Hepatocellular carcinoma (HCC) is the sixth most frequently occurring cancer and the third most common cause of cancer deaths in the world (1). About 80% of all HCCs occur in Eastern Asia and Sub-Saharan Africa, but the incidence of HCC is increasing in the United States. The prognosis of HCC is poor; 1-year survival rate in the United States is only 50%, and survival rates are even lower in developing countries (2).

Most HCCs develop in cirrhotic livers. Evidence suggests that the risk of HCC among persons with cirrhosis varies by the etiology of the underlying liver disease and by geographic location. The reported risks of HCC in persons with hepatitis B virus (HBV)-related cirrhosis are between 1% and 14% per year (3, 4), similar to the risks (4%-14% per year) reported for persons with hepatitis C virus (HCV)-related cirrhosis (3–6). In contrast, the HCC risk associated with alcohol-related cirrhosis has been reported to be approximately 1% per year (7, 8). Although not yet well defined, the risk associated with nonalcoholic steatohepatitis (NASH)-related cirrhosis was 2.6% per year in one study (5), suggesting that persons with NASH-related cirrhosis may have HCC risks as high as those for persons with viral hepatitis–related cirrhosis. The wide ranges of HCC risks in the literature may reflect variation by geographic location. In general, studies from Japan (3, 9) have reported notably higher risks among cirrhosis patients than have studies conducted in Western countries (4, 5, 10). Why this risk differential occurs is not clear, but it is consistent with the significantly higher overall rate of HCC in Japan in comparison with western countries (1).

Antiviral therapy has been used to treat both HBV- and HCV-associated fibrosis and cirrhosis. In cases of chronic HBV infection, fibrosis and possibly cirrhosis can be reversed with antiviral drugs resulting in a reduced risk of HCC. Prolonged treatment with lamivudine, the least effective available antiviral drug, reduced the incidence of HCC by a significant 78% in a meta-analysis of 1,267 HBV patients with advanced fibrosis or cirrhosis compared with 1,022 similar patients not treated with lamivudine (11). Up to 75% of patients treated with lamivudine become resistant after 5 years. Newer antiviral drugs have much lower drug resistance rates and much greater suppression of HBV replication. One such drug, entecavir, caused regression of fibrosis in 88% of chronic HBV infection patients and only 0.7% became resistant to the drug after 5 years (12). Nevertheless, it is still not certain that treatment of either HBV-associated compensated (without complications) or decompensated cirrhosis (with one or more complications including ascites, bleeding esophageal varices, encephalopathy, or hepatorenal syndrome) with antiviral drugs results in a reduced risk of HCC. The evidence is clearer in HCV-associated advanced fibrosis and cirrhosis, where prolonged anti-HCV therapy with interferon-α2b does not reduce the risk of HCC (13, 14). It is possible that one of the new protease inhibitors, boceprevir or telaprevir, might reduce the risk of HCC in established HCV-associated cirrhosis, but this has yet to be shown in randomized clinical trials. At present, there is no known therapy that will reduce the risk of HCC in persons with HCV-associated cirrhosis.

Therefore, the report in this issue of the journal by Nkontchou and colleagues (15) of an association of treatment with the β-blocker (β-adrenergic–signaling blocker) propranolol with a reduced incidence of HCC in patients with advanced HCV-associated cirrhosis and esophageal varices is of great interest. The investigators conducted a retrospective analysis of HCC incidence in 50 of these patients who were treated with propranolol versus in 43 such patients who were not treated. β-Blockers have been used for many years to reduce the risk of hemorrhage from esophageal varices. This surprising finding requires confirmation, but the result is biologically plausible. Epidemiologic studies have linked β-blockers with reduced rates of metastasis of other cancers and reduced cancer mortality. Laboratory studies suggest biologic mechanisms for anticancer effects of β-blockers.
esophageal varices by reducing pressure in the portal vein and its tributaries. Portal hypertension is a severe, common complication of cirrhosis. Measurement of the hepatic venous pressure gradient (HVPG) is the best available method to evaluate the presence and severity of portal hypertension. The goal of β-blocker treatment is to reduce HVPG to less than 12 mm Hg, a level at which there is little risk of bleeding (16). Once started on β-blocker treatment to reduce the risk of variceal hemorrhage, patients are maintained on therapy indefinitely.

In the study conducted by Nkontchou and colleagues, 38 of 50 propranolol-treated patients and 34 of the 43 non–propranolol-treated patients had ligation of esophageal veins (banding). After 5 years of follow-up, HCC developed in 4% of the propranolol-treated patients and 20% of the non–propranolol-treated patients. This difference was highly statistically significant by multivariate analysis (HR, 0.16; 95% CI, 0.0005). This is a retrospective, observational study, and so the result could have been influenced by unknown confounders. Therefore, it would be helpful (albeit nonconclusive) if this study was repeated by use of data on similarly treated patients who are likely already available. Several centers must have many patients with HCV-associated cirrhosis and esophageal varices who were treated with either nonspecific β-blockers like propranolol and nadolol or specific β-1-blockers like atenolol. If other similarly designed observational studies supported Nkontchou and colleagues results, then randomized clinical trials would be warranted.

Even without supportive studies, there are other lines of evidence suggesting that β-blockers could have a preventive or, possibly, a therapeutic role in HCC. In a recent observational study, β-blockers were associated with reduced mortality from advanced melanoma (HR, 0.81) and reduced all-cause mortality (HR, 0.87; ref. 17). An important record-linkage study (connecting 2 independently collected sources of data) using a national prescription database and the cancer registry in Ireland indicated that the nonspecific β-blocker propranolol, but not the specific β-blocker atenolol, reduced breast cancer mortality (18).

If propranolol has an antitumor effect, it will be important to understand the mechanism of this action. Recent reviews noted that inflammation, angiogenesis, stress, anoikis, apoptosis, cell motility, and activation of tumor viruses contribute to the initiation and progression of cancer and that all these processes are regulated to some degree by β-adrenergic signaling. In experimental cancer models, activation of the sympathetic nervous system promotes metastasis of solid epithelial tumors. β-Adrenergic receptors on tumor and stromal cells are activated by norepinephrine from sympathetic nerve fibers and by epinephrine in the circulation.

A study of neurotransmitter-driven regulation using PC-3 prostate carcinoma cells implanted in athymic BALB/c nude mice showed that lumbar lymph node metastases increased with administration of norepinephrine, whereas propranolol inhibited this effect (22). Growth of the primary tumor was not affected by either treatment. Other preclinical laboratory models suggest that β-adrenergic receptor antagonists like propranolol are likely to inhibit the microscopic spread or invasion of early-stage tumors rather than reducing the burden of large tumors or preventing the occurrence of new tumors (23).

If this hypothesis is correct, then treatment with nonspecific β-blockers like propranolol might prevent HCC in patients with cirrhosis by preventing intrahepatic micrometastases or invasion of surrounding liver parenchyma from a small localized tumor rather than actually preventing the formation of new HCCs. Furthermore, propranolol does not seem to be affected by the underlying etiology of the cirrhosis and therefore might ultimately be useful in reducing the risk of HCC in cirrhosis from any cause. Whatever the mechanism might be, the role of propranolol in cirrhosis and HCC could be a fertile field for further investigation.

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W.T. London has expert testimony in Motley Rice LLC.

Authors’ Contributions
Conception and design: W.T. London
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References


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W. Thomas London and Katherine A. McGlynn


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