Editorial Commentary

Aspirin, chronic hepatitis B (CHB) and hepatocellular carcinoma (HCC)—will there ever be enough data?

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Chronic hepatitis B (CHB) infection remains the leading cause of hepatocellular carcinoma (HCC) worldwide, a malignancy with a poor prognosis and an age-adjusted incidence that is rising at an alarming rate. HCC invariably occurs on a background of chronic liver disease, thus chemoprevention therapy for at-risk populations, although not widely used in mainstream clinical practice, is an intriguing strategy which may help to address this significant public health challenge. A growing body of evidence suggests that aspirin may be effective as a chemopreventative agent (1). Aspirin has added appeal due to its low cost and ubiquitous presence throughout the developing world, where there is a disproportionate HCC burden, inadequate access to antiviral therapy and low screening uptake (2). Despite accumulating evidence of an overall beneficial effect of aspirin, it is still unknown which specific populations would benefit from aspirin chemoprophylaxis, or what the overall risks would be.

Jang and colleagues report their findings from a large retrospective South Korean population-based cohort study (3). Using data from the Korean National Health Insurance Service database the authors evaluated the effect of aspirin in patients with CHB infection, stratified by presence or absence of cirrhosis. The primary outcome was HCC incidence, and the secondary outcomes were liver-related mortality and incidence of major bleeding. The final propensity matched analysis included 19,003 matched pairs, including 2,479 pairs with cirrhosis. The authors observed a significant reduction in the overall incidence of HCC and of liver-related mortality in the aspirin group of 15% and 16%, respectively. Interestingly, this benefit was driven by the non-cirrhotic subgroup, with no significant benefit observed among patients with cirrhosis. There was no significant difference in overall incidence of major bleeding between groups, although the aspirin-treated subgroup without cirrhosis were observed to have a higher incidence of major bleeding.

The lack of an aspirin effect on HCC incidence in cirrhosis is intriguing. Intuitively, the low hanging fruit of a chemopreventative strategy would be to target patients with cirrhosis who are at the highest risk of HCC and liver-related mortality, however, that is not born out in this study. Rather, this study suggests that the "window of opportunity" to intervene with chemoprevention is prior to the development of cirrhosis. The reason for this has not been defined in the study, but a number of factors could be considered. Biologically, cirrhosis may impact the postulated mechanism of aspirin's action. The platelet-dependent effects of aspirin may be limited by thrombocytopenia, and the platelet-independent effects on fibrogenesis mediated via hepatic stellate cells may be mitigated by advanced fibrosis. Genetic factors may also be important as this was a Korean population, in contrast to the large Swedish population registry study which demonstrated a

chemoprotective effect of aspirin even amongst cirrhotic patients (4). The reduced overall aspirin exposure in cirrhotics of 24 versus 39 months may have also contributed to the lack of effect. The low use of nucleoside analogues, known to mitigate HCC incidence, in 13% of the matched population, presumably mainly prescribed to those with cirrhosis and advanced fibrosis, may have favoured aspirin's benefit in the non-cirrhotic population. It should not be forgotten that recent meta-analyses have identified benefit in cirrhosis with smaller effect size than the non-cirrhotic populations supporting these findings (1,5).

Clearly there are limitations to the conclusions that can be drawn from the retrospective population data-base study design. HCC risk in patients with CHB is influenced by a multitude of factors related to patient, virus, use of antiviral therapy, and status along a wide spectrum of liver disease. Such studies will always be at risk of bias from unmeasured confounders. The true risks of aspirin beyond major gastrointestinal bleeding may be similarly difficult to assess from retrospective database population research. Notwithstanding the potential bias, it remains unknown what individual or viral factors ought to influence the decision to prescribe chemoprophylaxis, beyond simply the absence of cirrhosis. Non-cirrhotic CHB is a heterogenous group with greatly divergent HCC risk, and this study lacks the granular level of detail required to inform clinical decision making. Ultimately, achieving a deep understanding of which individuals and when they should receive aspirin chemoprophylaxis and the risk to benefit ratio may be beyond the realms of what is possible with observational research.

While a well-designed randomised controlled (RCT) study of aspirin in liver disease would answer the role of aspirin and its side-effects it is far from clear whether this would ever be feasible. Key to this would be the size of any study. The main effect of aspirin in Jang *et al.*'s study was in the non-cirrhotic population. Given the lower incidence of HCC in this population any RCT would need a very large population to be powered appropriately to determine an effect. Furthermore, given aspirin is a cheap and off patent medication it would likely need government or Non-government Organisation rather than Pharma funding. At this point, the question should be when is there enough data to start using aspirin in chronic liver disease? Given the huge (and growing) worldwide burden of disease attributable to HCC, this study further adds valuable data to the impetus to consider using aspirin as a chemopreventative agent.

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