Published OnlineFirst April 23, 2012; DOI: 10.1158/1940-6207.CAPR-11-0450

Cancer Prevention Research

Research Article

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Effect of Long-term Propranolol Treatment on Hepatocellular Carcinoma Incidence in Patients with HCV-Associated Cirrhosis

Gisèle Nkontchou[1], Mounir Aout[2], Amel Mahmoudi[1], Dominique Roulot[1], Valérie Bourcier[1], Véronique Grando-Lemaire[1], Nathalie Ganne-Carrie[1], Jean-Claude Trinchet[1], Eric Vicaut[2], and Michel Beaugrand[1]

Abstract

Propranolol bears antioxidant, anti-inflammatory, and antiangiogenic properties and antitumoral effects and therefore is potentially active in the prevention of hepatocellular carcinoma (HCC). We retrospectively assessed the impact of propranolol treatment on HCC occurrence in a cohort of 291 patients with compensated viral C (HCV) cirrhosis, prospectively followed and screened for HCC detection.

Of the 291 patients included in the cohort, 93 patients [50 males: mean age, 59.5 ± 12 years; body mass index (BMI), 25.7 ± 4.4 kg/m^2; and platelet count, 111 ± 53 Giga/L] developed esophageal varices (OV) or had OV at inclusion and 198 patients (111 males: mean age, 55.8 ± 13 years; BMI, 25.7 ± 5 kg/m^2; platelet count, 137 ± 59 Giga/L) did not. Among patients with OV, 50 received treatment by propranolol. During a median follow-up of 54 months interquartile range (32–82), 61 patients developed an HCC. The 3- and 5-year HCC incidence was 4% and 4%, and 10% and 20% for patients treated and not treated by propranolol, respectively (Gray test, $P = 0.03$). In multivariate analysis, propranolol treatment was associated with a decrease risk of HCC occurrence [HR, 0.25; 95% confidence interval (CI), 0.09–0.65; $P = 0.004$], and was the only independent predictive factor of HCC occurrence in patients with OV (HR, 0.16; CI, 0.06–0.45; $P = 0.0005$). The benefit of propranolol was further supported by propensity scores analyses.

Conclusion: This retrospective long-term observational study suggests that propranolol treatment may decrease HCC occurrence in patients with HCV cirrhosis. These findings need to be verified by prospective clinical trial. *Cancer Prev Res; 5(8); 1007–14. ©2012 AACR.*

Introduction

The drastic decrease of hepatocellular carcinoma (HCC) incidence in HCV cirrhotic patients who achieved a sustained virological response to viral treatment (1–3) strongly suggests that oxidative stress, inflammation, and angiogenesis linked either directly with the viral replication or with the host immune response are involved in hepatocarcinogenesis. Indeed, high hepatic level of 8-hydroxy-2′-deoxyguanosine (marker of DNA damage induced by oxidative stress), as well as histologic markers of liver angiogenesis are associated with a higher incidence of HCC in patients with HCV cirrhosis (4, 5). In liver, HCV proteins induce NADPH oxidase 4 expression and subsequent reactive oxygen species (ROS) production through an autocrine TGFβ-dependent mechanism, trigger mitochondrion-derived ROS and angiogenesis (6–8). DNA damage and the activation of mitogen-activated protein, extracellular signal–regulated kinases, or angiogenesis induced by higher ROS levels may contribute to carcinogenesis (9 10). In addition to its β-adrenergic antagonist activity, propranolol has antioxidant and anti-inflammatory properties, that are in part linked to the protection of membranes against lipid peroxidation (11). Propranolol reduces intracellular Ca_2^+ overload and attenuate mitochondrial dysfunction by its action on electron mitochondrial membrane transport and also by inhibiting Bax-mediated cytochrome *C* release (12, 13). It also inhibits NADPH oxidase and protein kinase C activity (14) and decreases VEGF/(bFGF) basic fibroblast growth factor genes expression (15, 16). These effects, requiring cellular uptake of the drug, are not mediated by the β-adrenoreceptors, and are not shared by most other β-blockers (17–19). In experimental models, propranolol administration was shown to prevent or reduce cancer progression, by inhibiting cAMP—responsive element–binding protein (CREB), NF-κB, and activator protein (AP-1), inducting apoptosis, or reducing matrix metalloproteinase (MMP)-9 activation and tumor angiogenesis (20–23). In humans, propranolol was recently reported to control the growth of

Authors'Affiliations: [1]Liver Unit, Hôpital Jean Verdier, Bondy; and [2]Unit of Clinical Research Hôpital Lariboisiere, Assistance Publique-Hôpitaux de Paris, Université Paris 13, Paris, France

Corresponding Author: Gisèle Nkontchou, Service d'Hépatogastroenterologie, Hôpital Jean Verdier, avenue du 14 juillet, Bondy 93143 cedex, France. Phone: 00-33-1-48-02-62-80; Fax: 00-33-1-48-02-62-02; E-mail: gisele.nkontchou@jvr.ap-hop-paris.fr

doi: 10.1158/1940-6207.CAPR-11-0450

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proliferative infantile hemangioma (24). About breast cancers, 2 recent retrospective studies reported a remarkable reduction in the risk of recurrences and improved survival in women receiving β-blockers therapy. Patients treated with propranolol were significantly less likely to present with a T4 tumor, node-positive (N2/N3), or metastatic disease. In the study of Barron and colleagues, this benefit effect was observed in patients treated by propranolol but not in those receiving atenolol (25, 26).

In patients with cirrhosis, propranolol is commonly used to reduce portal hypertension and to prevent variceal bleeding in patients with esophageal varice (OV). The main alternative to β-blockers for the management of OV is band ligation (27). In our practice, both methods are used in association or alone, according to the clinician's choice, giving us the opportunity to retrospectively evaluate the impact of propranolol treatment in the incidence of HCC based in a large cohort of patients with HCV cirrhosis bearing or not OV and included in a screening program for HCC.

Patients

We retrospectively analyzed the prospectively collected data of a cohort of patients included in a screening program for HCC detection between 1994 and January 2007 satisfying the following criteria: (i) a compensated, histologically proven cirrhosis and absence of suspicion of HCC, (ii) presence of serum anti-HCV antibodies and serum HCV RNA by reverse transcription PCR; (iii) absence of hepatitis B virus or human immunodeficiency virus infections, hemochromatosis, biliary cirrhosis, Wilson's disease, α-1 antitrypsin deficiency; (iv) no severe life-threatening disease; (v) regular screening program for the detection of OV. Patients who achieved a sustained virological response after treatment during the follow-up were excluded.

Materials and Methods

In our institution, patients with cirrhosis and persistent HCV infection are screened for OV by endoscopy every 18 months. The physician in charge of the patient, according to the patient's preferred choice and potential contraindications to β-blockers, decide to treat or not by propranolol in case of large OV (≥grade II). The alternative choice being the band ligation, associated or not with propranolol. Two dosages of propranolol were used: long-acting propranolol (160 mg) once a day or propranolol (40 mg) twice a day.

To evaluate the impact of exposure to propranolol, clinical and biologic data of patients who had or developed OV were collected at the time of diagnosis of OV and decision to treat, and in those without OV at the date of inclusion in the screening program.

The cause of cirrhosis was considered as mixed (HCV + alcohol) in patients with past or ongoing daily ethanol intake >30 g/d. Diabetes status was collected as a binary parameter (yes/no) and was defined by a fasting serum glucose level higher than 126 mg/dL or by previous antidiabetic treatment. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared (kg/m^2).

Follow-up and HCC assessment

Patients were screened for HCCs by abdominal ultrasonography and serum α—fetoprotein (AFP) levels every 3 to 6 months. The diagnosis of HCC was assessed though histology or noninvasive criteria since EASL conference recommendations (28). Patients were prospectively followed and data were retrospectively analyzed. The observance and tolerance of propranolol were also reported.

Statistical analyses

Baseline continuous variables were expressed as means ± SD or median interquartile range (IQR) and compared using Student *t* test or, if not applicable, Mann–Whitney *U* test. Categorical variables were expressed as frequencies (percentages) and compared using χ^2 or Fisher exact test.

For the outcome of the study (HCC occurrence), the time frame was defined as the interval from the date of diagnosis of OV in the case of patients who developed OV or the date of inclusion in the screening program in the case of those who did not develop OV until the HCC occurrence. Follow-up was censored at the date of death, liver transplantation, or last visit until December 2007.

The cumulative incidence of HCC according to propranolol treatment, taking death or liver transplantation as a competing risk into account, was compared using the Gray test. Univariate analysis was conducted using the Cox regression model. All variables found to be significant on univariate analysis ($P < 0.1$) were entered into a stepwise multivariate model analysis. Because OV is also risk factors of HCC, we specifically address the influence of propranolol in the subgroup of patients with OV. The hazard rates were reported with 95% confidence intervals (CI).

As the patients treated by propranolol differed from those not treated by propranolol in terms of demography and liver impairment, we used propensity score methods to adjust for these differences. Propensity score methods permit control for observed confounding factors that might influence both group assignment and outcome using a single composite measure and attempts to balance patient characteristics between groups (29). The clinical and biologic variables at inclusion were used to calculate the propensity score. All analyses were 2-sided and *P* values less than 0.05 were considered statistically significant. Analyses were conducted with SAS 9.2 software (SAS Institute), and the graphics were done on R 2.12 (30).

Results

Patient data

Between 1994 and December 2006, 332 consecutive patients with viral C cirrhosis and no detectable HCC

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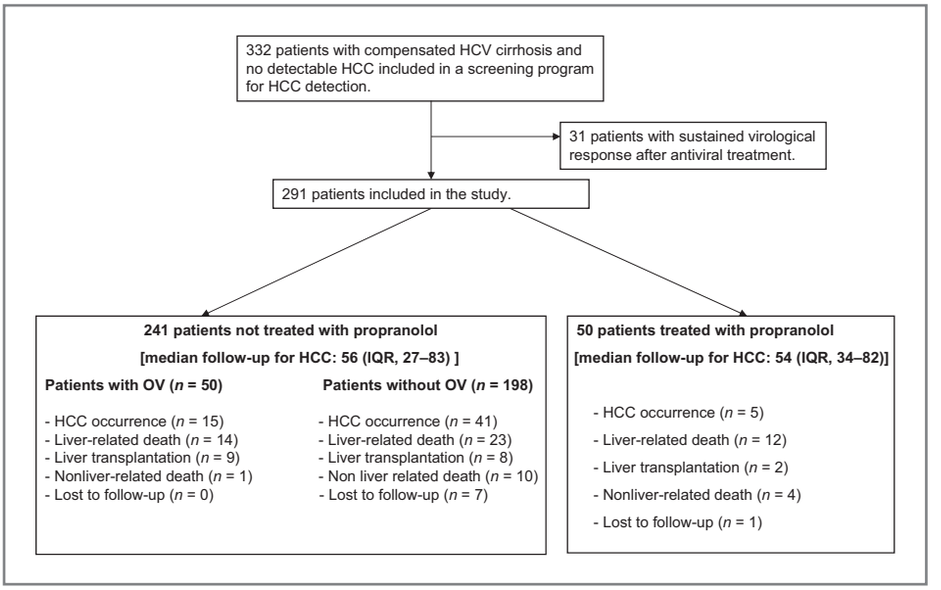

Figure 1. Patient's selection and outcomes.

referred to our Unit for liver biopsy were included in a screening program for HCC detection. Among these, 96 patients developed OV and 226 did not. Three patients in the group with OV and 28 patients without OV achieved sustained viral eradication after antiviral treatment and were excluded (Fig. 1).

Among the patients with OV, 50 received treatment by propranolol alone ($n = 12$) or in association with band ligation for large varices ($n = 38$). Long-acting 160 mg propranolol was administered once a day to 43 patients and 40 mg propranolol twice a day to 7 patients. The others ($n = 43$) had either no treatment ($n = 9$) or were treated by band ligation alone ($n = 34$). No patients without OV received propranolol.

The main clinical and biologic patient's characteristics at inclusion, according to propranolol treatment or not, are reported in Table 1. Patients treated by propranolol were older and had a lower platelet count than those not treated by propranolol. Conversely there was not statistically significant difference in clinical and biologic characteristics in

Table 1. Clinical and biologic characteristics of patients in the whole population according to the propranolol treatment or not

Variables	Patients not treated by propranolol (N = 241)	Patients treated by propranolol (N = 50)	*P*
Age, y	55.7 (44.59–67.14)	63.5 (52.9–69.07)	0.010[a]
BMI, kg/m^2	24.9 (23.03–27.97)	23.8 (21.86–26.83)	0.095[a]
Male	139 (57.7%)	23 (46%)	0.13
Mixed etiology	91 (38.7%)	15 (30%)	0.24
Diabetes	70 (31.3%)	17 (35.4%)	0.57
Serum AFP, ng/mL	8 (5–12)	7 (5–11)	0.74[a]
Prothrombin activity (%)	80 (69–91)	77 (61–90)	0.31[a]
Serum albumin, g/L	41.03 ± 5.58	40.49 ± 5.07	0.53
Serum bilirubin, μmol/L	13 (9–20)	15 (10–24)	0.28[a]
Platelet count ($\times 10^9$/L)	124 (90–170.5)	91.5 (64–130)	0.0005[a]
ALT (ULN)	2.2 (1.5–3.8)	2.05 (1.5–3.1)	0.75[a]
AST (ULN)	1.8 (1.3–2.8)	2 (1.5–3)	0.43[a]
Alkaline phosphatase (ULN)	1 (1–1.4)	1.1 (1–1.6)	0.09[a]
Child–Pugh B	12 (5%)	5 (10%)	0.18[a]
GGT (ULN)	2 (1.2–3)	1.9 (1–3.5)	0.57[a]

NOTE: Mixed etiology for past or ongoing daily alcohol intake >30 g/d AST, ALT, GGT.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ULN, upper normal limit range.

[a] For quantitative variables.

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Table 2. Univariate and multivariate analyses of predictors of HCC occurrence in the whole population (N = 291).

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1.03 (1.01–1.05)	0.0049	1.06 (1.04–1.09)	<0.0001
BMI	1.1 (1.05–1.16)	0.0002	1.09 (1.04–1.15)	0.0008
Male sex	1.54 (0.92–2.6)	0.10	2.8 (1.53–5.12)	0.0008
Mixed etiology	0.81 (0.47–1.41)	0.46		
Diabetes	1.42 (0.84–2.4)	0.19		
AFP	1 (1–1)	0.84		
Prothrombin activity	0.99 (0.98–1.01)	0.30		
Albumin	0.96 (0.91–1.01)	0.09		
Bilirubin	1.01 (0.99–1.03)	0.49		
Platelet count	0.99 (0.98–0.99)	<0.0001	0.98 (0.98–0.99)	<0.0001
ALT	0.97 (0.88–1.07)	0.51		
AST	0.88 (0.7–1.1)	0.27		
Alkaline phosphatase	0.96 (0.59–1.57)	0.88		
Child–Pugh class B	0.19 (0.01–3.08)	0.24		
GGT	0.98 (0.91–1.06)	0.65		
Propranolol treatment	0.44 (0.18–1.11)	0.08	0.25 (0.09–0.65)	0.0044

NOTE: Mixed etiology for past or ongoing daily alcohol intake >30 g/d AST, ALT, GGT.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

patients with OV, according to propranolol treatment or not. (Table 2).

Propranolol tolerance

Propranolol was stopped within 6 months in 3 patients due to side effects: bronchospasm in a patient with chronic obstructive pulmonary disease, symptomatic arterial hypotension and bradychardia in one patient, sexual deficiency in the third case. These 3 patients were included in the group not treated by propranolol.

Band ligation

Band ligation was conducted under general anesthesia. Esophageal pain with dysphasia or chest pain occurred respectively in 5 and 2 patients and spontaneously resolved after symptomatic treatment except for one patient who developed a stenosis of the lower esophagus. Two patients experienced transient bleeding episodes due to postbanding ulcers without hemodynamic consequences.

HCC development during the follow-up

After a median follow-up time of 54 months (IQR, 32–82): 56 (IQR, 27–83) for patients not treated and 54 (IQR, 34–82) for those treated by propranolol; 61 had developed HCC. HCC was histologically proven in 28 cases and was based on noninvasive criteria in 33 cases.

Eight patients were lost to follow-up (one patient treated with propranolol and 7 not treated with propranolol).

The 3- and 5-year HCC incidence rates were 4% and 4%, and 10% and 20% in patients treated and not treated by propranolol, respectively (Gray test $P = 0.03$; Fig. 2).

In multivariate analysis, absence of propranolol treatment, older age, male gender, higher BMI, and lower platelet count were risk factors of HCC development (Table 3).

In addition, using propensity score, we still found an association between propranolol use and incidence of HCC (HR, 0.31; CI, 0.12–0.83; $P = 0.019$).

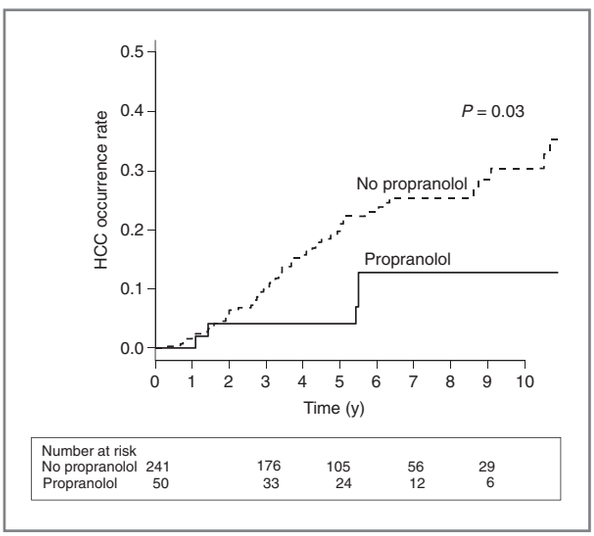

Figure 2. The 3- and 5-year HCC incidence was 4% and 4%; and 10% and 20% in patients treated and not treated by propranolol, respectively (Gray test, $P = 0.03$).

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Table 3. Clinical and biologic characteristics of patients with HCV cirrhosis and varices (OV) according to the propranolol treatment or not

Variables	Patients treated by propranolol (N = 50)	Patients not treated by propranolol (N = 43)	*P*
Age, y (±SD)	61.1 ± 12	57.7 ± 12	0.18
BMI, kg/m^2	24.8 ± 4	26.7 ± 5	0.06
Male	23 (46%)	27 (62%)	0.07
Mixed etiology	15 (30%)	18 (42%)	0.23
Diabetes (yes)	17 (35%)	15 (38%)	0.84
Serum AFP, ng/mL	32 ± 148	9.6 ± 9	0.61
Prothrombin activity (%)	76 ± 16	72 ± 19	0.35
Serum albumin, g/L	40.5 ± 5.1	38.8 ± 5.8	0.14
Serum bilirubin, μ/mL	19.7 ±16	21.5 ± 17	0.70
Platelet count, ×10^9/L	107 ± 57	117 ± 48	0.19
Alkaline phosphatase (ULN)	1.1	1.1	0.9
Varices grade ≥2 (%)	30 (60%)	28 (65%)	0.82
Child–Pugh B	5 (10%)	5 (11.6%)	1.00
Band ligation (%)	38 (76%)	34 (79%)	0.70

NOTE: Data are expressed as mean ± SD, median (IQR), or number (percentage). Mixed etiology for past or ongoing daily alcohol intake >30 g/d.

Abbreviations: ALT, ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ULN, upper normal limit range.

Subgroup populations

Patients with OV. In patients with OV ($n = 93$; Table 4), propranolol treatment was the only factor associated with the absence of HCC occurrence (HR, 0.16; 95% CI, 0.06–0.45; $P = 0.0005$ and HR, 0.13; 95% CI, 0.04–0.40; $P = 0.0020$), after adjusting by propensity score.

Patients with OV treated by propranolol and patients without OV. When excluding patients with OV not treated

Table 4. Univariate and multivariate analyses of predictors of HCC occurrence in patients with viral C cirrhosis with OV ($n = 93$)

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1 (0.96–1.04)	0.91		
BMI	1.1 (1.02–1.19)	0.014		
Male sex	2.6 (1–6.79)	0.050		
Mixed etiology	0.92 (0.35–2.41)	0.86		
Diabetes	0.99 (0.39–2.48)	0.99		
AFP	1 (0.96–1.03)	0.76		
Prothrombin activity	1 (0.97–1.03)	0.99		
Albumin	1.01 (0.93–1.1)	0.76		
Bilirubin	0.98 (0.95–1.02)	0.38		
Platelet count	1 (0.99–1.01)	0.81		
ALT	0.97 (0.72–1.3)	0.82		
AST	0.5 (0.25–1)	0.051		
Alkaline phosphatase	0.96 (0.41–2.25)	0.93		
GGT	0.98 (0.84–1.14)	0.78		
Child–Pugh B	0.22 (0.01–3.92)	0.30		
Propranolol treatment	0.16 (0.06–0.45)	0.0005	0.16 (0.06–0.45)	0.0005

NOTE: Mixed etiology for past or ongoing daily alcohol intake >30 g/d.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

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by propranolol ($n = 248$), the corresponding HR for propranolol treatment adjusted for propensity score was HR, 0.36; 95% CI, 0.13–0.995; $P = 0.049$.

It has been checked that similar results were found when the 3 patients who interrupted propranolol treatment within 6 months were classified as treated in an intention to treat analysis (data not shown).

Liver-related death or transplantation

After a mean follow-up of 60 ± 36 months, liver-related death or liver transplantation occurred in 38 patients with OV: 14 patients (28%) treated by propranolol and 24 patients (55%) not treated by propranolol. Death directly related to esophageal or gastric bleeding occurred in 4 patients: 2 treated by propranolol and 2 not treated by propranolol. Severe sepsis was the cause of death in 7 patients: 2 treated by propranolol and 5 not treated by propranolol.

In patients without OV and not treated by propranolol, 42 patients died of liver causes or were transplanted.

Discussion

In this large observational study, we assessed the impact of propranolol treatment on HCC occurrence in patients with compensated HCV cirrhosis and persistent infection prospectively and closely followed for a median period of 54 months and found that long-term use of propranolol reduced the incidence of HCC. In our study, propranolol treatment was still associated with low HCC occurrence using propensity score. The other main risk factors observed in our study (male sex, BMI, platelet count) are in accordance with previous studies (31). In addition and as expected, patients bearing OV are at higher risk to develop HCC, which justify a subgroup analysis in the patients (32).

The major limitations of our study are the observational and retrospective nature. However, we did not believe that potential confounding factors as the severity of the cirrhosis or the level of portal hypertension could have influenced the physician in charge of the patient to decide to treat by propranolol or not. There was no statistically significant difference in terms of epidemiologic characteristics, liver function tests, and prevalence of band ligation between patients with OV who received or not propranolol, suggesting that the severity of the cirrhosis had not influenced the decision to treat by propranolol or not. Furthermore, propranolol treatment was the only risk factor for HCC occurrence in patients with OV, with an HR that was not modified when adjusting with propensity score. The patients treated by propranolol (bearing with OV) were at a more advanced stage of cirrhosis. Therefore, if there was a bias, it will be against propranolol treatment.

As the median follow-up and the percentage of patients at risk treated or not by propranolol did not differ during the first 7 years, we can exclude that a bias related to premature death of patients with a more severe disease could explain our findings.

In our series of patients, compliance with screening and propranolol treatment was mainly due to the fact that all patients included in the study agreed to participate in a screening study and that we excluded patients with potential contraindications to treatment.

In randomized trials testing β-blockers for primary or secondary prevention of variceal bleeding, the incidence of HCC is minimal or unreported. It should be stressed that these studies were usually short termed and included a high rate of patients with alcoholic cirrhosis and advanced cirrhosis with a poor prognosis (33–36). The only large randomized study to evaluate the long-term effects of β-blockers was the one by Grosszmann and colleagues (37). In that study, the β-blocker treatment showed no influence on HCC occurrence, overall survival, or even the development of varices, which was the endpoint of the study in which the β-blocker used was timolol. This nonselective adrenoreceptor antagonist provides none of the membrane stabilizing properties, antioxidant effects, or protection against lipoperoxidation shown by propranolol (17–19). Additional effects of propranolol also include inhibition of liver phospholipase A2, phospholipase C, diacylglycerol formation (38, 39). Thus the protective effect of propranolol observed in our study could be presumably explained by one or several of these mechanisms that have been previously shown in *in vitro* studies and *in vivo* animal studies and may influence carcinogenesis. It is also suggested that the effects of β-adrenergic signaling in the regulation of immune response, on the inhibition of apoptosis, or on the induction of angiogenesis are inhibited by β2 receptor antagonists (20–23, 40–43).

Although propensity score methods have become increasingly used in analysis of population-based cohorts, conclusions about treatment effectiveness drawn from observational data are inherently limited. Propensity scores may reduce selection bias, but they can only control measured characteristics, and therefore cannot completely replicate the random treatment assignment of a clinical trial. We cannot exclude the possibility that the results were due to chance. Clearly, randomized placebo-controlled trials in this area would be required to provide definitive evidence of the benefit of propranolol in this group of patients and further define the underlying mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Received October 19, 2011; revised March 7, 2012; accepted March 19, 2012; published OnlineFirst April 23, 2012.

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Cancer Prev Res 2012;5:1007-1014. Published OnlineFirst April 23, 2012.

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