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Dose and duration of aspirin use to reduce incidental hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) incidence in the U.S. is increasing in specific subgroups of patients such as white men with hepatitis C and Hispanics with non-alcoholic fatty liver disease.(1) HCC is the only cancer type with increased mortality over the past three decades throughout the nation, and with still dismal 5-year survival less than 18%.(2) HCC chemoprevention in individuals at high risk is likely the most impactful strategy to improve patient prognosis, although no such therapy has been established to date after a series of failed clinical trials of agents such as low-dose interferon.(3) Epidemiological and experimental studies have suggested that the use of anti-inflammatory agents in addition to statins and anti-diabetic drug, especially metformin, may be associated with reduced risk of HCC development.(4) However, dose and duration of aspirin use required to achieve clinically meaningful chemopreventive effect is still elusive, and it has been a major obstacle in designing prospective trial to test the agent.

Simon *et al.* attempted to address the issue by leveraging long-term longitudinal medication records available from large population-based cohorts, the Nurses' Health Study and Health Professionals Follow-Up Study cohorts.(5) The cohorts consist of 133,371 participants, who have been prospectively and regularly followed up for more than 26 years. Among them, 108 incidental HCC cases were diagnosed during follow-up. Regular aspirin users, defined as at least two 325-mg tablets per week, showed a lower HCC incidence rate compared to non-regular users (hazard ratio [HR], 0.51; 95% confident interval [CI], 0.34–0.77). Of note, the study identified a threshold effect and possible dose-dependent association between aspirin use and HCC incidence. Participants taking less than 1.5 tablets per week did not show a favorable effect (HR, 0.87; 95% CI, 0.51–1.48), whereas those who took 1.5 to 5 tablets or more than 5 tablets per week had HRs of 0.51 (95% CI, 0.30–0.86) and 0.49 (95% CI, 0.28–0.96), respectively, compared to non-users. Furthermore, HCC risk was low in long-term aspirin users. Among individuals who took at least 1.5 tablets per week, more than 10 years of aspirin use was significantly associated with reduced HCC incidence with an HR of 0.55 (95% CI, 0.32–0.93), whereas the use for 5 to 10 years was accompanied with

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only marginal reduction (HR, 0.62; 95% CI, 0.31–1.13). Importantly, such protective effect disappears if aspirin is discontinued for 8 years or more compared to active users (HR, 1.77; 95% CI, 1.06–2.97). When the dose and duration were jointly analyzed, regular use of 1.5 tablets or more per week for at least 5 years was needed to observe significant decrease of HCC incidence (HR, 0.41; 95% CI, 0.21–0.77). There was no association between HCC incidence and use of non-aspirin non-steroid anti-inflammation drugs, which may suggest aspirin's role beyond modulating hepatic and systemic inflammation.

This study demonstrated feasibility of quantitatively assessing effect sizes for an HCC chemopreventive intervention in a systematic way and showcased utility of clinical cohort with longitudinal medication records. Such data will inform and guide planning of future clinical evaluation of the drug. However, there are several issues to note in translating the finding to HCC chemoprevention in a clinical setting. First, the study analyzed incident HCC in a general population, and therefore it is unclear if the results can be extrapolated to patients with chronic liver diseases particularly cirrhosis, the primary target for HCC chemoprevention. HCC incidence in the general population is too low to design properly powered clinical trials with practically feasible sample sizes and observation time. Second, cirrhosis patients often have coagulation disorders and thrombocytopenia, which may limit use of aspirin due to concern about bleeding complications. Further, the risk of life-threatening gastrointestinal bleeding would rationalize prophylactic use of anti-acids, e.g., proton pump inhibitors (PPI) and H2-receptor antagonists. Recent clinical studies have reported that PPI use may facilitate liver disease progression toward HCC development possibly by inducing intestinal dysbiosis.(6) This suggests that a concomitant anti-acid agent should be carefully chosen to not compromise aspirin's possible HCC chemopreventive effect. Third, although the authors carefully adjusted potential confounding factors in the multivariable modeling to estimate the effect sizes, it is still possible there are unknown and residual confounding factors and biases. Aspirin is less likely to be prescribed to cirrhotic patients, at risk of HCC because of potential coagulopathy, which could lead to a selection bias. The self-reported medication history also may be affected by recall and/or measurement bias. In addition, use of other drugs which may have HCC preventive effects may not be fully adjusted despite the careful effort of multivariable modeling.(4, 7) Nevertheless, similar dose-dependent protective effect of aspirin was recently reported in an independent Asian national cohort study, suggesting that the finding is reproducible.(8)

Nevertheless, the study by Simon and colleagues represents a step forward to facilitate clinical evaluation of pharmacological HCC chemoprevention strategies, and warrants future follow-up studies to clarify the issues. Clinical context such as disease etiology, stage, and/or other patient characteristics can be critical to unequivocally determine benefit and harm of aspirin given the paradoxically increased colorectal cancer mortality when aspirin is given to the elderly.(9) Furthermore, similar exploration of longitudinal medication records may enable identification of other candidate chemoprevention agents applicable to cirrhotic patients at risk of HCC development.

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