Published in final edited form as:

J Surg Oncol. 2012 July 1; 106(1): 84–88. doi:10.1002/jso.23036.

Comparison of Hepatocellular Carcinoma in American and Asian Patients by Tissue Array Analysis

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Abstract

Background—Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Although some epidemiologic and etiologic differences between Asian and Western HCC are known, detailed comparative studies with pathologic correlations have not been performed.

Methods—Paraffin sections of resected HCC specimens from Memorial Sloan-Kettering Cancer Center and Korea University Medical Center were used to construct tissue microarrays. Immunohistochemical staining of microarray sections was performed using antibodies against markers of proliferation and regulators of cell cycle. Patient data were correlated with staining results.

Results—When comparing cohorts, significant differences were found in expression of p53 and In the Asian group, more frequent positive staining for p53 (24%) was observed compared with the American group (9%; $P = 0.037$). For MDM2, 26% of American cases stained positive compared with 2% of Asian cases ($P = 0.0003$). No significant differences were found in expression of Ki67, p21, p27, cyclin D1, or bcl2. Female gender, vascular invasion, and lack of viral hepatitis infection correlated with positive MDM2 staining.

Conclusion—These data likely correlate with differences in molecular pathogenesis of HCC based on racial and regional differences. These findings may have implications in choice of molecular targeted therapies based on patient ethnicity.

Keywords

immunohistochemistry; South Korean; molecular characterization; HepPar1

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is responsible for 1 million deaths worldwide each year.(1–3) HCC can arise anywhere in the liver parenchyma, with or without the presence of liver cirrhosis. Major risk factors include chronic hepatitis B and C, ingestion of dietary aflatoxin B1 (AFB1), vinyl chloride exposure, and alcohol consumption.

There are many geographic differences related to the prevalence of HCC. (1;4;5) While endemic to Asia and Africa, the incidence of HCC is increasing in the United States and Europe. (4–6) In the United States, the frequency of HCC has increased from 1.4 per 100,000 population in 1980, to 2.4 per 100,000 in 1995, with 6.7 per 100,000 males and 3.1 per 100,000 females in 2000.(6;7) In 2006, American Cancer Society (ACS) surveillance research showed 18,510 estimated new cases and 16,200 estimated deaths for both sexes for cancers of the liver and intrahepatic bile ducts.(8) In South Korea, the incidence of HCC is 12.2 per 100,000 and 16.3 per 100,000 males, making it the second leading cause of cancer death for men.(9) Hepatitis B prevalence is as high as 8% to 15% in China, Southeast Asia, most Pacific islands, and the Amazon basin, and is the estimated cause of 30% of cirrhosis and 53% of HCC worldwide. There is a low prevalence (less than 2%) of hepatitis B in the United States, Western Europe, and Australia. Hepatitis C is estimated to be the cause of 27% of cirrhosis and 25% of HCC worldwide, with a prevalence of only 1.7% in the Americas and 1.03% in Europe, but it is much higher in Africa (5.3%) and Egypt (15%).(10) The prevalence rates of hepatitis B and C in South Korea are 5% and 1%, respectively. The annual incidence of HCC is attributable to HBV (68%) and HCV (12%) in South Korea.(11) The current study examines the expression of cell cycle–regulating proteins in HCC and whether the findings correlate with pathologic variables and outcome. Studies of these proteins are central to current investigations in pathogenesis and progression of cancer. (12;13) Strategies targeting these proteins and their related metabolic pathways are under intensive investigation for various cancers. In this study, we sought to determine if HCC in American patients has a different molecular profile compared with that observed in Asian patients. The secondary objective of this study was to determine if therapies tested in Asia—where HCC is more prevalent—may be immediately applicable to an American population.

MATERIALS and METHODS

After approval by the Institutional Review Board, a total of 86 patients were identified in a database at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, as having had a resection for HCC between 1981 and 1998. The mean age of these patients at time of operation was 62 years (range, 26–83 years). Of these, 70 patients—40 males and 30 females—qualified for the study. Fourteen patients classified as Asian Americans were excluded, leaving 56 for study. These excluded patients who did not emigrate from Asia were classified as “American.” Another 51 HCC patients—46 males and 5 females—operated on from 1994 to 2001 at Korea University Medical Center in Seoul were included in the study. All South Korean patients were ethnically Asian. Clinical data were collected from patient medical records.

For tissue array production, paraffin blocks (Beecher Instruments, Silver Spring, MD) from all resected HCCs were obtained to construct a tissue microarray. Hematoxylin and eosin (H&E)-stained slides were examined to identify normal and tumor tissue. At MSKCC, a precision manual arrayer was used to procure 0.6-mm cores in triplicate from representative normal and tumor areas, which were then embedded into a recipient paraffin block as previously described by Hoos et al.(14) The tissue arrays from South Korea were produced by placing single 3-mm cores of normal and tumor tissue in a recipient block with holes

created manually. The difference was necessitated by the inability to transport tissue blocks of active patients across international borders.

Immunohistochemical staining was performed on 5- μ m sections using the streptavidinbiotin-horseradish peroxidase technique. The tissue was deparaffinized, rehydrated, and pretreated for antigen retrieval as required by the specific staining profiles for each antibody (Table 1). Endogenous peroxidase was quenched in 3% hydrogen peroxide, and the tissue blocked using bovine serum albumin (BSA). The specific antibodies used, sources, dilutions, and pretreatment conditions are listed in Table 1. After washing in phosphate-buffered solution (PBS), a biotinylated antimouse secondary antibody (1:500, Vector Inc., Burlingame, CA) was added followed by a second PBS washing with peroxidase-conjugated streptavidin (1:500, DakoCytomation, Carpinteria, CA). Diaminobenzidine was used as the chromogen, and hematoxylin as the nuclear counterstain. The first H&E stain was used to confirm the presence and morphology of tumor tissue in the sections stained for the above markers.

For evaluating the staining, the intensity (0, 1+, 2+, 3+, 4+) and percentage of cells staining for p53, p21, p27, BCL-2, MDM2, and cyclin D1 were assessed, while for Ki-67 only the percentage of the cells that stained was assessed. For p53, p21, p27, BCL-2, MDM2, and cyclin D1, staining was considered positive if the intensity was 2+ or higher and >10% of the cells were labeled. For Ki-67, the average percentage of labeling in the neoplastic tissue was recorded. All patient indicators were removed after clinical analysis as required by the Health Insurance Portability and Accountability Act (HIPAA). Patient data including sex, age, tumor size, tumor differentiation, status of cirrhosis, presence of vascular and peripheral invasion, lymph node status, margin status, coincidental presence of hepatitis, and α -fetoprotein (AFP) levels were correlated with the staining data for significance (Table 2).

In the statistical analysis, the chi-square test, Fisher exact test, or Wilcoxon signed rank test were used where appropriate for univariate comparisons. For univariate survival analysis, plots were made using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis of variables significant in univariate analysis was used to determine the hazard ratio of the prognostic factors. Differences were considered significant at $P=0.05$. All statistics were performed by a biostatistician with an appropriate statistical package (SPSS, Chicago, IL; or SAS, Durham, NC).

RESULTS

Comparison of demographics and clinical characteristics

The group of patients at MSKCC is referred to as the “American group” and excluded Asian American patients. The “Asian group” refers to the patients from South Korea. The comparison of clinical and pathologic data is presented in Table 3. The mean age of the cohorts varied significantly between Asians (56 years) and Americans (64 years) ($P<0.01$). Gender ratio was almost equal in the American group, but a higher ratio of males in the Asian group (90%) was observed ($P<0.01$). Tumor size was larger in the American group (mean 10.96 ± 5.37 cm) compared with the Asian group (mean 5.60 ± 4.11 cm; $P<0.01$). This size difference was even more significant for tumors >8 cm [71% in the American group versus 29% in the Asian group ($P<0.01$)]. When comparing tumor differentiation, the Asian tumors were more often poorly differentiated (Asian 28% vs. American 21%; $P<0.01$). Cirrhosis was present in 26% of American patients and 72% of Asian patients ($P<0.01$). Vascular invasion was more common in American patients compared with Asian patients (72% vs. 25%, respectively; $P<0.01$). Invasion to adjacent organs such as the stomach, colon, or renal capsule was more common in Asian versus American patients (50% vs. 5%, respectively; $P<0.01$). Nodal metastasis was found in only 1 American patient; none

was found in the Asian patients ($P < 0.01$). No difference was found between the American and Asian patients in margin positivity or hepatitis C status. Hepatitis B was more prevalent in the Asian patients compared with the American patients (71% vs. 31%, respectively; $P = 0.01$). There was no difference in AFP levels between the groups (<15 ng/mL, 15–2000 ng/mL, and >2000 ng/mL; $P = 0.71$) (Table 4).

Comparison of protein expression by immunohistochemical staining

The results of staining for p53, p21, p27, BCL-2, MDM2, cyclin D1, Ki-67 and HepPar1 are listed in Table 4. A significant difference was noted in only 2 proteins, p53 and MDM2. Expression of p53 was more frequent in HCC from Asian patients (24% vs. 9%; $P = 0.037$), whereas MDM2 was more common in tumors from American patients (26% vs. 2%; $P = 0.0003$). HepPar1 staining was more commonly positive in Asian tumors compared with American tumors (80% vs. 65%, respectively; $P = 0.09$).

Correlations with MDM2 and p53 expression

Female gender was associated with MDM2 positivity (73%; $P < 0.01$) (Table 2). Vascular invasion was also more common in MDM2-positive tumors (88%; $P = 0.02$). AFP levels >2000 ng/mL were more common in MDM2-positive tumors (70% vs. 10%, respectively, for values <15 ng/mL; $P < 0.01$). This would be consistent with the observation that higher AFP levels are associated with a higher incidence of vascular invasion.(10) Liver cirrhosis was more common in patients with p53-positive tumors (71%; $P = 0.0645$) (Table 2). There were no statistically significant associations between the staining results and other clinical or prognostic factors.

DISCUSSION

The incidence of HCC is rising in the Western world. Knowledge of this disease and most therapeutic trials have originated from regions where this cancer is endemic, namely Southeast Asia. The purpose of the current study was to determine whether the molecular pathologic characteristics of HCC in American and Asian patients were similar. The secondary goal of the study was to determine if there is a biologic basis supporting the extrapolation of results from therapeutic trials conducted in Asian patients with HCC, to American patients.

In this study, tissue microarray technology was used, which allowed high-throughput immunohistochemical profiling of cancer specimens.(14–16) The validity of microarrays for immunohistochemical evaluation has been previously confirmed for use in the initial screening of large numbers of tumors for clinical research purposes.(16–18)

The results demonstrate a significant difference between Asian and American HCCs in the expression of 2 proteins, p53 and MDM2. The *p53* gene, mapped to chromosome 17p13, is a relatively well-investigated tumor-suppressor gene, which encodes a protein that regulates a cell cycle checkpoint and the induction of programmed apoptosis in response to DNA damage, cell stress, or the aberrant expression of some oncogenes.(19;20) *p53* mutations frequently result in an immunohistochemically detectable accumulation of the p53 protein in tumor cells.(21) (22) Missense mutations in the *p53* gene, which inactivate its growth-suppressing activities, have been noted in $>60\%$ of all human tumors. In a number of cases, elevated transcription of the *p53* gene contributes to the overall high levels of the mutant protein in tumor cells. Unlike other tumor suppressors, where loss of function is sufficient to promote tumorigenesis, $>75\%$ of the observed mutations in p53 are missense mutations that, in some cases, may confer some growth advantage to cells expressing them. (20;23)

A number of studies have examined the incidence of p53 mutation in HCC occurring in Asian patients. In areas endemic for hepatitis B–related HCC, such as South Korea, China, Hong Kong, and Taiwan, the incidence is reported to be approximately 30%. (24–26) (27) In regions with hepatitis C–related HCC such as Japan, the incidence is as high as 67%. (23;28–31) The current study confirmed an incidence of p53 overexpression of 24% in Asian patients and documents a much lower rate of 9% in American patients. However, no significant association with presence or type of viral hepatitis could be demonstrated. Of note, the incidence of hepatitis C in Korean patients is very low (<1% typical). Thus, no definitive statements regarding correlation of hepatitis C, gene expression, and ethnicity can be made.

The *MDM2* gene is a proto-oncogene (32) that codes for a protein that binds and perhaps limits the effectiveness of cellular p53 protein. (33;34) The oncogenic potential of MDM2 is partially explained by the inhibition of p53 activity. (32;34) More dramatically, p53 is targeted by MDM2 for rapid degradation. The *MDM2* gene itself is activated by p53, which allows for feedback control of p53 activity. Controlling p53 is most likely the major task of MDM2 during early development. (21) MDM2 protein forms a complex with the p53 tumor-suppressor protein and downregulates p53 function. (35) (36;37) Recently, in addition to MDM2-mediated inactivation of p53, a p53-independent role for MDM2 in tumorigenesis was found (35). MDM2 was expressed in 26% of American HCCs and had a significantly negative correlation with expression of p53. (38) MDM2 represents a target for cancer therapy, (13) with many strategies that include antagonists to MDM2 action or compounds that sensitize to p53-dependent apoptosis. Our data suggest that these would be more reasonable therapies in the American population than in Asian patients. These data also suggest that profiling of tumors would be necessary for selection of patients for trials of such agents.

CONCLUSIONS

The data suggest differences in the molecular pathogenesis of HCC based on distinct racial and/or regional differences. Vascular invasion is the single most significant predictor of survival in multivariate analysis for all these factors. These results suggest differences in the molecular pathogenesis of HCC according to ethnicity and support the potential use of molecular analysis in choosing patients for trials and treatment using targeted therapies.

Acknowledgments

Supported by grants R01CA75461 and R01CA72632 from the National Institutes of Health (Y.F.) and by grant MBC-99366 from the American Cancer Society (Y.F.)

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Table 1

Mouse antihuman monoclonal antibodies used in this study

Name of antibodies	dilutions	sources and pretreatment conditions
p53	1:500	clone D07 ^a
BCL-2	1:50	clone 124 ^a
Ki-67	1:200	clone MIB1 ^a
p21 ^{Waf-1}	1:100	– ^b
p27 ^{Kip-1}	1:2000	clone SX53G8 ^a
MDM2	1:2000	– ^b
cyclin D1	1:1000	clone DCS6 ^a

^aDakoCytomation, Carpinteria, CA.^bOncogene Science, Cambridge, MA.

Table 2Prognostic factors^a according to MDM2 and p53 for all patients

	MDM2	<i>P</i> value	p53	<i>P</i> value
Sex [F (%) / M (%)]				
Negative	22 (24) / 69 (76)	<0.01	28 (32) / 60 (68)	1.00
Positive	11 (73) / 4 (27)		5 (29) / 12 (71)	
Age (<60 / >60)				
Negative	41 (45) / 50 (55)	0.6	38 (43) / 50 (57)	0.29
Positive	8 (53) / 7 (47)		10 (59) / 7 (41)	
Tumor (<8 cm / >8cm)				
Negative	46 (52) / 42 (48)	0.4	39 (46) / 45 (54)	0.19
Positive	5 (36) / 9 (64)		11 (65) / 6 (35)	
Differentiation (Well-moderate / poor)				
Negative	42 (57) / 32 (43)	1.0	38 (58) / 27 (42)	0.78
Positive	4 (57) / 3 (43)		8 (53) / 7 (47)	
Cirrhosis (No/Yes)				
Negative	40 (49) / 42 (51)	0.4	42 (55) / 34 (45)	0.06
Positive	8 (67) / 4 (33)		5 (29) / 12 (71)	
Vascular invasion (No/Yes)				
Negative	38 (59) / 26 (41)	0.02	30 (53) / 27 (47)	0.77
Positive	1 (13) / 7 (88)		9 (60) / 6 (40)	
Peripheral invasion (No/Yes)				
Negative	23 (68) / 11 (32)	0.3	23 (74) / 8 (26)	0.66
Positive	5 (100) / 0 (0)		5 (63) / 3 (38)	
Node (Negative/Positive)				
Negative	35 (100) / 0 (0)	0.10	30 (97) / 1 (3)	1.00
Positive	3 (75) / 1 (25)		8 (100) / 0 (0)	
Margin (Negative/Positive)				
Negative	74 (88) / 10 (12)	0.7	71 (89) / 9 (11)	0.43
Positive	12 (86) / 2 (14)		14 (82) / 3 (18)	
Hepatitis B or C (Negative/Positive)				
Negative	19 (34) / 37 (66)	0.09	19 (38) / 30 (61)	0.60
Positive	5 (71) / 2 (29)		4 (31) / 9 (69)	
α-fetoprotein (AFP) (ng/mL; <15 / 15–2000 / >2000)				
Negative	27 (36) / 35 (47) / 12 (16)	<0.01	24 (35) / 29 (43) / 15 (22)	0.34
Positive	1 (10) / 2 (20) / 7 (70)		3 (20) / 8 (53) / 4 (27)	

^aResults given as n (%).

Table 3

Demographic data for American and Asian patients with hepatocellular carcinoma

Factors	American	Asian	P value
Age, y (mean $\pm$ SD)	63.75 $\pm$ 11.73	56.47 $\pm$ 10.01	<0.01
60 y, n (%)	18 (33)	31 (61)	0.01
>60 y, n (%)	38 (67)	20 (39)	0.01
Gender F:M n (%)	29 (51)/27 (49)	5 (10)/46 (90)	<0.01
Tumor size (cm, mean $\pm$ SD)	10.96 $\pm$ 5.37	5.60 $\pm$ 4.11	<0.01
Poor differentiation %	21	28	<0.01
Cirrhosis %	26	72	<0.01
Vascular invasion %	72	25	<0.01
Margin positive %	18	6	0.12
Hepatitis B %	31	71	<0.01
Hepatitis C %	9	0	0.2
α -fetoprotein (AFP) (ng/mL) n(%)			
<15	15 (38)	13 (30)	0.7
15–2000	13 (33)	24 (55)	0.7
>2000	12 (30)	7 (16)	0.7

Table 4

Comparison of protein expression by race

Proteins	American *	Asian *	P value
p53			
Negative (%)	52 (91)	38 (76)	0.037
Positive (%)	5 (9)	12 (24)	
p21			
Negative (%)	46 (81)	41 (80)	1.000
Positive (%)	11 (19)	10 (20)	
p27			
Negative (%)	41 (72)	37 (74)	0.8
Positive (%)	16 (28)	13 (26)	
BCL-2			
Negative (%)	44 (77)	39 (80)	0.8
Positive (%)	13 (23)	10 (20)	
MDM2			
Negative (%)	42 (74)	50 (98)	0.0003
Positive (%)	15 (26)	1 (2)	
Cyclin D1			
Negative (%)	53 (95)	47 (94)	1.0000
Positive (%)	3 (5)	3 (6)	
Ki-67			
10% express (%)	57 (100)	49 (96)	0.9
>10% express (%)	0 (0)	2 (4)	
HepPar1			
Negative (%)	20 (35)	10 (20)	0.09
Positive (%)	37 (65)	40 (80)	

* Result given as n (%).