reduced risk for CLD mortality but not HCC incidence is intriguing, particularly because aspirin use was associated with reduced risk of both of these outcomes when compared to non-use. In addition to simply being based on chance, this finding may reflect differences in COX-inhibitory actions of aspirin and nonaspirin NSAIDs (25). Aspirin irreversibly inhibits and modifies both isoforms of COX, the constitutive COX1, which is expressed in most normal tissues, and the inducible COX2, which, although undetectable in most normal tissues, is highly expressed in response to a broad spectrum

Table 2. Associations of type, combinations, and frequency of NSAID use and development of hepatocellular carcinoma or death due to chronic liver disease in the National Institutes of Health (NIH)–AARP Diet and Health Study cohort*

	Incident hepatocellular carcinoma			Death due to chronic liver disease		
Category of use	**Participants who developed hepatocellular carcinoma**	**Person-years**	**RR (95% CI)†**	**Participants who died due to chronic liver disease**	**Person-years**	**RR (95% CI)†**
Aspirin						
None	90	738 742	Referent	161	901 852	Referent
Any	159	2 031 162	0.59 (0.45 to 0.77)	265	2 487 733	0.55 (0.45 to 0.67)
Frequency of any use						
Monthly	55	875 939	0.55 (0.40 to 0.78)	109	1 076 752	0.58 (0.46 to 0.75)
Weekly	37	468 613	0.65 (0.44 to 0.96)	54	575 928	0.50 (0.37 to 0.68)
Daily	67	686 611	0.59 (0.43 to 0.81)	102	835 052	0.54 (0.42 to 0.69)
Nonaspirin NSAIDs						
None	112	1 193 333	Referent	225	1 453 467	Referent
Any	136	1 567 006	1.08 (0.84 to 1.39)	202	1 924 666	0.74 (0.61 to 0.90)
Frequency of any use						
Monthly	70	917 800	0.96 (0.71 to 1.30)	93	1 128 541	0.60 (0.47 to 0.76)
Weekly	32	369 888	1.13 (0.76 to 1.67)	62	454 982	0.99 (0.74 to 1.31)
Daily	34	279 318	1.38 (0.94 to 2.03)	47	341 143	0.89 (0.64 to 1.22)
Type and combinations of NSAIDs						
Neither	51	365 150	Referent	101	443 475	Referent
Aspirin only	61	825 518	0.51 (0.35 to 0.75)	123	1 006 791	0.50 (0.38 to 0.65)
Nonaspirin NSAIDs only	38	369 627	0.96 (0.63 to 1.47)	60	453 549	0.66 (0.48 to 0.91)
Both aspirin and nonaspirin NSAIDs	97	1 190 024	0.64 (0.45 to 0.90)	141	1 462 091	0.43 (0.33 to 0.56)
Either aspirin, nonaspirin NSAIDs, or both	196	2 385 169	0.63 (0.46 to 0.87)	324	2 922 432	0.49 (0.39 to 0.61)

* In the "Type and combinations of NSAIDs" analysis presented in the table, individual categories of NSAIDs use (ie, only aspirin, only nonaspirin NSAIDs, both, either) were compared against the referent category of "neither," which refers to individuals taking neither aspirin nor nonaspirin NSAIDs. CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; RR = hazard rate ratio.

† Cox proportional hazards regression models were used to calculate the hazard rate ratios and two-sided 95% confidence intervals, with adjustment for age, sex, race/ethnicity, body mass index, cigarette smoking, alcohol consumption, and diabetes.

of proinflammatory stimuli, including those that mediate hepatic carcinogenesis (8). Nonaspirin NSAIDs have a wide range of inhibitory potencies (ie, selectivity) toward COX1 and COX2 (8). Among the nonaspirin NSAIDs assessed in our study, some have moderate selectivity for COX1 (eg, ketoprofen, piroxicam), others inhibit both COX isoforms (dual inhibitors; eg, indomethacin, naproxen, ibuprofen), and others favor COX2 inhibition (eg, sulindac) (8,25). Because the questionnaire did not inquire about individual drug types, duration of use, and indication, it is highly likely that the nonaspirin NSAID use represents a heterogeneous exposure, perhaps resulting in an inconsistent association with HCC incidence. Furthermore, the lack of a dose response and the finding that only monthly (but not daily or weekly) use of nonaspirin NSAIDs was associated with reduced risk suggests that the findings should be interpreted with some caution, because they may also reflect an unmeasured confounder. Although sex differences did not affect risk estimates, males had a higher incidence of HCC and greater mortality due to CLD than females. Whether hormonal differences affect inflammation-mediated HCC risk (eg, estrogen-mediated inhibition of proinflammatory cytokines) is unknown and needs further investigation in translational studies (29). Although it was not possible to disintegrate the effect of NSAIDs on preexisting liver disease, in the lag analysis we did not observe different patterns of results when excluding outcomes in the first 5 years of follow-up (data not shown).

This is the first large-scale, population-based evidence for reduced risks of liver cancer incidence and liver disease mortality associated with the use of NSAIDs. In a previous US-based, multicentric, case–control study, regular NSAID users had a non-statistically significant lower risk for liver cancer (odds ratio = 0.9; 95% CI = 0.3 to 2.9), but the study had a limited number of individuals with liver cancer (n = 49) and low power to detect a statistically significant association (22). In a population-based study in Canada, rheumatoid arthritis patients who were on long-term NSAID therapy were followed up over a mean period of 17 years, and their records were linked to population-based cancer registry diagnoses (23). Based on five patients with liver and/or gallbladder cancer, the standardized incidence ratio (SIR) (ratio of observed rates in the cohort vs expected rates in the population) suggested an elevated risk that was not statistically significant (SIR = 1.93; 95% CI = 0.62 to 4.5). Thus, the evidence from both previous human studies on NSAID use and HCC risks are inconclusive. With 250 individuals with incident HCC, plus additional evaluation of noncarcinogenic liver disease–related mortality outcomes (n = 428), our analysis in the NIH–AARP cohort is larger than previous studies and substantially expands the evidence base in this area.

Among the limitations of our study was the lack of information on some major risk factors for CLD and HCC. Although we adjusted for the participant's alcohol intake, there was no information on hepatitis B virus and hepatitis C virus status of the participants. Although the chronic hepatic inflammatory process is a hallmark of HCC or CLD, the underlying carcinogenic pathways may differ between viral or nonviral etiologies, which might affect the role of NSAIDs in persons chronically infected with either hepatitis B virus or hepatitis C virus. It is worth noting that a recent prospective study from Taiwan that investigated the chemopreventive role of statins on risk of HCC in persons infected with hepatitis B virus reported a protective effect in persons concomitantly taking statins and aspirin (30). Our study also lacked information on duration and indication of NSAID use. The sensitivity analysis after excluding persons with self-reported history of heart disease and hypertension at baseline (a proxy for cardiovascular indication and longer duration of NSAID use, particularly low-dose aspirin), yielded hazard rate ratios similar to those of the overall cohort and suggested minimal potential for confounding by indication. In addition, use of NSAIDs was only ascertained at one time point, and we lacked information regarding NSAID use during the cohort follow-up period. Individuals might have changed their pattern of NSAID use during the follow-up period, which might bias the results toward the null. Our study also lacked information on the dosage and strength of NSAIDs. In particular, we were unable to distinguish between the use of low-dose aspirin (typically 81 mg) vs full-strength (typically 325 mg) tablets. The difference in chemopreventive benefits by differing dosages and frequencies of use is an active area of investigation, particularly given the competing risk-vs-benefit profile of aspirin (10). An important risk associated with long-term use of NSAIDs, particularly aspirin, is gastrointestinal bleeding. This is of particular importance in patients with CLD, in whom gastrointestinal bleeding from esophageal varices or portal hypertensive gastropathy are common clinical problems (31). Unfortunately, we did not have the individual-level clinical data to determine the proportion of deaths from CLD resulting from underlying gastrointestinal bleeding due to long-term NSAID use. Although any risk associated with gastrointestinal bleeding may negate the benefits conferred by NSAIDs, further work is necessary to clarify the overall risk-vs-benefit ratio. All data in our investigation were self-reported as part of a questionnaire; thus, misreporting of both exposure and confounding variables is possible; the potential for residual confounding is also possible. Finally, our cohort was comprised of older adults (mean age = 62.8 years), and results may not be applicable to other age groups, although there is potential for a chemopreventive benefit for the millions of people aged 50 years or older who are already daily aspirin users.

In summary, our results suggest that use of NSAIDs among men and women aged 51 to 74 years is associated with reduced risk of developing HCC and reduced risk of dying from CLD in comparison with non-use. These associations are prominent with the use of aspirin, and if confirmed, might open new vistas for chemoprevention of HCC and CLD.

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