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.

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References

Notes
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