

## Clinical Science

# The changing characteristics of hepatocellular cancer in Hawaii over time



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**KEYWORDS:**

Hepatocellular cancer;  
Liver resection;  
Liver transplant;  
Viral hepatitis;  
Metabolic factors

**Abstract**

**BACKGROUND:** The incidence of hepatocellular cancer (HCC) is increasing, and we sought to characterize the differences and trends in HCC over 2 decades in Hawaii.

**METHODS:** This retrospective study of 821 HCC cases analyzed risk factors, diabetes, alpha-fetoprotein (AFP), tumor characteristics, and treatment, comparing 5-year eras (1993 to 2012).

**RESULTS:** With succeeding eras, there were fewer Asians, immigrants, and hepatitis B-related HCC. Hepatitis C, diabetes, hyperlipidemia, and body mass index have increased. Over time, more patients had normal AFP, and normal AFP was seen more often in nonviral HCC (49.6% vs 33.2%,  $P = .007$ ). Over time, the proportion of patients who underwent resection or transplant was stable, but fewer patients underwent no therapy.

**CONCLUSIONS:** Characteristics of HCC are changing, and diagnosis may be more difficult as metabolic factors are becoming more important than viral factors. AFP seems to be a less important biomarker, and clearly, better diagnostic tools will be necessary to identify HCC in the future.

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Hepatocellular cancer (HCC) is the fifth most common cancer in men and ninth most common cancer in women globally with an estimated 750,000 new cases diagnosed in 2012. Overall, this is a deadly cancer with one of the highest mortality to incidence ratios at .95. It is the second most common cause of cancer mortality with 600,000 deaths annually.<sup>1</sup> Although 85% of these cases occur in less

developed countries, HCC is one of the few cancers that is increasing in incidence in the United States. In 2010, there were 24,304 new cases and 20,304 deaths because of HCC.<sup>1,2</sup>

Globally, an estimated 80% of HCC cases have hepatitis B or C as a risk factor with more of these cases related to hepatitis B (75%) and a smaller proportion (10% to 20%) because of hepatitis C.<sup>3</sup> Diabetes, obesity, and nonalcoholic steatohepatitis are increasingly identified as risk factors that will likely play a greater role in the upcoming years.<sup>4,5</sup> Many epidemiologic studies from various places in the world have shown these risk factors have different influences on the incidence of HCC.<sup>6-13</sup> This is likely related to the prevalence of a particular risk factor in that country. It is often difficult to quantify this risk exactly as underdeveloped countries may have limited resources to support detailed tumor registries. In the United

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States, we have comprehensive tumor registries and administrative or billing databases; however, these databases often have limited information on ethnicity, viral hepatitis, body mass index (BMI), and some of the newer risk factors such as diabetes, obesity, and nonalcoholic steatohepatitis. These databases are often based on billing codes and may be dependent on the variable skills of the staff entering this information.

Hawaii is the state in the United States with the highest incidence of HCC at 10.8 per 100,000 and the second highest death rate at 5.9 per 100,000.<sup>2</sup> The large proportion of Asian and Pacific Islander ethnic groups and continued immigration probably account for this high incidence for many years. Our group of physicians has been carefully collecting detailed information on HCC cases for more than 20 years. This study hopes to reveal the changing patterns of risk factors and presentation of HCC over time in Hawaii.

## Methods administrative or billing

### Patients

This is a retrospective analysis of 821 HCC cases referred over a 20-year period (1993 to 2012) to our group of physicians who are associated with the medical center with the only liver transplant program in Hawaii and the only referral center for liver disease and surgery for American territories of the Pacific Basin (including Samoa, Guam, Saipan, and the Marshall Islands). Patients also included foreign nationals from Asian countries, including China, Japan, Korea, and the Philippines, who sought medical care in the United States. This clinic and the transplant center were initially affiliated with Hawaii Medical Center East (formerly St Francis Medical Center) and after 2012, the Queens Medical Center. This center sees about 60% to 70% of the HCC cases in Hawaii. This study was approved by the University of Hawaii Institutional Review Board.

HCC was diagnosed histologically by percutaneous biopsy or at surgery. In the first decade and consistent with the previous United Network for Organ Sharing 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 2 imaging studies (ultrasound, computed tomographic [CT] scan, or MRI) and one of the following<sup>1</sup>: vascular blush seen on CT scan or MRI,<sup>2</sup> alpha-fetoprotein (AFP) greater than 200 ng/mL, or<sup>3</sup> arteriogram confirming the tumor.<sup>14</sup> More recently, the diagnosis of HCC was made with only imaging if a contrast-enhanced study (dynamic CT or MRI) showed typical arterial enhancement with “washout” in the venous phase as described by the American Association for the Study of Liver Disease guidelines.<sup>15,16</sup>

Information on demographics, medical history, laboratory results, tumor characteristics, treatment, and survival was collected via clinical interview. Demographic data included age, sex, birthplace, and the patient’s self-reported ethnicity. Ethnicity was then categorized as “White,”

“Asian” (including Filipinos), or “Pacific Islander.” Patients who did not fit into one of these categories or were of mixed ethnicity were subsequently classified as “other.” Patients of mixed race with 50% Pacific Islander ethnicity were categorized as “Pacific Islander.” Data collected on medical history included diabetes mellitus, hyperlipidemia, smoking, and risk factors for HCC including viral hepatitis, alcohol abuse (defined as >2 alcoholic beverages daily for at least 10 years), and other chronic liver diseases. Information was based on available medical records and interview by a single physician, without use of a structured questionnaire. Patients who did not report hyperlipidemia but had a lipid-lowering agent on their current medication list were also classified as having hyperlipidemia. Measured height and weight were used to determine BMI. Obesity was defined as BMI of 30 or more.

Laboratory data collected included bilirubin, albumin, prothrombin time, creatinine, alanine aminotransferase, aspartate aminotransferase, platelet count, and AFP. Laboratory data that were used for the study had been obtained within 2 weeks of initial visit or drawn at the time of the visit. Bilirubin, prothrombin time with international normalized ratio, and creatinine were used to calculate the Model for End-Stage Liver Disease score. The size, number, and location of the tumors were used to determine the Tumor–Node–Metastases stage according to the *American Joint Commission on Cancer* (AJCC) staging manual.<sup>17</sup>

The proportion of patients with HCC detected by screening was noted. Although our Liver Center recommends that community physicians screen viral hepatitis and chronic liver disease patients with AFP and liver ultrasound every 6 months, there was no uniform screening protocol used in the cohort. Referring physicians used a combination of AFP and imaging (ultrasound, CT scan, or MRI) at variable intervals. HCC was deemed to be found on “screening” if the referring physician stated that screening was done and the patient had a previous imaging study from 3 to 12 months prior. HCC not found on screening was either found with symptoms (pain, abdominal mass, weight loss, jaundice) or asymptotically with imaging done for unrelated reasons.

### Treatments

Treatments included liver resection, transplantation, ablative therapies (including radiofrequency ablation, cryosurgery, transarterial chemoembolization, and percutaneous ethanol injection), and systemic therapies. Liver resection was considered in Child’s A patients and early Child’s B patients (Childs–Turcotte–Pugh score of 7, without any evidence of ascites or encephalopathy). Liver transplants were considered in patients who were unresectable but met Milan criteria (single tumor <5 cm or 2 to 3 tumors, each <3 cm). Liver transplant was also considered in patients who underwent resection but had a recurrence more than 6 months after surgery, provided the recurrent tumor met Milan criteria, and there was no disease progression while awaiting transplant. Since 2007, liver transplant was

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