neoplasia 2/3 or worse (CIN2/3+) was not statistically significant (−44.6%, 95% confidence interval = <0.0% to 8.5%) among subjects who were polymerase chain reaction positive and seropositive for the relevant HPV vaccine type at day 1 (1). If one assumes that the vaccine has no enhancing/therapeutic effect, one would expect the efficacy estimates from clinical trials to fluctuate around 0%. Thus, the negative empirically based estimate of efficacy is not surprising. However, the efficacy estimates should tend toward 0% with increasing sample size. To this effect, another clinical trial for Gardasil (study 015) showed a non-statistically significant positive efficacy against CIN2/3+ among individuals with prior evidence of infection (3). Second, the Gardasil group in study 013 had more baseline risk factors for the development of CIN2/3+ than the placebo group (1). For example, the baseline prevalence of high-grade cervical lesions was 1.86 times higher in the Gardasil group than the placebo group. Thus, it is not surprising that the Gardasil group had higher rates of CIN2/3+ during the trial (1).

Ecological surveillance studies are prone to bias and, consequently, cannot be used to conclude that there is a causal link between an exposition and an outcome. Suba et al. use data from an ecological study from Australia showing statistically significant higher incidence of high-grade cervical abnormalities among older women in the years after vaccination (increase of 0.18% compared with prevaccination) to support the hypothesis that HPV vaccines can enhance disease (2). However, high-grade cervical abnormality incidence started to increase in the period of 2005 and 2006 (before vaccination in 2007), which coincides with statistically significant decreases in low-grade cervical abnormalities (decrease of 0.60% compared with prevaccination) among older women (2), increased participation in cervical cancer screening of higher-risk women due to targeted campaigns, and changes to screening guidelines in 2006 (personal communication, J. Brotherton).

In conclusion, our modeling assumptions are based on reliable evidence. Furthermore, even if our model assumed that HPV vaccines enhance disease among individuals infected by a vaccine type, it would have no impact on the conclusions of our paper because the overwhelming majority of females are vaccinated before becoming sexually active or being exposed to HPV.

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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.

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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.