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Correspondence

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

We read with interest the recent article by Sahasrabuddhe et al. (1) demonstrating a reduced risk of hepatocellular carcinoma (HCC) among aspirin users (relative risk [RR] = 0.59) and a reduced risk of death due to chronic liver disease among aspirin users (RR = 0.55) and nonaspirin nonsteroidal anti-inflammatory drug (NSAID) users (RR = 0.74). We have serious concerns about residual bias that should be considered in interpreting these results.

Although the authors account for multiple confounders in their analysis, they do not include a measure of liver disease severity or cirrhosis. These factors are vital in examining the relationship between NSAID use and liver-related outcomes because they directly affect the decision to use NSAIDs in the first place. Gastroenterologists and hepatologists have long known that aspirin and nonaspirin NSAIDs induce renal vasoconstriction and reduce glomerular filtration in patients with cirrhosis (2, 3). Such renovascular effects are particularly problematic in the setting of cirrhosis and portal hypertension, in which reduced renal perfusion can blunt the response to diuretics used for ascites management and trigger the hepatorenal syndrome. For this reason, clinical practice guidelines from the American Association for the Study of Liver Diseases advise against NSAID use in these patients (4). Furthermore, NSAIDs predispose patients with cirrhosis to variceal bleeding (5).

Consequently, patients with cirrhosis are much less likely to be taking NSAIDs (6), presumably on the advice of their physicians. HCC in the United States develops in the setting of cirrhosis in the vast majority of cases (7), and liver related mortality is obviously linked to cirrhosis. Therefore, cirrhosis represents a major confounder that probably explains the observed inverse relationship between NSAIDs and the liver-related outcomes. In other words, the very patients most likely to die from liver failure or develop HCC are avoiding NSAIDs already, whereas those at much lower risk (noncirrhotics) are still able to take NSAIDs. The authors address confounding from cardiovascular disease and hypertension (1), but we believe that the presence of cirrhosis represents the much more pertinent bias.

Our other concern is that the protective effects of aspirin on HCC and death due to chronic liver disease are independent from the frequency of use and that the relationship between nonaspirin NSAIDs and chronic liver disease death is only apparent for monthly users. Given the short half-life of aspirin and common nonaspirin NSAIDs, a benefit of monthly dosing lacks biologic plausibility. The authors rightly point out that the findings should be interpreted with caution because of this lack of dose response (1), but we would argue further that this finding is again reflective of unmeasured confounding due to cirrhosis.

The potential relationship between NSAIDs, HCC, and chronic liver disease is an important issue that deserves further investigation. Our concerns about this study highlight the need to consider the diagnosis of cirrhosis in future epidemiologic studies.

References


Notes

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

Sahasrabuddhe et al. report on a reduced risk for primary hepatocellular carcinoma (HCC) and chronic liver disease in participants from the National Institutes of Health–AARP Diet and Health Study...
cohort when using aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) (1). However, we have serious doubts about the validity of their study methods and hence question their conclusions. For example, we note that the effect of aspirin on the risk for HCC is not dose-dependent and a protective effect is observed even when medication is used only monthly. Such an effect is pharmacologically most unlikely, and we believe that three major shortcomings cause this effect: 1) the presence of immortal time bias; 2) inappropriate exposure assessment; and 3) the validity of the reference groups.

First, exposure to aspirin and NSAIDs is measured once, 6 months after cohort entry. In itself this provides a risk of so-called immortal time bias because patients must survive the first 6 months before exposure can be measured. This bias often results in an overestimation of protective effects of medicines in cohort studies (2–4).

Second, in a study period of more than 11 years, exposure to aspirin and NSAIDs should not be measured only once. Both can be used variably on an on-and-off basis and by almost any person or chronically. Measurement at 6 months after baseline is therefore inappropriate because it results in misclassification of exposure and biased results (5).

Third, the reference categories may distort the observed effects and even cause bias. From Table 1, it is clear that only 13.8% of subjects had not used any aspirin or NSAIDs in the year preceding the questionnaire. Aspirin and NSAIDs are used extensively as analgesics and at low-dose for the prevention of cardiovascular disease (aspirin). Subjects who have not used any aspirin or NSAID are very likely to differ substantially from users. It is likely that such nonusers have a contraindication for aspirin or NSAID use, which may be related to an increased risk of liver diseases. Such confounding by contraindication increases the number of events in the unexposed arm, causing an overestimation of the protective effect.

In addition, the first two models presented in Table 2 should be interpreted with caution because the reference groups contain both never users and users of the comparator drug. The group of nonaspirin users in the first model for example, comprises patients using neither aspirin nor NSAIDs as well as patients using NSAIDs only. This choice in reference group may have considerable impact on the risk estimates because about half the number of patient-years is made up by NSAID-only use.

Because of these three shortcomings in the design and conduct of the study, we consider a chemopreventive effect of aspirin and NSAIDs on the risk for primary HCC or death from chronic liver disease unlikely.

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References

Note
The authors declare no conflicts of interest.

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Response
We recently published a population-based cohort study of 300 504 men and women aged 50 to 71 years who participated in the National Institutes of Health–AARP Diet and Health Study. We analyzed their self-reported use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in the year before enrollment and examined associations with registry-confirmed diagnoses of hepatocellular carcinoma (HCC) and deaths due to chronic liver disease (CLD) over a period of 10 to 12 years. We demonstrated an inverse association between NSAID use, particularly aspirin, and the risk of HCC and CLD mortality, after adjusting for age, sex, race/ethnicity, cigarette smoking, alcohol consumption, diabetes, and body mass index. In response to our paper, the letters sent by Singh and Singh, Orman and Hayashi, and Duijnhoven and De Bruin have raised several thoughtful questions, which we are pleased to have the opportunity to address.

A common concern expressed in the letters is that the referent group of nonusers of NSAIDs may have been more likely to include individuals with cirrhosis [the most severe form of CLD and the precursor to most HCC (1)]. These individuals would be less likely to take aspirin and nonaspirin NSAIDs because of gastrointestinal or other side effects, which the commentators believe led to an overestimation of the protective benefit observed in our study. As we have acknowledged, the lack of linkages with medical records precluded us from evaluating if the proportion of individuals who had preexisting liver disease or cirrhosis differed among users vs nonusers. However, to partially overcome this limitation, we reported conducting a lag (sensitivity) analysis by excluding participants who developed HCC or died of CLD in the initial 5 years (until December 31, 2001) of study follow-up. This was done to rule out the possibility of the results being affected by those with severe and overt preexisting liver disease (such as those with cirrhosis) who would have avoided NSAIDs in the 5 years preceding their diagnosis or death. The results of this lag analysis suggested that the pattern of results did not differ from those of our main effects model (Table 1) and provide a robust verification of the main study results within the obvious constraints of an observational study.

It is also conceivable that adverse effects associated with NSAID use (eg, gastrointestinal bleeding) would have led to more frequent medical contacts and clinical care, and consequently a higher likelihood of being diagnosed with CLD and HCC, a detection bias that would paradoxically imply that our hazard rate ratios are actually underestimate of the true risk reduction associated with NSAIDs (2). Nonetheless, we agree with Orman...