HEPATOCELLULAR CANCER: RISK FACTORS AND SURVIVAL IN PACIFIC ISLANDERS COMPARED TO CAUCASIANS IN HAWAII

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Background: Hepatocellular cancer (HCC) is increasing in the United States. Although studies indicate that Asian and Pacific Islanders have an especially high incidence, no study has characterized HCC in the subgroup of Pacific Islanders (PI) alone.

Objective: To describe risk factors/survival of HCC in PI compared to Caucasians in Hawaii.

Patients: Of 523 HCC patients referred 1993–2008, 72 PI patients were compared to 85 Caucasian patients.

Measurements: In this retrospective-cohort study, data collected included demographics, risk factors, tumor characteristics, laboratory studies, treatment and survival. Chi-square analyses and *t*-tests identified difference between groups. Cox-proportional hazards model determined regression analysis of survival data.

Results: Mean age and sex distribution were not significantly different between groups. PI were more likely to have hepatitis B (36% vs 6%, $P<.05$), symptoms at presentation (60% vs 40%, $P=.003$), and larger tumors ($P=.02$). Caucasians were more likely to have hepatitis C (65% vs 43%, $P=.01$) and encephalopathy. Mean survival was significantly different between PI and Caucasians (10.9 months vs 43.3 months, $P=.01$). Multivariate-regression analysis showed late stage III/IV, increased Childs score, hepatitis B infection, and alcohol history associated with decreased survival. PI ethnicity was independently associated with increased hazard ratio. Treatment regardless of modality reduced hazard ratio for survival.

Conclusion: PI with HCC were more likely to have hepatitis B, symptoms and larger tumors, though they were just as likely to have their HCC found upon screening. PI ethnicity independently affected survival. Better education of the community/physicians on detection of hepatitis B and recognizing this risk for HCC in PI is needed. (*Ethn Dis.* 2010;20:169–173)

Key Words: Hepatocellular Cancer, Pacific Islanders, Hepatitis B

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INTRODUCTION

Hepatocellular cancer (HCC) is the fifth most common cancer and the third most common cause of cancer mortality worldwide. In 2002, approximately 626,000 new cases and 598,000 deaths were identified.[1] In the United States, while most cancers were decreasing in incidence and mortality rate, liver and bile duct cancers had the highest increase in death rate and second highest increase in incidence of all cancers between 1995 and 2005.[2] In the late 1990s, the estimated US incidence was 2.4 per 100,000, but using the Survival, Epidemiology, End Results (SEER) data from 2000–2004, the overall age-adjusted incidence of these cancers is currently estimated at 6.2 per 100,000 with about 19,000 new cases diagnosed in 2007.[2,3]

HCC is a distinctly different cancer in various geographic regions of the world. It differs in incidence, risk factors and natural history and these differences have been attributed to ethnicity, endemic viral hepatitis, and other risk factors.[4–6] A clear association has been established between the development of HCC and viral hepatitis, alcohol use, genetic metabolic diseases, environmental exposures, smoking, cirrhosis, and oral contraceptives. Viral hepatitis C has been associated with approximately 60% of cases of HCC in the US and Europe, while in Japan 70% of HCC is related to hepatitis C and 20% associated with hepatitis B.[7,8]

In the United States, the incidence of HCC is about 4-fold higher in Asian/Pacific Islanders than Caucasians and incidence rates vary greatly among subpopulations such as a particularly high incidence and death rates of HCC in Samoan males.[9,10] Risk factors for viral hepatitis and HCC may be different in Asian compared to Pacific Islanders, yet the data are frequently pooled into one seemingly heterogeneous group; the SEER data did not separate Asian and Pacific Islanders racial categories until 1991.

Pacific Islanders constituted approximately 0.1% (399,000 people) of the US population in 2000 and consists of 25 diverse cultural groups, of which Native Hawaiians (58%) are the largest group followed by Samoans (17%).[11] Few study populations have enough patients in these specific ethnic groups to make any definite statement about them separately. Little is known about HCC in Pacific Islanders alone as the literature frequently compares differences in HCC survival in Asians and Caucasians.[12–15]

Hawaii is the ideal state to study HCC in this population. Hawaii had the highest incidence (10.3 cases per 100,000) and death rate (7.9 per 100,000) of HCC in the United States in 2005. The population of Hawaii is approximately 40% Asian and 8.5% Pacific Islander ethnicity and an estimated 60% of all native Hawaiians in the United States live in Hawaii.[15,16] This study describes risk factors and survival rates of HCC in Pacific Islanders compared to Caucasians in Hawaii.

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METHODS

This is a retrospective cohort study of a prospectively-collected database of patients with HCC. A total of 523 cases, of which 72 (14%) self-identified as Pacific Islanders and 85 (16%) self-identified as Caucasian, were referred either to the Liver Center or a group of surgeons at a tertiary medical center in Honolulu, Hawaii from August 1992 to June 2008. This site is a participant in the National Cancer Institute's SEER Program, requiring the highest standards of data quality, as judged by completeness, accuracy, and timeliness. This medical center has the only clinic dedicated to liver diseases, the only transplant center in the state and the only referral center for liver diseases for American territories of the Pacific Basin (including American Samoa, Guam, Saipan, and the Marshall Islands). All patients signed informed consent that their medical charts could be used for retrospective research and that all personal identifiers would be kept strictly confidential and all data would be stored in a secured computer system in the author's private office. IRB approval was submitted and the institution determined the study did not require further approval.

We collected demographic data including age, sex, birthplace, and primary ethnicity as identified by the patient. Patients who self-reported to be at least 50% Pacific Islander in ethnicity were included as Pacific Islanders; these included Native Hawaiians, Samoans, Marshallese, Chuukese, Chamorro, Guamanian, and Tongan. Filipinos were not included as Pacific Islanders. We recorded a history of diabetes, other cancer, smoking, and family history of cancer. Risk factors for HCC including viral hepatitis B or C, alcohol abuse (defined as greater than 2 alcoholic beverages daily for at least 10 years), and other chronic liver diseases were identified. We also collected data on possible etiology of viral hepatitis including as vertical transmission, previous blood transfusions, intravenous drug use (IVDA), tattoo placement and high-risk occupations.

HCC was diagnosed histologically by percutaneous biopsy, liver biopsy at the time of surgery or examination of the resected liver removed at surgery. Similar to United Network for Organ Sharing (UNOS) policy regarding transplant for HCC, patients without histologic confirmation were included if they had a history of chronic liver disease and a mass at least 2 cm in size seen on two imaging studies (ultrasound, CT scan or MRI) and one of the following: (1) a vascular blush seen on CT scan or MRI; (2) AFP >200 ng/mL or; (3) an arteriogram confirming the tumor.[17]

Size, number, and location of the tumor were recorded in order to determine tumor node metastases (TNM) stage. Additional laboratory data included bilirubin, albumin, and prothrombin time. Clinically, the presence of ascites (defined as fluid on abdominal ultrasound or patient on diuretics for the treatment of ascites) and encephalopathy were noted in order to calculate Childs-Turcotte-Pugh (CTP) scores. Serum alpha-fetoprotein (AFP) was also recorded. The CTP scores were also expressed as Child's class A (CTP 5–6), B (CTP 7–9) or C (CTP >9). Finally, type of treatment and dates of diagnosis and death were recorded in order to calculate the survival in days from diagnosis. Liver resection was considered in Child's A patients or early Child's B (CTP score of 7) patients without any evidence of ascites or encephalopathy. Liver transplant was considered in patients who were unresectable for technical reasons or had decompensated liver disease, but had TNM stage T1 or T2 lesions (Milan criteria). Patients on the transplant waiting list in our center underwent either radiofrequency ablation or transarterial chemoembolization while waiting for a donor.

Chi-square analyses were used to identify differences in characteristics and risk factors between Pacific Islander and Caucasian groups. Kaplan-Meier Survival analysis compared HCC survival in Pacific Islanders to Caucasians. Cox proportional hazards model was used to determine regression analysis of survival data. The model included basic demographic characteristics (age, sex, race/ethnicity) and potential effect modifiers, smoking status and alcohol consumption. *T*-tests ($\alpha=0.05$) and 95% confidence intervals were utilized to determine statistical significance. We added potential confounding variables to each of the models, including diabetes status, hepatitis B and C status, symptoms at presentation, presence of encephalopathy, tumor size ($<$10cm or $\geq$10cm), HCC screening status, cirrhosis status, ascites status, or stage I/II vs III/IV. Backwards selection was used to model the outcome of survival. SAS v9 software was used for statistical analysis (SAS Institute, Cary NC).

RESULTS

The Pacific Islander population was significantly younger (median age: 55.7 years, SD=12.1 years vs 60.5 years, SD=8.95 years) and more likely to be born in Hawaii or another Pacific Island ($P=.001$) than the Caucasian population (Table 1). Men comprised 81% of the sample. There was no significant difference in sex distribution, smoking status, alcohol consumption, or diabetes status between Pacific Islanders and Caucasians. Bivariate analyses of risk factors showed that Pacific Islanders had a significantly higher prevalence of hepatitis B (40% vs 12%, $P<.001$), were more likely to have symptoms at

Table 1. Population characteristics, *n*=157

Characteristics	Pacific Islanders (%)	Caucasians (%)	
Age (years)	55.7 (mean), 54 (median), SD: 12.1	60.5 (mean), 58 (median), SD: 8.95	*P*-value
Sex			.92
Male	81	81	
Female	19	19	
Birthplace			<.001
Hawaii	56	22	
Pacific Islands	44	0	
Mainland US	0	60	
Non-US	0	7	
Smoking	66	65	.98
Alcohol consumption	58	54	.60
Diabetes	21	20	.93

presentation (60% vs 43%, P=.03), had larger tumor size ≥10cm (31% vs 14%, P=.02) than Caucasians (Table 2). However, Caucasians had significantly higher prevalence of hepatitis C (66% vs 43%, P=.01) and encephalopathy (31% vs 13%, P=.01) (Table 2). There was no statistically significant difference between cirrhosis, ascites, later stage, or HCC screening status (Table 2). Bivariate analyses of treatment showed Pacific Islanders were significantly less likely to receive liver transplants (3% vs. 18%, P=.04) than Caucasians, but there was no statistically significant difference between other treatment modalities (Table 2).

Median survival for HCC was significantly decreased in Pacific Islanders compared to Caucasians (10.9 months vs. 43.3 months, P=.01) up to 48 months (Figure 1).

Multivariate survival analysis showed late stage (III/IV) at presentation, increased CTP score, alcohol consumption, and hepatitis B infection significantly increased the hazard ratio for mortality. Pacific Islander ethnicity independently increased one's hazard ratio for mortality by 70% (Table 3). Although presence of both hepatitis B and C act synergistically, this occurred in only 3 individuals in the study population and was not statistically significant. Treatment modality was found to be protective for survival in both resection or transplant (HR=0.29; P<.001), as well as for other types of treatment (HR=0.46; P=.01) (Table 3). Presence of hepatitis C infection, smoking status, sex, symptoms at presentation, HCC screening, tumor size >5cm, encephalopathy, and presence of ascites were not statistically significant in the model for survival.

DISCUSSION

Our study demonstrated that Pacific Islanders were more likely to have hepatitis B, symptoms at presentation, and larger tumors than Caucasians. This is consistent with previous literature that identifies the etiology of HCC in Asian/Pacific Islanders to be primarily due to chronic viral hepatitis B infection.[18] Caucasians were more likely to present with hepatitis C and encephalopathy, which is also consistent with previous literature.[19,20] Because hepatitis B-related HCC can develop without evidence of decompensated cirrhosis, these patients may have clinically silent disease until a large space-occupying mass or advanced disease is detected. In addition Pacific Islanders may have limited access to and/or awareness of health care services such as hepatitis B screening, HCC screening and hepatitis B vaccination. There may also be differences in socioeconomic status, such as delayed seeking of medical care until symptomatic, or cultural differences in perception of illness which could delay seeking medical attention. However, although this study did not demonstrate a difference in the proportion of HCC, which was identified with screening measures between these two races, HCC was found at a more advanced stage.

Liver transplant is the only curative measure for HCC and significantly fewer Pacific Islanders received transplants compared to Caucasians. Other studies have described such healthcare disparities, in which African Americans and Asians were significantly less likely than Caucasians to receive liver trans-

Table 2. Bivariate analysis of risk factors and treatment type, *n*=157

	Pacific Islanders	Caucasians	*P*-value*
Risk Factors	(%)	(%)	
Hepatitis B	41	12	<.001
Hepatitis C	43	66	.01
Symptoms at presentation	60	43	.03
Encephalopathy	13	31	.01
Tumor size, >10cm	31	14	.02
HCC screening	17	7	.06
Treatment type			
None	40	28	.04
Resection	18	16	
Liver transplant	3	18	
Other treatment	38	37	

* Cirrhosis, ascites, later stage were not significantly different between groups

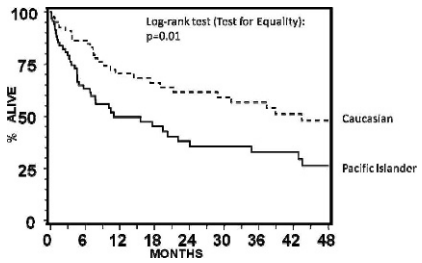

Fig 1. Survival curve. Caucasians compared to Pacific Islanders with HCC

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plants for localized HCC.[21] This may reflect a delay in access to medical care or perhaps the larger tumor size prevented Pacific Islanders from qualifying for liver transplant. Additionally, since Pacific Islanders have more hepatitis B without cirrhosis, these patients may have been resection candidates. Due to small sample size, it is difficult to directly correlate our study population to a study by Robbins et al who observed a declining disparity in liver transplantation of Asian/Pacific Islanders to Caucasians after the UNOS 2002 policy changes for MELD point assignments.[22]

Our study also found that Pacific Islanders had significantly shorter median survival time than Caucasians and multivariate regression showed that Pacific Islander ethnicity independently increased the hazard for poor survival. This may reflect either a genetic predisposition or other contributing factors that our analysis was unable to account for. Other factors such as late stage III/IV, higher CTP score, hepatitis B infection, and alcohol use appeared to be most strongly associated with decreased survival. Treatment modality decreased the hazard ratios, showing resection/transplant or other treatment as predictive of improved survival. Since Pacific Islanders received significantly fewer liver transplants than Caucasians and no significant difference in other treatment types, it is possible that this may contribute to their decreased survival. It is likely that confounding effects that we did not account for may be contributing to the survival difference between Pacific Islanders and Caucasians, despite hepatitis B infection and liver transplant rates being significantly different between the groups in the bivariate analysis.

One of the limitations of this study is that ethnicity was self-reported and we included patients of mixed ethnicity as long as they reported that they were at least 50% Pacific Islander. Pacific Islanders of mixed race may have diluted any genetic risk factor or cultural factor of unique risk for Pacific Islanders developing HCC. Also, HCC is a fairly rare disease, thus our study was a small sample size (though this sample represents about 60% of HCC patients in the state of Hawaii). Lastly, our sample represents HCC patients referred to surgeons and may have excluded some cases of advanced HCC who were non-surgical candidates. Strengths of our study include the following: biometric measures were utilized, this is the largest collection of Pacific Islanders with HCC in the U.S., and the cohort represents referrals to the state of Hawaii's only Liver Center.

Hepatocellular cancer in Pacific Islanders is a serious problem and hepatitis B is the main etiologic factor. The incidence of hepatitis B in this population is not completely known but the incidence of hepatitis B in Hawaii from mass screening is 3.6% and Pacific Islanders were over seven times more likely to have hepatitis B than Caucasians.[23] Efforts should be made to educate community physicians on the association between hepatitis B and HCC in Pacific Islanders, especially among those who consume alcohol. Primary prevention of viral hepatitis B infections should be emphasized. This has been partly achieved for younger generations with the implementation of universal infant hepatitis B vaccination programs in 1991, however, newly immigrated Pacific Islanders are not likely to have been vaccinated and may be unaware of their hepatitis B status.[24] Studies have indicated that hepatitis B screening programs that included treatment and vaccination of close contacts in the Asian and Pacific Islander population would be highly cost effective.[25]

There should be improved recognition of the risk for HCC in Pacific Islanders among both gastroenterology specialists and primary care providers. Practice guidelines from the American Association for the Study of Liver Disease recommends that Asian males >40 years and females >50 and all cirrhotic hepatitis B carriers should undergo surveillance for HCC. Ultrasound examination is recommended

Table 3. Age-adjusted multivariate hazards model for HCC survival, *n*=134*

	Hazard Ratio	95% CI	*P*-value
Race, Pacific Islander	1.70	(1.06, 2.74)	.03
Late stage III/IV at presentation	2.62	(1.58, 4.34)	<.001
Elevated CTP score	1.44	(1.07, 1.93)	.02
Alcohol use	1.70	(1.06, 2.71)	.03
Hepatits B infection, positive	1.74	(1.02, 2.97)	.04
Treatment: resection/transplant	.29	(.14, .59)	<.001
Treatment: other	.46	(.27, .80)	.01

* Model was adjusted for age, sex, smoking, hepatitis C, encephalopathy, symptoms at presentation, screening

every 6–12 months for surveillance and use of AFP alone is not advisable.[26] Our database indicates that approximately 10% of HCC cases were found with screening, in comparison to the US national average where 22–28% of HCC cases were discovered from screening, in comparison to China and Japan where 50–60% of HCC cases were discovered from screening.[21] Much work is needed to educate the medical professionals in Hawaii on this health problem.

Finally, the health community needs to better educate Pacific Islanders about hepatitis B and the synergistic effect of alcohol on development of HCC.[27] Knowledge about viral hepatitis in this population has not yet been studied but it would be essential for them to understand their high risk for hepatitis B and the value of treatment and follow up, as well as vaccination of close contacts that do not have hepatitis B. Exploring social/cultural beliefs about organ donation and improving knowledge about organ donation and transplant may also impact the patterns of HCC risk and treatment among Pacific Islanders.

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