

Des-Gamma Carboxyprothrombin Can Differentiate Hepatocellular Carcinoma From Nonmalignant Chronic Liver Disease in American Patients

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Mortality due to hepatocellular carcinoma (HCC) has not improved over the last 20 years. This is in part due to the poor performance of available tumor markers leading to delays in diagnosis. Des-gamma carboxy-prothrombin (DCP) has been reported to be more sensitive and specific for the diagnosis of HCC in Japanese patients compared with α -fetoprotein (AFP). We conducted a cross-sectional case control study to evaluate whether DCP is more sensitive and specific than AFP for differentiating HCC from nonmalignant liver disease in a cohort of American patients from a single referral center. Four groups were studied: G1, normal healthy subjects; G2, patients with noncirrhotic chronic hepatitis; G3, patients with compensated cirrhosis; and G4, patients with histologically proven HCC. A total of 207 subjects were enrolled. Both DCP and AFP levels increased progressively from G1 to G4, but DCP values had less overlap among the groups than AFP. ROC curve indicated that a DCP value of 125 mAU/mL yielded the best sensitivity (89%; 95% CI, 77%-95%) and specificity (95%; 95% CI, 82%-96%) for differentiating patients with HCC from those with cirrhosis and chronic hepatitis. The optimal AFP cutoff value was 11 ng/mL and was inferior to the DCP value of 125 mAU/mL, the area under the ROC curves being 0.928 versus 0.810, respectively ($P = .002$). In conclusion, DCP was more sensitive and specific than AFP for differentiating HCC from nonmalignant chronic liver disease. Prospective studies to evaluate the role of DCP in early HCC are underway. (HEPATOLOGY 2003;37:1114-1121.)

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States.¹ However, patient survival in HCC has improved minimally over the last 2 decades. Between 1981 and 1998, the 5-year survival rate only rose from 2% to 5%.² The poor

survival rate is in part related to the diagnosis of HCC at advanced stages where effective therapies are lacking.³⁻⁵ Surveillance of patients at the highest risk for developing HCC, *i.e.*, patients with cirrhosis, is an important strategy that can potentially decrease the cancer-related mortality rate. Although HCC meets the criteria of a tumor that would benefit from a surveillance program,⁶ the poor sensitivity and specificity of currently available tools has prevented widespread implementation of HCC surveillance. For example, α -fetoprotein (AFP) has been the serum marker that is most widely used for diagnosis as well as surveillance of HCC.^{7,8} However, AFP levels may be normal in up to 40% of patients with HCC, particularly during the early stages (low sensitivity).⁹ Furthermore, elevated AFP levels may be seen in patients with cirrhosis or exacerbations of chronic hepatitis (low specificity).¹⁰ Prospective studies evaluating the performance characteristics of AFP for HCC surveillance reported sensitivities of 39% to 64%, specificities of 76% to 91%, and positive predictive values of 9% to 32%.¹¹⁻¹³ Abdominal ultrasound is the most common imaging modality used in the surveillance of HCC. The sensitivity, specificity, and pos-

Abbreviations: HCC, hepatocellular carcinoma; AFP, α -fetoprotein; DCP, des-gamma carboxy-prothrombin; CTP, Child-Turcotte-Pugh; ROC, receiver operating characteristic; AUROC, area under the ROC curve; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPV, positive predictive value; NPV, negative predictive value.

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itive predictive value have been reported to be 71% to 78%, 90% to 93%, and 14% to 73%, respectively.^{9,13,14} However, the accuracy of ultrasound is dependent on the operator and his or her ability to differentiate HCC from non-neoplastic lesions such as regenerative nodules.¹⁵ Therefore, there is a need for additional serum markers that will improve the detection rate of early HCC.

Des-gamma carboxyprothrombin (DCP) or prothrombin induced by vitamin K absence-II (PIVKA-II) is an abnormal prothrombin protein that is increased in the serum of patients with HCC. Generation of DCP is thought to be a result of an acquired defect in the post-translational carboxylation of the prothrombin precursor in malignant cells.¹⁶ The reduction of gamma-carboxylase activity had been determined to be due to defective gene expression in HCC.¹⁷ In 8 large case-controlled studies, serum DCP was found to have a sensitivity of 48% to 62%, a specificity of 81% to 98%, and a diagnostic accuracy of 59% to 84% in differentiating patients with HCC from those with cirrhosis.¹⁸⁻²⁵ In these studies, AFP had a sensitivity of 40% to 54%, a specificity of 88% to 97%, and a diagnostic accuracy of 64% to 76%. Five of these studies showed an improved sensitivity of DCP over AFP; the other 3 studies found no significant difference between the 2 markers but the combination of DCP and AFP was more sensitive than either marker alone. These studies suggest that DCP is more sensitive in the diagnosis of HCC than AFP but a range of DCP (40, 60, or 100 mAU/mL) and AFP (20 to 200 ng/mL) cutoff values were used in these studies. Two studies in Italian patients using DCP cutoff values of 40 and 90 mAU/mL found that DCP was not superior to AFP. The authors recommended a combination of DCP and AFP for the diagnosis of HCC.^{26,27} Therefore, additional studies are warranted to determine the role of DCP in the diagnosis of HCC in Western populations.

Given the rising incidence of HCC in the United States and the lack of data on the role of DCP as a marker of HCC in American patients, we conducted a cross-sectional study to compare the accuracy of DCP versus AFP in the differentiation of HCC from nonmalignant chronic liver disease, and to define the DCP level that has the best sensitivity, specificity, and positive predictive values for the diagnosis of HCC in American patients.

Patients and Methods

Patients. All the patients were enrolled from the liver and liver transplantation clinics at the University of Michigan Medical Center between September 2001 and May 2002. This study was approved by our Institutional Review Board. Written informed consent was obtained from

each patient. Demographic and clinical information was collected from each subject. Four groups of consecutive subjects were enrolled. Group 1 (G1) included normal healthy subjects with no history of liver disease, alcohol consumption less than 40 g/wk, and no risk factors for viral hepatitis. All subjects were documented to have normal liver biochemistry. Group 2 (G2) consisted of patients with histologically confirmed noncirrhotic chronic hepatitis. Group 3 (G3) consisted of patients with histologically proven cirrhosis and compensated liver disease (*i.e.*, Child-Turcotte-Pugh [CTP] score <7). Group 4 (G4) consisted of patients with histologically proven HCC. Etiology of underlying liver disease was attributed to hepatitis C virus based on detection of hepatitis C antibody/hepatitis C virus RNA in serum, hepatitis B virus based on hepatitis B surface antigen in serum, alcohol based on a daily alcohol intake of more than 40 g/ethanol per day for more than 15 years, hereditary hemochromatosis if they had a positive genetic testing or hepatic iron index greater than 1.9, primary biliary cirrhosis based on serum anti-mitochondrial antibody and compatible histology, and primary sclerosing cholangitis based on beading on cholangiogram. The etiology of liver disease was considered to be cryptogenic if no cause was identified after exhaustive testing as described above. Tumor staging was determined using the modified TNM staging system for HCC.²⁸ Computed tomography and magnetic resonance imaging studies of patients with HCC were reviewed by a radiologist who was not aware of the serum marker results. A 20-mL blood sample was drawn from each subject for AFP and DCP testing more than 2 weeks after liver biopsy was performed. Blood samples were spun and serum aliquoted and stored at -80°C until testing. Blood samples from G4 subjects were drawn prior to initiation of HCC treatment. None of the subjects received vitamin K during the week prior to entry into this study.

AFP Assay. AFP was tested using commercially available immunometric assays utilizing enhanced chemiluminescence at the University of Michigan Hospital Clinical Diagnostic Laboratory. The upper limit of normal was 8 ng/mL.

DCP Assay. DCP level was measured using an enzyme-linked immunosorbent assay kit (Eitest PIVKA-II; Eisai Co., Tokyo, Japan) per the manufacturer's instructions and were performed in duplicate. Briefly, plates pre-coated with anti-PIVKA-II monoclonal antibody were incubated with either serially diluted standards or serum samples for 16 to 24 hours at 4°C. After washing with 0.9% sodium chloride, enzyme-conjugated anti-human prothrombin antibody was added and incubated at room temperature for 1 hour. The plate was then washed and

Table 1. Demographic Information and Etiology of Liver Disease

	Group 1 (n = 48)	Group 2 (n = 51)	Group 3 (n = 53)	Group 4 (n = 55)	P ($\alpha > .05$)
Gender	26:22	24:27	28:25	34:21	NS
M:F					
Age (y)	51 \pm 11	50 \pm 6	52 \pm 8	56.2 \pm 13	NS
% NHW/AA/H/A	90/10/0/0	78/16/4/2	69/11/9/11	88/6/4/2	NS
MELD	4 \pm 0.7	5 \pm 0.8	7.2 \pm 1.3	9.4 \pm 2.3	<.03*
Etiology (%)					
HCV		80	64	46	<.001†
HBV		10	11	4	NS
Alcohol		0	2	13	<.001‡
Autoimmune		6	4	2	NS
PBC		2	13	2	NS
Hemochromatosis		0	2	0	NS
Cryptogenic		2	4	33	<.001‡

NOTE. All data are expressed as mean \pm SD. NS = $P > .05$.

Abbreviation: NHW, non-hispanic white; AA, African American; H, Hispanic; A, Asian; MELD, model for end-stage liver disease score; HCV, hepatitis C; HBV, hepatitis B; PBC, primary biliary cirrhosis.

*Group 4 versus 1 and 2.

†Group 4 versus Group 2.

‡Group 4 versus Groups 1, 2, and 3 as well as Group 3 versus Group 2.

the substrate was added to the plate for 60 minutes at room temperature prior to the addition of the stop solution. Subsequently, the plates were read on a microtiter plate reader at 405 nm. Samples with values above 1,000 mAU/mL (the upper limit of the standard curve) were diluted 10, 100, and 1,000 fold and remeasured.

Statistical Analysis. A sample size of 50 per group will allow us to have 90% power to detect at least a 15% difference between DCP and AFP in distinguishing HCC from nonmalignant liver disease. The DCP and AFP values were reported as mean \pm SD and median:range. Log transformation was used on the AFP and DCP values to account for the large range of values among the groups for both markers. The descriptive statistics for the transformed markers were compared by box plots and then by analysis of variance. The Youden's index was calculated as an index of sensitivity and specificity.²⁹ To determine the optimal cutoff value for DCP and AFP in the diagnosis of HCC, receiver operating characteristic (ROC) curves were constructed using all possible cutoffs for each assay. The area under the ROC (AUROC) curves were calculated and compared as described previously.^{30,31} Univariate analysis was performed on patients with HCC to identify potential factors affecting AFP and DCP levels. Variables with P values $< .10$ in the univariate analysis were then subjected to multivariate analysis by forward logistic regression to identify independent factors associated with AFP or DCP levels. The variables entered in the analysis included albumin, international normalized ratio, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, model for end-

stage liver disease score, CTP score, TNM staging, gender, age, presence of hepatic encephalopathy, and presence of ascites. To combine the markers, we found the linear coefficient to maximize the area under the curve for the combination AFP and DCP.³² A bivariate normal distribution for the two markers was assumed. A 2-tailed P value of $< .05$ was used to determine statistical significance. All analyses were performed using SAS software (Cary, NC).

Results

A total of 207 subjects were enrolled. There were 48 subjects in G1, 51 in G2, 53 in G3, and 55 in G4. The four groups were comparable in gender, age, and race (Table 1). Hepatitis C was the most common etiologic factor among all 3 groups of subjects with liver disease, but other etiologies, specifically alcohol and cryptogenic liver disease, were more common in those with HCC compared with patients in groups 2 and 3 ($P < .001$). The median CTP score in G3 patients was 5 (95% CI, 5-5.9) and the median CTP score in G4 patients was 6 (95% CI, 5.3-7.3), which were not significantly different ($P = .075$).

DCP and AFP Values Among the 4 Groups of Subjects Studied. DCP levels increased from G1 to G4 with median (range) levels of 25 (11-63), 31 (14-180), 36 (14-155), and 1,925 (20-233,200) mAU/mL ($P < .001$) (Fig. 1). Twelve (25%) normal subjects had DCP values above 40 mAU/mL, the upper limit of normal reported in Japanese subjects.²³ Using a cutoff value of 63 mAU/mL

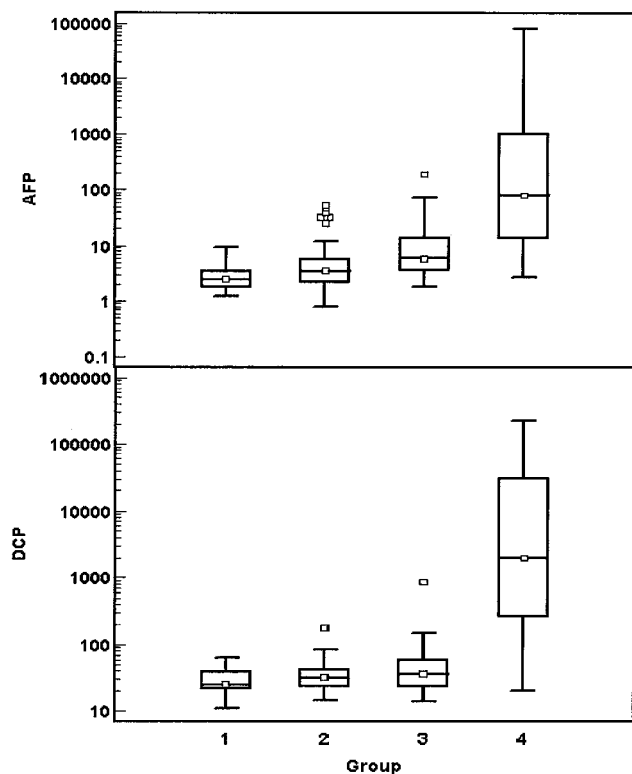


Fig. 1. Box plot for DCP and AFP values in the 4 groups of subjects. The box indicates the 25th and 75th percentile of the data and the middle line indicates the median. A line extends from the minimum to the maximum value, excluding outliers that are displayed as separate points. Outliers are smaller than the lower quartile minus 3 times the interquartile range or larger than the upper quartile plus 3 times the interquartile range.

as the upper limit of normal for Americans, 3 (5%), 9 (17%), and 50 (90%) subjects in G2, G3, and G4, respectively had elevated DCP values.

The AFP levels also increased with median (range) levels of 2.5 (1.2-8.9), 3.5 (0.8-53.1), 5.9 (1.8-190.2), and 79 (2.7-82,752) ng/mL for G1 to G4 ($P = .001$) (Fig. 1). Seven (14%), 22 (41%), and 43 (79%) subjects in G2, G3, and G4 had elevated AFP values. Of the patients with HCC, 18 (33%) had AFP values <20 ng/mL, 11 (20%) had AFP between 21 and 100 ng/mL, and 20 (36%) had AFP >400 ng/mL.

Optimal Cutoff Values for DCP and AFP in Differentiating HCC From Nonmalignant Chronic Liver Disease. ROC curves were plotted to identify a cutoff value that would best distinguish HCC (G4) from nonmalignant chronic liver disease (G2 and G3). The optimal cutoff values for DCP and AFP were 125 mAU/mL and 11 ng/mL, respectively (Fig. 2). These values yielded a sensitivity and specificity for DCP of 89% (95% CI, 77%-95%) and 95% (95% CI, 82%-96%), and for AFP of 77% (95% CI, 62%-88%) and 73% (95% CI, 63%-88%), respectively. The AUROC curve indicated a better

sensitivity and specificity for DCP than AFP for differentiating HCC from nonmalignant chronic liver disease (0.928 vs. 0.830, $P = .002$). To see if the combination of AFP and DCP was better than either of these markers by itself, we created a new variable combining AFP and DCP ($\log\text{AFP} + 4.6 \cdot \log\text{DCP}$). The combination had a sensitivity of 88% (95% CI, 76%-96%), a specificity of 95% (95% CI, 88%-98%), and an AUROC of 0.930. However, this was not different from DCP alone ($P = .198$).

The optimal values for DCP and AFP in differentiating patients with HCC (G4) from those with cirrhosis (G3) were 150 mAU/mL and 13 ng/mL, respectively (Fig. 3). These values gave a sensitivity of 89% (95% CI, 75%-96%) and a specificity of 96% (95% CI, 84%-99%) for DCP, and 75% (95% CI, 59%-86%) and 78% (95% CI, 62%-88%) for AFP. The AUROC curve indicated a better sensitivity and specificity for DCP than AFP for differentiating HCC from cirrhosis (0.921 vs. 0.815, $P = .0149$). There was no significant difference between the DCP value of 125 mAU/mL used to distinguish HCC from nonmalignant chronic liver disease, and the DCP value of 150 mAU/mL ($P = .154$). When AFP and DCP were combined, there was no significant improvement compared with DCP alone (AUROC = 0.924, $P = .187$).

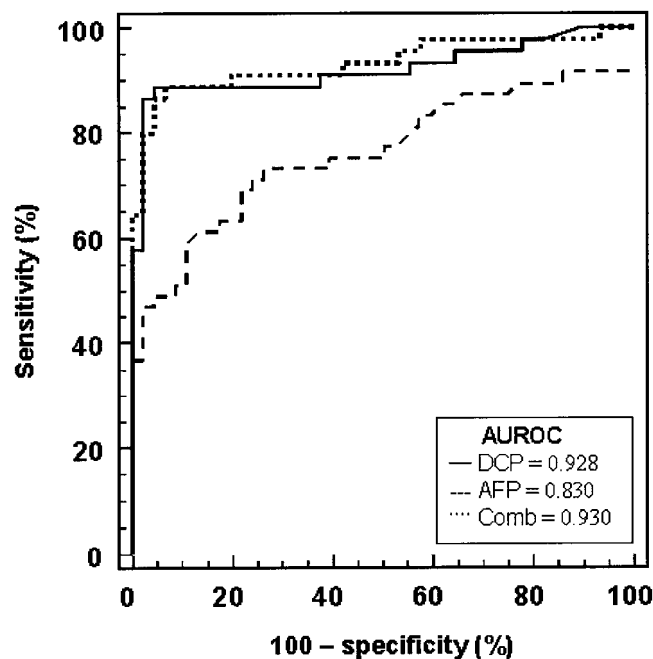


Fig. 2. ROC curves comparing DCP, AFP, and a combination of AFP and DCP in patients with HCC (G4) versus those with chronic liver disease (G2 and G3). The curves show the optimal cutoff value for DCP of 125 mAU/mL and for AFP of 11 ng/mL. The AUROC curves for DCP, AFP, and Comb are indicated in the inset. $P = .002$ for DCP versus AFP and $P = .198$ for DCP versus Comb.

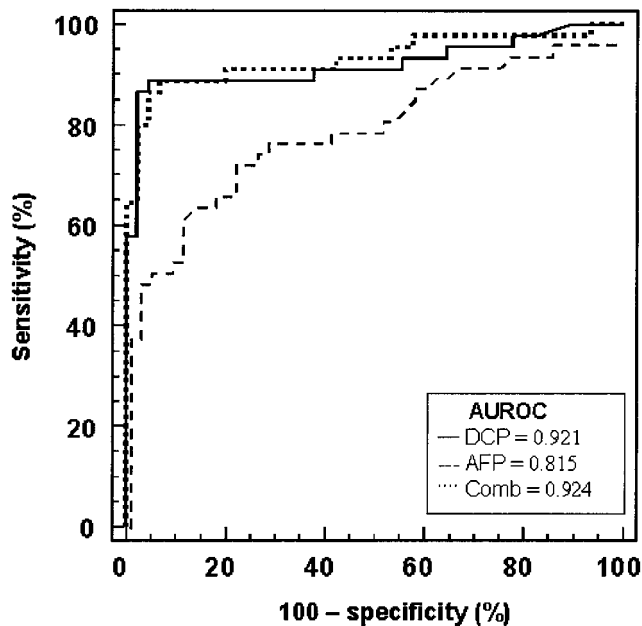


Fig. 3. ROC curves comparing DCP, AFP, and a combination of AFP and DCP in patients with HCC (G4) versus those with cirrhosis (G3). The curves show the optimal cutoff value for DCP of 150 mAU/mL and for AFP of 13 ng/mL. The AUROC curves for DCP and AFP are indicated in the inset. $P = .0149$ for DCP versus AFP and $P = .187$ for DCP versus Comb.

Sensitivity, Specificity, and Predictive Values of DCP and AFP in Differentiating Patients With HCC From Those With Cirrhosis or Chronic Liver Disease.

A DCP value >125 mAU/mL had better sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) than DCP values of 40, 60, or 100 mAU/mL used in other published studies for the diagnosis of HCC as indicated by the ROC curves and Youden's index (0.7431, 95% CI, 0.468-0.817) (Table 2). As the cutoff AFP value increased from 11 ng/mL to 400 ng/mL, the specificity and PPV increased but the sensitivity and NPV decreased. A DCP value >125 mAU/mL had better sensitivity and specificity than AFP, regardless of the cutoff value chosen, in differentiating patients with HCC (G4) from those with cirrhosis (G3) or chronic liver disease (G2 and G3) ($P < .05$).

DCP and AFP Values According to Tumor Staging.

Of 55 patients with HCC, 50 (91%) had a DCP value >125 mAU/mL of whom only 37 (74%) had an AFP value >11 ng/mL. Forty-three (78%) patients with HCC had an AFP value >11 ng/mL of whom 39 (89%) had a DCP value >125 mAU/mL. Based on modified TNM classification, 20 patients had stage I, 11 stage II, 12 stage III, and 12 stage IV tumors. There was no difference in the distribution of patients among the different tumor stages ($P = .4346$). The median (range) DCP values were 773 (20-81,460), 29,710 (158-80,975), 2,049 (133-

233,200), and 9,472 (31-180,527) mAU/mL for patients with stage I, II, III, and IV HCC, respectively. The corresponding AFP values were 25 (2.7-64,916), 50 (4.5-82,752), 130 (4-2,284), and 447 (3.2-9,058) ng/mL for stage I, II, III, and IV HCC, respectively. There was no significant difference in DCP or AFP values among the tumor stages ($P = .335$ for DCP, $P = .564$ for AFP). A DCP value of 150 mAU/mL had a PPV and NPV of 92% and 91%, respectively, for differentiating stage I HCC and those with cirrhosis and no HCC, whereas the corresponding values for an AFP value of 13 ng/mL were 54% and 90%, respectively ($P = .269$).

Univariate analysis identified albumin ($P = .014$), ALT ($P = .01$), AST ($P < .0001$), and CTP score ($P = .001$); and albumin ($P = .039$), AST ($P = .054$), creatinine ($P = .08$), and CTP score ($P = .06$); as variables that had significant correlation with DCP and AFP, respectively. In the multivariate analysis, AST was the only variable that significantly correlated with DCP values ($P = .0003$), and also the only variable that significantly correlated with AFP values ($P = .0124$).

Discussion

In this report of the role of DCP in the diagnosis of HCC in American patients, we showed that DCP is more

Table 2. DCP Versus AFP in Differentiation of Patients With HCC From Those With Chronic Liver Disease

	Sensitivity	Specificity	PPV	NPV
DCP (mAU/mL)				
>125				
HCC vs. CLD	89	95	87	95
HCC vs. cirrhosis	90	91	85	90
>150				
HCC vs. CLD	87	97	89	94
HCC vs. cirrhosis	89	96	91	88
AFP (ng/mL)				
>11				
HCC vs. CLD	77	79	75	80
HCC vs. cirrhosis	77	71	81	74
>20				
HCC vs. CLD	68	86	67	82
HCC vs. cirrhosis	68	82	76	67
>100				
HCC vs. CLD	47	98	95	78
HCC vs. cirrhosis	47	98	95	63
>400				
HCC vs. CLD	34	100	100	75
HCC vs. cirrhosis	34	100	100	59
DCP & AFP*				
HCC vs. CLD	88	95	87	94
HCC vs. cirrhosis	90	95	90	88

NOTE. CLD = Groups 2 and 3; cirrhosis = Group 3; HCC = Group 4. Values are expressed in percent.

Abbreviation: CLD, chronic liver disease.

Combination obtained from variable $\log\text{AFP} + 4.6\log\text{DCP}$.

accurate than AFP in differentiating patients with HCC from those with nonmalignant chronic liver disease. We found that DCP levels increased according to the stepwise progression of liver disease, *i.e.*, from chronic hepatitis to cirrhosis to HCC, and according to tumor stage. ROC curve identified the optimal cutoff DCP value to be 125 mAU/mL for differentiating patients with HCC from those with nonmalignant chronic liver disease. Although the optimal cutoff DCP value for differentiating patients with HCC from those with compensated cirrhosis was slightly higher, 150 mAU/mL, the performance of a DCP value of 150 versus 125 mAU/mL was not significantly different. Taken together, our results suggest that a DCP value of 125 mAU/mL is associated with a very high probability (~90%) of a diagnosis of HCC in a subset of American patients with underlying chronic liver disease.

Using a cutoff value of 125 mAU/mL, DCP was superior to AFP in the diagnosis of HCC regardless of the AFP value chosen. This DCP value is higher than values used in studies from Asia (40-100 mAU/mL).^{20,21,24,33} The higher value identified in our study may be related to higher DCP values among American subjects without liver disease. It is also possible that the cutoff DCP value we chose was more appropriate as it was identified by the ROC curve while values in the majority of previous studies were chosen arbitrarily through sensitivity and specificity or Youden's index. We found that the optimal cutoff AFP value for the diagnosis of HCC was 11 ng/mL (upper limit of normal 8 ng/mL). This is substantially lower than values used in other studies and is related to the high proportion (21%) of HCC patients with AFP values within the normal range. Our results are in accordance with recent studies showing the poor performance of AFP in the diagnosis of HCC.⁵ Several studies found that a combination of AFP and DCP was more sensitive and specific for the diagnosis of HCC compared with either marker alone.^{22,34,35} We found that the combination of DCP and AFP was not significantly better than DCP alone in differentiating HCC from nonmalignant liver disease. In our multivariate analysis, we found that AST was the only factor that independently affected AFP and DCP levels. A higher AST:ALT ratio has been reported in patients with HCC compared with those with cirrhosis, likely due to an increase in cytosolic AST.^{36,37}

Our results are very encouraging but there are several important limitations in our study. The sample size was powered to detect only a difference between malignant and nonmalignant chronic liver disease; not a difference among tumor staging. The vast majority (>80%) of our subjects were white. It is possible that the cutoff values for DCP and AFP may be different in different ethnic groups. A study from California found that AFP was less

sensitive for the diagnosis of hepatitis C virus-related HCC in African Americans compared with whites.³⁸ It is possible that there may be ethnic differences in the performance of DCP in differentiating HCC from nonmalignant chronic liver disease. Previous studies have used varying cutoff DCP values for Italian, Japanese, and Chinese subjects.^{18,39} We found that normal American subjects have DCP values up to 63 mAU/mL whereas studies in Japan have used 40 mAU/mL as the upper limit of normal. It is also possible that the etiology of liver disease can alter DCP levels. Hepatitis C was the underlying etiology in most (~70%) of our patients with chronic liver disease and in approximately half of our patients with HCC. Some studies found that the performance of AFP in the detection of HCC may be dependent on the cause of the underlying liver disease.⁴⁰ Furthermore, DCP levels may be higher in those with alcohol-induced liver disease when compared with those with chronic viral hepatitis.⁴¹ Our study only included patients with compensated Child's class A cirrhosis, which is the ideal target population for HCC surveillance based on the recommendations from a recent consensus conference.⁴² It is possible that patients with decompensated cirrhosis may have higher DCP values because of alterations in vitamin K production secondary to cholestasis, malnutrition, renal failure, or use of medications that alter gut flora.⁴³ However, our study showed that neither cholestasis nor impaired renal function were significant predictors of DCP values.

The most important question is whether DCP will be a better or complementary marker for the detection of early HCC than AFP. Our study was a cross-sectional study and was not designed to address this question. Nevertheless, we showed that a higher proportion of patients with stage 1 HCC had DCP values above the cutoff compared with AFP, PPV of 91% versus 54% ($P = .269$). The National Cancer Institute has recommended 5 phases for screening biomarker development and validation: pre-clinical exploratory studies, assay detection of disease, retrospective longitudinal, prospective screening, and cancer control.⁴⁴ Our study was performed to determine the ability of DCP to distinguish American subjects with HCC from American subjects with chronic liver disease (second phase). A prospective study of patients with cirrhosis is underway to further validate the utility of DCP as a marker for the detection of early HCC.

In conclusion, our cross-sectional study showed that DCP was better than AFP in differentiating HCC from nonmalignant chronic liver disease in American patients. A DCP value of >125 mAU/mL among patients with underlying chronic liver disease was associated with a high probability of HCC (sensitivity and specificity ~90%). Prospective studies on a large number of patients with

diverse ethnic backgrounds and a broad spectrum of underlying etiologies of liver disease are needed to confirm if DCP is a more reliable marker than AFP for the early diagnosis of HCC. Additional studies are also needed to verify the optimal cutoff DCP value for HCC diagnosis and to determine if the same value can be applied to all ethnic groups and all underlying etiologies of liver disease. Data from these studies may help to improve the outcome of patients with HCC by enabling the diagnosis to be made at an earlier stage of the disease when curative treatment is possible.

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