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Hepatocellular Carcinoma Screening Practices and Impact on Survival among Hepatitis B-Infected Asian Americans

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Abstract

Asians Americans have a high burden of hepatitis B (HBV) associated hepatocellular carcinoma (HCC). HCC screening practices in this population are unknown. We aimed to investigate predictors and patterns of HCC screening and its impact on survival in HBV-infected Asian Americans. Clinical data were obtained from a retrospective cohort of 1870 HBsAg-positive Asians in San Francisco's safety net clinics. In 824 patients at-risk for HCC, screening (1 imaging and/or AFP per year) decreased from 67% to 47% to 24% from the first to second to tenth year after HBV diagnosis, respectively. AFP, imaging, and imaging plus AFP were used in 37%, 14%, and 49% during the first year after diagnosis, and imaging plus AFP increased to 64% by the tenth year. Among 1431 patients followed in 2007, age 40–64 years, female gender, cirrhosis, hepatologist evaluation, HBV diagnosis after 2003, and testing for HBeAg were associated with HCC screening. Of the 51 patients with HCC, more cirrhotics received screening and were diagnosed with early stage disease. Median survival following HCC diagnosis was higher in screened patients (1624 vs. 1111 days, $p=0.02$). MELD score at HCC diagnosis (HR 1.2, 95%CI: 1.1–1.3) and receipt of curative therapy (HR 0.3, 95%CI: 0.08–0.94) were associated with survival. Screening rates in at-risk Asian Americans, particularly among non-cirrhotics, were suboptimal and decreased over time. Among patients with HCC, receipt of prior screening improved survival, and this survival benefit was related to better liver function at HCC diagnosis and receipt of curative therapy.

Keywords

liver cancer; hepatitis B; safety net healthcare system; cirrhosis; mortality

Worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality; its incidence has more than doubled in the U.S. over the past thirty years, from 1.6 per 100,000 in 1975 to 4.9 per 100,000 in 2005.(1, 2) The age adjusted incidence of HCC among Asian men and women in California is even higher at 23.6/100,000 and 8.8/100,000, respectively.(3) Approximately 80% of HCC cases worldwide occur in developing countries, with over half diagnosed in China alone and 70% attributable to chronic hepatitis B virus (HBV).(4) In the U.S., Asians have the highest incidence of chronic HBV, ranging

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from 8.9-15%. (5, 6) The HCC disparity among Asian Americans is therefore quite vast, with over 70% of HBV-related cases of HCC in the U.S. diagnosed among Asian Americans.(7)

The American Association of the Study of Liver Diseases (AASLD) recommends HCC screening with interval ultrasounds (US) in at-risk patients with chronic HBV including Asian females over 50 years old, Asian males over 40 years old, all cirrhotic patients, and those with a family history of HCC. (8) Traditionally, the recommended screening interval had been every 6-12 months, though recently updated guidelines now recommend every 6 months.(8, 9) Although combining AFP and ultrasound increases HCC detection, it also increases cost and false positive rates (10). However, due to operator variability in US interpretation, clinicians may choose both US and AFP for HCC screening.(11) The use of AFP alone is inadequate and therefore not recommended for HCC screening.(12) Despite the large number of Asian Americans with chronic HBV, it remains unclear what HCC screening protocols are being performed in this at-risk population. In addition, data assessing HCC screening practices over time are limited among Asian Americans.(13, 14) Given the documented benefits of screening, as well as available curative treatment for early HCC, it is critical to describe the adequacy of HCC screening and potential survival benefits of screening in the Asian American community.(15) In this study we aim to describe screening practice over time and factors associated with screening in a large Asian American cohort followed in the San Francisco public health safety net system. We also evaluate the impact of screening on patient survival in this at-risk population.

Methods

Study Design and Subjects

This is a retrospective cohort study of HBV-infected Asian Americans, defined by positive hepatitis B surface antigen (HBsAg) testing, who were followed between January 1, 1997 and January 15, 2008 in 11 primary care clinics within the San Francisco safety net healthcare system. This includes one acute care hospital (San Francisco General Hospital) with on-site primary and specialty care clinics. This healthcare system provides care to over 150,000 patients, including most uninsured residents.(16) The racial/ethnic distribution of patients within this safety net healthcare system reflects the diversity of the City of San Francisco and includes approximately 25% non-Hispanic Whites, 20% African American, 30% Latino, 20% Asian and Pacific Islander, and 5% other. Among 1,870 patients from our initial cohort of HBV-infected Asian Americans, 1,646 were considered active patients, defined by one primary care clinic visit in the past 24 months, or were known to be deceased as of January 15, 2008. As of December 31, 2007, 1,431 were alive and had been followed from their first positive HBsAg test through the entire 2007 calendar year. A total of 51 of the 1,870 patients were followed from diagnosis with HCC at age 18 or older to death, loss to follow-up, or the end of the follow-up period.

The study was approved by the Committee on Human Research of the University of California San Francisco.

Data collection

Data were extracted from electronic medical records and included patient characteristics, liver imaging studies, laboratory tests, HCC diagnoses, and therapies. Patient characteristics included age, gender, primary language, cirrhosis status, attendance in liver clinic, and date of death. Laboratory data included dates and results of total bilirubin, ALT, INR, creatinine, AFP, hepatitis B serologies (HBsAg and HBeAg), and HBV viral load. The Model for End-Stage Liver Disease (MELD) score was computed for HCC patients.(17) Radiologic data

included dates, results, and type of abdominal imaging (US, CT scan and MRI). Asian Americans at risk for HCC were defined as males >40 years old, females >50 years old, and those with cirrhosis confirmed by imaging. HCC screening was assessed by evaluating frequency of AFP and radiologic imaging. HCC was identified by radiologic imaging and categorized as very early (single lesion < 2cm), early (single lesion < 3cm or three or less lesions < 3cm with normal performance status), intermediate (multinodular HCC without portal vein thrombosis and normal performance status), and advanced stage (metastatic HCC with or without portal invasion or impaired performance status). HCC therapies were categorized as curative (liver transplantation, resection, and ablation therapy) or non-curative (transcatheter arterial chemoembolization (TACE) and systemic chemotherapy). (12)

Statistical Analysis

Analyses of HCC screening over time—Among active patients (n=1646), the proportion of at-risk patients receiving imaging and/or AFP tests in each full year of follow-up after diagnosis with chronic hepatitis B was computed. In addition, the proportion of at-risk patients receiving imaging tests in each of the first 5 years of follow-up was computed for those with 5 full years of follow-up.

Analyses of HCC screening in the most recent calendar year of follow-up—Patient characteristics among those with follow-up for the entire 2007 calendar year (n=1,431) were summarized using mean $\pm$ SD, median (range), and frequencies. HCC screening was defined as abdominal imaging (US, CT, or MRI) during the 2007 calendar year. To evaluate categorical variables with potential association with HCC screening, bivariate analysis was performed using chi-square tests. Multivariable logistic regression modeling was performed to evaluate the association between these variables and HCC screening. We also stratified logistic regression models by presence of cirrhosis as cirrhosis is expected to be strongly associated with screening.

Analyses of HCC survival—Kaplan-Meier curves were computed, and the log-rank test was used to compare survival after HCC diagnosis (n=51) in those who received HCC screening (at least one imaging test 6-15 months before diagnosis) versus those who did not. A Cox proportional hazards model assessed the independent effects of factors associated with survival, including HCC screening, age over 50 years, gender, presence of cirrhosis, stage of HCC disease (dichotomized by very early and early stage versus intermediate and advanced stage), MELD score, and receipt of curative HCC therapy. To better understand the impact of these factors on survival, bivariate analyses of the associations between pairs of independent variables were performed using chi-square tests and t-tests or analysis of variance as appropriate. Statistical significance was assessed at the 0.05 level (2-sided) in all models. All analyses were performed using SAS version 9.2 (SAS Institute, Inc., 2007. Cary, NC).

Results

The overall study population of 1,870 patients was 48% male and 64% were $\geq$ 40 years old at the time of HBV diagnosis. Among 1,431 patients with follow-up during 2007, 47% were male, 72% were $\geq$ 40 years old at the time of HBV diagnosis, and 72% were non-English speaking. Approximately half of the patients were diagnosed with HBV after 2003, and a quarter had attended liver specialty clinics. On laboratory evaluation, 21% had high ALT levels (ALT $\geq$ 60 IU/ml in men and $\geq$ 40 IU/ml in women) and of the 425 (30%) patients with available HBV DNA, 57% had high viral load defined as either $> 2,000$ IU/mL among

HBeAg negative patients or > 20,000 IU/mL among HBeAg positive patients. HBeAg status was available in 560 patients (39%), of whom 81% were HBeAg negative.

Screening practice

Among the 1,646 active patients, 947 (58%) were at risk for HCC: 407 (25%) non-cirrhotic males >40 years old at first positive HBsAg test, 305 (19%) non-cirrhotic females >50 years old at first positive HBsAg test, and 235 (14%) cirrhotic patients. In this at-risk cohort, 824 patients had at least one year of follow-up, and 554 (67%) had undergone HCC screening, defined as one or more imaging and/or AFP tests per year during the first year after diagnosis. The rate of screening decreased by almost a third, to 47% (341/725) during the second year of follow-up and decreased to 24% (11/46) by the 10th year of follow-up (Figure 1). Among the 436 patients with at least 5 complete years of follow-up, the rate of screening by imaging declined by more than 40%, from 39% in the first year of diagnosis to 23% in the second year of diagnosis, but remained stable thereafter. Screening modalities included AFP alone (37%), imaging alone (14%), and imaging combined with AFP (49%) in the 554 screened in the first year after diagnosis and 43%, 10% and 47% respectively, in the 171 patients screened by the 5th year after diagnosis (Figure 1). The most common screening imaging modalities in the first year after diagnosis were US at 51% (177/348), followed by CT at 31% (108/348) and MRI at 3% (10/348). On follow-up the use of US decreased while the rates of CT and MRI increased over time (Figure 2).

Factors associated with HCC screening

In bivariate analysis, factors associated with HCC screening in 2007 included age over 40 years (21% vs. 6%, $p<0.0001$), liver clinic attendance (41% vs 9%, $p<0.0001$), cirrhosis (58% vs. 10%, $p<0.0001$), date of HBV diagnosis in 2003 or later (20% vs. 14%, $p=0.0007$), testing for HBeAg test (30% vs. 8%, $p<0.0001$), and testing for HBV viral load (34% vs. 9%, $p<0.0001$). On multivariable analysis, predictors of HCC screening in 2007 were age 40-64 years, female gender, presence of cirrhosis, liver clinic attendance, recent HBV diagnosis, and testing for HBeAg (Table 2). High ALT was negatively associated with receiving screening. When stratified by presence of cirrhosis, having high HBV viral load was independently associated with screening among cirrhotic patients (Table 2).

Factors associated with survival in HCC patients

We identified 51 patients with HCC and their characteristics were as follows: 78% male, 82% were > 50 years of age, 61% were cirrhotic, and 35% had early stage disease at the time of HCC diagnosis. No non-cirrhotic patients received HCC screening whereas 45% of cirrhotics were screened ($p=0.0004$). Among HCC patients, a significantly higher proportion of cirrhotics were diagnosed with early stage disease (vs. intermediate and advanced stage) compared to non-cirrhotics (52% vs. 10%, $p=0.002$). Although a higher percentage of cirrhotics compared to non-cirrhotics received curative HCC treatment (48% vs. 30%, $p=0.2$), this did not reach statistical significance. Mean MELD scores at time of HCC diagnosis were similar among cirrhotics and non-cirrhotics (11.5 vs. 11.4, $p=0.9$). In contrast, mean MELD scores were significantly lower among patients with early stage HCC (9.4% vs. 12.6%, $p=0.04$) and in those who received curative HCC therapy (8.9% vs. 13.3%, $p=0.004$). Patients who received screening were more likely to be diagnosed at early stage (79% vs. 19%, $p<0.0001$) and receive curative treatment (71% vs. 30%, $p=0.007$), with a trend towards lower mean MELD scores (9.1 vs. 12.4, $p=0.055$). Median survival was significantly higher among those screened (1624 vs. 111 days, $p=0.02$) (Figure 3). In multivariable analysis, survival was associated with lower MELD scores (HR 1.2, 95% CI 1.1-1.3) and receipt of curative therapy (HR 0.3, 95% CI 0.1-0.9) (Table 3).

Discussion

This is the first study to date investigating HCC screening modalities as well as patient and viral factors associated with HCC screening among HBV-infected Asian Americans. We also evaluated the impact of screening on patient survival. We showed that HCC screening decreased significantly over time in at-risk Asian Americans, and that the most common screening modalities were imaging (CT, MRI or US) in combination with AFP, followed by AFP alone, and imaging alone. The use of CT and MRI over ultrasound also increased over time. Independent predictors of HCC screening included cirrhosis, testing for HBeAg, recent HBV diagnosis, age between 50-64, and liver subspecialty clinic attendance. In patients with HCC, screening improved survival, which was attributed to receipt of curative therapy.

At the time of this study, the AASLD HCC screening guidelines recommended US with or without AFP at 6-12 month intervals in at-risk HBV-infected patients. This included Asian women > 50 years old, Asian men >40 years old, all cirrhotic patients, and those with a first degree relative with HCC.(9) In this study, two thirds of at-risk Asian Americans received initial HCC screening with imaging and/or AFP, despite resource limitations associated with the safety net healthcare system. The benefits of cancer screening are optimized when monitoring of disease occurs at regular intervals, resulting in early disease detection which allows for curative therapies that may improve patient survival.(18) In our study HCC screening rates decreased by half after the first year following HBV diagnosis. This is an unexpected finding since it occurred during a period in which better defined guidelines for HCC screening had been disseminated. Therefore, despite adequate initial HCC screening rates, subsequent screening rates were low. Further research is needed to determine if this low rate of interval screening is due to patient, provider, or system related factors.

Published literature suggests that more clinic attendance is associated with HCC screening.(13) However, evaluation of records from 436 patients with at least five years of clinic follow-up showed significantly decreased screening rates by the second year after HBV diagnosis. Provider factors likely contribute to the screening patterns observed. Nguyen et al. have shown that physician screening behavior is influenced by the belief that screening improves HCC related mortality, as well as concern about malpractice and quality control.(19) In addition, provider knowledge of HCC and HBV may influence performance of routine screening. In a recent study evaluating HBV and HCC screening practices among providers in the San Francisco safety net healthcare system, ~70% of providers believed that HCC screening in patients with chronic hepatitis B reduced HCC mortality, and over half believed that screening was cost-effective and failure to screen posed a malpractice risk.(20) Among these providers, having a high proportion of Asians in practice and having a higher knowledge of HBV and HCC were the only independent predictors of performing recommended AASLD-based HCC screening.(20)

In this study, which included a comprehensive set of factors that may influence HCC screening, screening was positively associated with older age, female gender, presence of cirrhosis, testing for HBeAg, more recent HBV diagnosis, and hepatologist evaluation, with an inverse association noted for high ALT levels. High viral load was also associated with screening among cirrhotics. It is unclear why high ALT levels were negatively associated with screening, though this effect was not observed among cirrhotic patients who attended liver subspecialty clinic. Limited studies have shown that non-cirrhotic hepatitis B-infected Asians are less frequently screened for HCC compared to cirrhotics, and patients seen by gastroenterologists or hepatologists are more likely to receive regular HCC screening, with higher rates of screening rates reported among gastroenterologists compared to internists or family practitioners.(13, 19, 21)

The use of imaging as the sole screening modality in this study was infrequent and imaging studies were most commonly combined with AFP. Although the AASLD has no official recommendations regarding use of CT or MRI when US visualization may be inadequate (8), the use of CT and MRIs in this study did increase over time. Interestingly, a provider survey of this safety net system performed at the same time as the current study showed that the most commonly used modalities for HCC screening reported by providers were AFP (90%) and US (78%).(20)

Limited randomized controlled trials and one large prospective cohort study suggest that HCC screening reduces mortality, specifically when curative therapies are an option.(15, 22-26) This is likely due to earlier detection of HCC where potentially curative therapies are offered. The largest randomized controlled trial to date found that among 19,000 Chinese patients with chronic HBV, screening with AFP and US every 6 months was associated with a 37% reduced mortality. With less than 60% patient adherence, this study likely underestimates the true survival benefit of HCC screening.(15) Wong et al. compared survival of 579 HCC patients of whom the majority were HBV-infected. They found that those who underwent screening had a longer median survival than those in the unscreened group (88 weeks versus 26 weeks, $p < 0.001$). In addition, more patients in the screened group had smaller and fewer lesions, and subsequently received more curative therapy with resection or surgery as compared to the unscreened group.(14) These results were replicated in a more recent study of 78 Asian Americans with HCC, where screening identified patients with smaller tumors and better liver function who more frequently received liver transplantation.(24) In the current study we identified 51 patients with HCC; approximately 40% were non-cirrhotic, highlighting that HBV-infected non-cirrhotics are also at significant risk for HCC. None of the non-cirrhotic patients received HCC screening. In this resource limited safety net system, there was preferential HCC screening among cirrhotic patients, who are among the highest risk patients for developing HCC. However, even among these patients, screening rates were suboptimal at 45%. A higher proportion of cirrhotics were ultimately diagnosed with early stage disease, and liver function was significantly better among those with early stage disease and in those who received curative HCC therapy. Most importantly, screening improved survival among HCC patients, which was related to receipt of curative therapy.

The main limitation of the current study is the retrospective design, while the primary strengths include the large sample size and long term patient follow-up of up to 10 years. Although family history of HCC could not be assessed, all other known host and viral factors associated with HCC were used to define our at-risk HBV-infected Asian American cohort. Only a subgroup of patients had HBeAg and HBV viral load evaluation, which limits the assessment of these factors on HCC screening. However, the observed rate of HBeAg and viral load testing likely represents that observed in the primary care setting where HCC screening is primarily performed. Generalizability to other non-safety net practice settings may also be limited. Nevertheless, our results uncovered important patterns and modes of screening, impact of screening on survival, and the suboptimal rates of screening, particularly among non-cirrhotic HBV-infected at-risk Asian Americans.

In summary, rates of HCC screening among at-risk Asian Americans are suboptimal at baseline and decrease over time. Female gender, older age, more recent diagnosis of HBV infection, and cirrhosis were associated with HCC screening. Provider or system factors associated with HCC screening included liver specialty clinic attendance and testing for HBeAg. While practitioners tended to screen cirrhotic patients, screening among non-cirrhotic HBV-infected Asian Americans was deficient. Finally, survival was significantly improved among patients diagnosed with HCC who had undergone prior screening. This was primarily due to curative therapy in patients with earlier stage HCC and less severe liver

disease. These results suggest that HCC screening is optimized in those receiving screening at regular intervals, and in resource limited settings may be best utilized in patients who are potential candidates for curative therapy.

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Abbreviations

AASLD	American Association for the Study of Liver Disease
AFP	alpha fetoprotein
CHB	chronic hepatitis B
CT	computerized tomography
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCVAb	hepatitis C virus antibody
MRI	magnetic resonance imaging
MELD	Model of End-Stage Liver Disease
US	ultrasound

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Figure 1.
Rates of HCC screening with AFP and/or imaging among 824 at-risk HBV-infected Asian Americans.

Figure 2.

Frequency of imaging modalities (Ultrasound, CT scan, MRI, or combined) used for hepatocellular carcinoma (HCC) screening among 824 at risk HBV-infected Asian Americans.

Figure 3. Kaplan Meyer survival curve comparing screened (6-15 months prior to diagnosis) and unscreened patients with HCC (n=51).

Table 1

Characteristics of Chronic HBV Patients Followed in 2007 with at Least One Year of Follow-up (n=1431)

Characteristic	Number (%)
Age (years):	
<40	398 (28)
40-49	280 (19)
50-64	539 (38)
>65	214 (15)
Male Gender	676 (47)
Language:	
English	397 (28)
Cantonese	793 (55)
Mandarin	74 (5)
Vietnamese	97 (7)
Other	70 (5)
Liver clinic attendance	327 (23)
Cirrhosis	199 (14)
High ALT	292 (21)
First Positive HBsAg Before 2003	789 (55)
HBV DNA High ^{†*}	244 (57)
HBeAg Negative ^{**}	453 (81)

* Available in 425 patients

[†]High: 2000 IU/mL if most recent HBeAg test was negative, 20000 IU/mL if most recent HBeAg test was positive

** Available in 560 patients

Table 2

Multivariable analysis of host and viral factors associated with receiving HCC screening by imaging in 2007

Variable	All Patients OR [†]	95% CI*	Cirrhotic Patients OR [†]	95% CI*
Female (vs. Male)	1.7	1.2-2.4	2.1	1.1-4.2
Age (vs. < 40):				
40-49	2.0	1.1-3.6	2.5	0.6-11.5
50-64	3.5	2.1-5.8	6.5	1.6-26.1
65	1.8	0.9-3.5	2.9	0.7-12.8
Language (vs. English):				
Cantonese	0.8	0.5-1.1	0.4	0.2-1.0
Mandarin	0.8	0.3-1.9	0.8	0.1-4.8
Vietnamese	1.4	0.7-2.9	0.8	0.2-3.6
Other	0.9	0.4-2.1	0.6	0.1-2.4
HBV Diagnosis 2003 or Later vs. Before 2003)	2.2	1.5-3.2	1.9	0.9-3.9
Cirrhosis (vs. No Cirrhosis)	7.9	5.2-11.9	-----	-----
Attending Liver Specialty Clinic (vs. Not Attending)	3.0	1.9-4.7	2.7	1.1-6.8
High ALT (vs. Low ALT)	0.4	0.2-0.6	0.4	0.2-0.8
Having Been Tested for HBeAg (vs. No Testing)	1.8	1.1-3.0	1.4	0.5-4.2
Positive HBeAg (vs. Negative)	1.1	0.6-2.0	0.6	0.2-1.6
Having Been Tested for HBV Viral Load (vs. not tested)	1.0	0.6-1.8	0.7	0.2-2.1
High HBV Viral Load [‡] (vs. Low Viral Load)	1.3	0.8-2.2	3.4	1.4-8.3

[†]Odds ratio,

* 95% Confidence interval;

[‡]High: 2000 IU/mL if most recent HBeAg test was negative, 20000 IU/mL if most recent HBeAg test was positive

Table 3

Multivariable analysis of factors associated with survival among patients with diagnosis of HCC

Variable	HR (95% CI)*
Age (vs. <50):	
50-59	0.8 (0.3-2.5)
60	0.6 (0.2-2.0)
Imaging 6-15 months before diagnosis	0.8 (0.2-2.9)
Female Gender	0.4 (0.1-1.9)
Cirrhosis	1.4 (0.5-4.1)
Early HCC Stage	0.4 (0.4-1.7)
MELD scores	1.2 (1.1-1.3)
Receipt of Curative Therapy	0.3 (0.1-0.9)

* Hazard ratio (95% confidence interval)