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Statins for chemoprevention of hepatocellular carcinoma: assessing the evidence

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Hepatocellular carcinoma (HCC) incidence rates have tripled in the United States over the last 30 years [1]. HCC has varied etiologies in different populations, including hepatitis B, mostly in Asia and sub-Saharan Africa, and hepatitis C in the West. Metabolic syndrome is becoming an increasingly recognized etiology of HCC worldwide, and may account for up to 30% of cases of HCC in the USA [2]. Hepatitis B vaccination programs have shown reductions in HCC incidence, but for those with other underlying risk factors, primary preventive efforts have been less successful.

About a third of adults in the USA have metabolic syndrome, and rates in Asia are now approaching those in the West [3,4]. Nonalcoholic fatty-liver disease (NAFLD) affects about a third of the US adult population and is the hepatic manifestation of metabolic syndrome. Finally, NAFLD includes a diverse group of liver disorders, ranging from nonalcoholic steatohepatitis to cirrhosis. Those with nonalcoholic steatohepatitis have about a twofold increased risk of developing HCC [5–7].

Patients with various components of metabolic syndrome may also have higher incidence of and mortality rates from HCC than those without metabolic syndrome [8,9]. For instance, diabetes and obesity both accentuate the risk of HCC in patients with known HCV [10,11]. In animal models, high-fat diets given to mice lead to larger and more proliferative liver tumors [12]. Therefore, one possible reason for their worse outcomes may be that patients with features of metabolic syndrome have more aggressive tumor characteristics, such as increased vascular invasion [13].

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There is biologic plausibility for a benefit of statins in reducing HCC risk, especially for patients with HCV or metabolic syndrome. Statins inhibit the formation of geranylgeranylated protein, necessary for HCV replication [14], and may augment response to hepatitis C therapy [15]. In patients with underlying heart disease and elevated liver function tests, statin use both reduced cardiovascular events and improved liver function tests, suggesting a benefit in patients with presumed NAFLD [16]. Further, there are several proposed mechanisms that might explain the anticancer effects of statins. Among these, statins prevent post-translational modifications of G-protein subunits, such as RAS [17]. They may also block lymphocyte adhesion and costimulation and have been shown to have proapoptotic effects [18,19].

Data for statin use in the prevention of other cancers have been conflicting. For instance, a meta-analysis of randomized and observational trials of statin use and breast cancer incidence revealed no significant decrease in cancer risk, although there was a suggestion of possible benefit in long-term users [20]. Colon cancer trials have showed similar inconsistent results. An initial case-control trial by Poynter *et al.* suggested an almost 50% risk reduction for those taking statins in northern Israel [21]. Nielsen *et al.* reported a significant decreased in all-cause and cancer-related mortality in statin users in Denmark [22]. Limitations of this report included lack of data on smoking and the fact that no dose-response relationship was seen. However, a meta-analysis including randomized, cohort and case-controlled trials failed to confirm a clear benefit to statin use [23]. Dale *et al.* reported a meta-analysis of randomized controlled trials of statins through July 2005, and found no significant effects on cancer incidence or cancer deaths [24].

Several observational studies suggest that statins may decrease the risk of HCC in patients with other underlying liver diseases. For instance, in a nested case-control study of diabetics performed using the US Department of Veterans Affairs databases, those who developed HCC were less likely to have filled a prescription for a statin than controls (34 vs 53% [25,26]). Statin use may be associated with decreased HCC recurrence after resection [27], and small randomized trials suggest that giving pravastatin to patients with existing HCC may improve outcome [28,29].

The most recent of these observational studies was conducted by Tsan *et al.* who reported a dose-dependent association between statin use and decreased risk of HCC development in patients with HCV in the high HCC incidence area of Taiwan [30]. The authors examined a population-based cohort of 260,864 patients infected with HCV with just over 10 years of follow up. A hazard ratio of 0.33 was seen for HCC development in those taking higher daily doses of statins. Similar results were not seen with other lipid-lowering agents (e.g., cholestyramine), and follow up was much longer than is typically seen in randomized trials of statin use. No increase in hepatotoxicity was seen, confirming other observational data, suggesting the safety of statins in patients with compensated HCV [31].

However, randomized data do not support a preventive effect for statins in HCC. A recent meta-analysis evaluated 4298 cases of HCC in 1,459,417 patients. The authors included both observational and randomized trials and found a 41% overall reduction in HCC risk with the use of statins. This was driven entirely by the observational studies (adjusted odds ratio

[OR]: 0.6), with no benefit seen in the randomized trials (adjusted OR: 0.95 [32]). Interestingly, the reduction in risk was found to be higher in Asian populations in the observational trials compared to western populations, potentially attributable to interactions between statins and HBV. It is also notable that the number of patients with HCC in the randomized trials was small. These differences between observational studies and randomized trials may also reflect length of follow-up, as well as different underlying etiologies of liver disease.

Observational studies of statin use in patients with underlying liver disease are subject to several types of biases. Most importantly, physicians might be hesitant to give statins to patients with underlying liver disease, leading to confounding by indication. In addition, differences between groups are sometimes reported after very short time on statin therapy. Finding such a quick onset of action is potentially concerning for a healthy patient bias. Finally, use of other potential medications that may also lower HCC risk, such as metformin, are often not adjusted for in these analyses.

A genetic polymorphism of the patatin-like phospholipase domain-containing (PNPLA3) protein has been shown to be linked to an increase in hepatic fat deposition as well as an increase in the risk of HCC development [33]. It provides a novel biomarker for risk stratification, and recent data suggest that this risk may be modifiable. A prospective study reported an increased risk of HCC over 15 years for obese subjects with the PNPLA3 variant. For those who underwent bariatric surgery, the genetic polymorphism no longer was associated with HCC risk [34]. These data have exciting implications for modifying genetic risk, not only with surgery but also possibly with exercise, statins or other intervention.

Another genetic polymorphism may help predict those who will benefit most from statin use. In colon cancer, those with the A/A genotype of the 3-hydroxy-3-methylglutaryl coenzyme A reductase gene, which codes for an enzyme involved in cholesterol synthesis, had an OR of 0.3 for developing colon cancer, while the OR was twice as high for those with a T/T genotype [35]. Again, this may help to better select patients for statin use in the future.

Several unanswered questions remain before we can move to a large-scale HCC prevention trial using statins. Understanding who will benefit, appropriate durations of treatment and relevant biomarkers will be crucial to design larger trials. In addition, studies to assess changes in steatosis and fibrosis with statin use will help to determine the best place to intervene in the pathological continuum. Tissue biomarkers, together with host factors, could then potentially be incorporated into a large randomized prevention trial. In the meantime, we now have additional data that shows that statins do not cause harm in patients with liver disease. With more study, we should soon be in a position to evaluate whether statins truly reduce the risk of HCC.

Biographies

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