Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second or third leading cause of death from cancer worldwide, with the uncertainty reflecting the paucity or absence of reliable and accurate estimates in high-incidence countries. Most HCC cases occur in hepatitis B virus (HBV) endemic areas such as East Asia and sub-Saharan Africa. However, the incidence of HCC has been increasing in Western countries over the past several decades, mainly as a result of increasing incidences of chronic hepatitis C, nonalcoholic fatty liver disease, diabetes, and obesity, which are known risk factors for HCC. Although several curative treatment modalities, including surgical resection, radiofrequency ablation, and liver transplantation have been developed to improve the prognosis of HCC, because of the lack of effective surveillance systems for early diagnosis of HCC in both low- and high-resource countries, the 5-year survival rate of HCC is still poor. Because of the dismal prognosis of HCC, chemoprevention is an appealing approach but is unproven at the present time. In this review, we highlight two promising drugs—statins and metformin—for the chemoprevention of HCC.

**STATINS**

**Mechanisms**

Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, are widely used for prevention of cardiovascular and cerebrovascular events because of their lipid-lowering effects. Thus, statins are the second most common prescription drug in the United States, and one in four Americans aged 45 years or older are prescribed.
Statins for cardiovascular disease. Statins have antitumor effects through the following mechanisms: (1) they down-regulate the RAF/mitogen-activated protein kinase 1/extracellular signal-regulated kinase (ERK) pathway, thus reducing cell survival and contributing to antitumor apoptotic responses; (2) they limit the degradation of the cyclin-dependent kinase inhibitors p21 and p27, which have growth-inhibitory and tumor-suppressor effects; (3) they prevent phosphorylation and activation of c-Myc, which is a critical step in hepatocarcinogenesis; and (4) they have anti-inflammatory and antioxidant effects mediated by effects on the phosphoinositide 3-kinase (PI3K)/V-AKT murine thymoma viral oncogene homolog 1 (AKT) pathway.

Evidence
A large, population-based, observational study in HBV-infected Taiwanese patients showed that statin users had a 53% risk reduction in HCC as compared with statin nonusers. Another population-based observational study among hepatitis C virus (HCV)-infected patients showed that statin use was associated with a 47% reduction in HCC risk. In a meta-analysis of 10 studies evaluating 4298 cases of HCC in 1,459,417 patients, statin use decreased the risk for HCC by 37% in both Asian and Western populations. Interestingly, the chemopreventive effect of statin was more pronounced in Asian populations [adjusted odds ratio (AOR) 0.52] as compared with Western populations (AOR, 0.67). However, two randomized controlled trials (RCTs) included in the earlier meta-analysis did not show significant chemopreventive effects of statins, possibly because of the small number of HCC occurrences, short duration of follow-up, and low risk for HCC development for enrolled patients. To date, no large RCTs have evaluated the chemopreventive effect of statins in patients who are at risk for HCC, such as those with liver cirrhosis or HBV or HCV infection with advanced fibrosis.

Limitations
Although favorable results have been shown in observational studies, suggesting a role for statins in chemoprevention, the strongest evidence of beneficial effect of statin for cancer prevention should be determined from RCT designs that minimize biases and confounders. Given the relatively low incidence of HCC in Western populations, it may be challenging to conduct an RCT of statins for HCC prevention. Singh et al. reported that,
assuming a 4% annual rate of progression to HCC among patients with cirrhosis and a 50% decline in the risk for HCC with the use of statins, as compared with placebo, 2,396 patients with cirrhosis would need to be followed for 1 year. Another limitation is that due to the propensity of statins to increase liver transaminases, physicians may have a high threshold for prescribing statin among patients with chronic liver disease, especially liver cirrhosis, which is one of the strongest risk factors for HCC. Consequently, the chemopreventive effect of statins has probably been overestimated in previous observational studies. Furthermore, previous observational studies failed to adjust for the concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, or antidiabetic medication (especially metformin), which may also be associated with decreases in risk for HCC, even though they adjusted for multiple other confounding factors in their analyses in an effort to minimize bias.

**METFORMIN**

**Mechanisms**

Metformin is one of the most commonly used drugs for the treatment of type 2 diabetes. In addition, metformin has been shown to be effective for prevention of progression of nonalcoholic fatty liver disease. Mounting evidence from both in vivo and in vitro studies suggests that metformin use is associated with a decreased risk for cancer in patients with diabetes. The postulated mechanisms are as follows: (1) inhibition of the mammalian target of rapamycin (mTOR) pathway through activation of adenosine monophosphate activated protein kinase (AMPK), (2) modulation of the insulin-like growth factor-1 (IGF-1) pathway, and (3) induction of cellular differentiation and apoptosis.

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**TABLE 2. SUMMARY OF STUDIES OF CHEMOPREVENTIVE EFFECT OF METFORMIN AGAINST HEPATOCELLULAR CARCINOMA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Location</th>
<th>Subjects</th>
<th>Metformin</th>
<th>HCC Cases</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliveria et al. (2008)²⁵</td>
<td>Population-based cohort</td>
<td>United States</td>
<td>191,223</td>
<td>NR</td>
<td>39</td>
<td>AOR: 0.7 (0.3–1.6)</td>
</tr>
<tr>
<td>Ruiter et al. (2012)²⁶</td>
<td>Population-based cohort</td>
<td>Netherlands</td>
<td>85,289</td>
<td>61.8%</td>
<td>31</td>
<td>OR: 0.7 (0.5–0.9)</td>
</tr>
<tr>
<td>Chen et al. (2013)¹¹</td>
<td>Population-based case-control</td>
<td>Taiwan</td>
<td>47,820</td>
<td>NR</td>
<td>22,047</td>
<td>AOR: 0.8 (0.7–0.8)</td>
</tr>
<tr>
<td>Kawaguchi et al. (2010)²⁷</td>
<td>Hospital-based case-control</td>
<td>Japan</td>
<td>241</td>
<td>3.7%</td>
<td>138</td>
<td>AOR: 0.6 (0.2–2.2)</td>
</tr>
<tr>
<td>Hassan et al. (2010)²⁸</td>
<td>Hospital-based case-control</td>
<td>United States</td>
<td>255</td>
<td>47.1%</td>
<td>140</td>
<td>AOR: 0.3 (0.2–0.6)</td>
</tr>
<tr>
<td>Donadon et al. (2010)²⁹</td>
<td>Hospital-based case-control</td>
<td>Italy</td>
<td>549</td>
<td>23.5%</td>
<td>190</td>
<td>AOR: 0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>Nkontchou et al. (2011)³⁰</td>
<td>Hospital-based cohort</td>
<td>France</td>
<td>100</td>
<td>26.0%</td>
<td>39</td>
<td>AOR: 0.2 (0.04–0.8)</td>
</tr>
<tr>
<td>RECORD (2010)³¹</td>
<td>RCT</td>
<td>International</td>
<td>4447</td>
<td>75.2%</td>
<td>4</td>
<td>AOR: 3.0 (0.2–55.3)</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; OR, odds ratio.

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**FIG 1** Antitumor mechanisms of statins and metformin. Abbreviations: MEK, mitogen-activated protein kinase; RAF, raf-1 kinase; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; p53, tumor protein 53; mTOR, mammalian target of rapamycin; AMPK, 5′-AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; RAS, rat sarcoma.
kinase (AMPK), (2) induction of apoptosis through either p53-dependent or independent mechanisms, (3) inhibition of angiogenesis through negative regulation of hypoxia-inducible factor-1α and vascular endothelial growth factor, and (4) blocking the cell cycle partly by decreasing levels of cyclin D1 expression and by retinoblastoma-like protein phosphorylation.\textsuperscript{10}

**Evidence**

In a large, population-based, case–control study, metformin showed a reduced risk for HCC in patients with diabetes, and each incremental year increase in metformin use resulted in a 7% reduction in the risk for HCC in patients with diabetes.\textsuperscript{11} In a meta-analysis of four studies, metformin was associated with an estimated 70% reduction in the risk for liver cancer among patients with type 2 diabetes.\textsuperscript{12} In another meta-analysis of 10 studies reporting 22,650 cases of HCC developing in 334,307 patients with type 2 diabetes, metformin use was associated with a 50% reduction in HCC incidence.\textsuperscript{13}

**Limitations**

Previous studies should be interpreted with caution because of the inherent drawbacks of observational studies. Time-related biases, including immortal time bias and time-lagging bias, may allow metformin to seem effective against HCC, as has been shown for other cancers.\textsuperscript{14,15} Another concern is that the chemopreventive effect of metformin may be overestimated by the use of other antidiabetic medications that might modify the risk for HCC, such as thiazolidinediones, sulfonylureas, and insulin, because diabetes medication regimens are frequently changed to optimize a patient’s glucose control. As mentioned earlier, some previous studies did not take into account concomitant medication use, particularly statins, as a substantial portion of patients with diabetes are also taking statins for lipid control. Physicians are generally reluctant to prescribe metformin for patients with diabetes with chronic liver disease. However, a recent study of a large cohort of diabetic patients with cirrhosis showed that metformin is safe and may be potentially beneficial, improving overall survival.\textsuperscript{16}

**CONCLUSIONS**

Evidence for the chemopreventive effect of statins and metformin is derived mainly from observational studies, and interpretation of these studies should be approached with caution. Considering their relatively low prices, satisfactory safety profiles, and the proven benefits for decreasing cardiovascular events for statins and controlling diabetes for metformin, the use of these two drugs/drug classes for chemoprevention against HCC could be an attractive option in patients at high risk for HCC. Additional well-designed RCTs are warranted to definitively establish the role of these two drugs in chemoprevention of HCC.


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