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ORIGINAL PAPER

Trends in early-stage hepatocellular carcinoma, California 1988–2010

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Abstract
Purpose California Cancer Registry data were used to explore the impact of hepatocellular carcinoma (HCC) surveillance on patient outcomes. The purpose of this analysis was to determine the trend in diagnosis of early-stage HCC in California from 1988 to 2010.
Methods Patients 20+ years old, diagnosed with early HCC during 1988–2010 in California, were included. Stratified proportions of early HCC were evaluated to estimate any trends and significant disparities. The primary endpoint was the average annual percent change (AAPC) of the proportion of early-stage HCC; 2- and 5-year survival trends were calculated for age, sex, race, SES, and stage.
Results A total of 13,855 patients were diagnosed with early HCC. The proportion of patients diagnosed early increased from 19.2 to 49.2 % between 1988 and 2010, at an AAPC of 4.3 %. The proportion of cases diagnosed with early HCC increased in all demographic groups. Both the 2- and 5-year cause-specific survival analyses showed that survival among HCC patients has been increasing since 1988.
Conclusion The proportion of HCC cases diagnosed early, and the 2- and 5-year survival trends of all HCC patients have increased in California since 1988. It is not entirely clear whether better diagnostic imaging or better surveillance has led to these findings and whether earlier diagnosis has led to improved patient survival. This increase in survival among patients with HCC may be correlated with the innovation of new treatments and most importantly that patients are being diagnosed earlier to receive such treatments.

Keywords Liver cancer · Hepatocellular carcinoma · Early HCC · Survival analysis · Average annual percent change (AAPC)

Background

Hepatocellular carcinoma (HCC) is the third leading cause of mortality among all cancers worldwide [1, 2] and is the most common type of liver cancer [3]. The incidence of HCC in the USA has tripled since the 1980s [4], and HCC is predicted to become the third leading cause of cancer-related death in the USA by the year 2030 [5]. California was ranked as one of the five states with the highest mortality rates in 2010 [6].

From 2001 through 2010, incidence rates of liver cancer among California men and women increased significantly (by 44 and 28 %, respectively). This increase in liver cancer incidence was detected among all racial and ethnic groups except Asian/Pacific Islanders, for whom rates fluctuated during this time period, but still remained the highest among all race groups. Mortality rates for liver cancer also increased in men and women of all racial and ethnic groups during this time period (by 31 and 14 %,

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respectively) except among Asian/Pacific Islander men, in whom mortality rates have declined significantly (by 16 %) since 1996 [7].

While the prognosis of HCC is generally dismal with a 5-year survival of 12 % or less, early detection allows treatment by radiofrequency ablation, partial hepatectomy, and liver transplantation which are associated with 5-year survival of 50–70 % [8]. Thus, early detection and treatment of HCC are paramount to improved patient survival [9].

In the 1980s, surveillance efforts shifted from the use of alpha-fetoprotein (AFP) screening in average risk individuals to periodic surveillance with AFP and abdominal ultrasound in increased risk individuals. At the time of the shift, some clinical evidence had become available which suggested that this combined screening method improved diagnosis rates of earlier-stage, asymptomatic cancer compared to AFP screening alone [10]. The purpose of this study was to determine trends in the detection of early HCC in California and survival trends since the implementation of abdominal ultrasound-based HCC surveillance.

Methods

Patients with HCC were identified through the California Cancer Registry (CCR). The CCR is a population-based database that contains data on all California residents diagnosed with any reportable cancer since 1988. Treatment facilities, hospitals, and health professionals are required to report all cancer. Reports include demographics, diagnosis, treatment information, and tumor characteristics. To ensure current follow-up for vital status and cause of death, the CCR database is linked annually to death certificates, hospital discharge data, Medicare files, the Department of Motor Vehicles, Social Security, and other administrative databases. Linkage to the National Death Index ensures capture of deaths occurring outside California as well as cause of death, and the follow-up is over 96 % for patients diagnosed since 2000. The CCR is a participant in both the Centers for Disease Control National Program of Cancer Registries and the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program, which requires the highest standards of data quality, as judged by completeness, accuracy, and timeliness.

Patients included in this study were males and females, aged 20 years and older, diagnosed with HCC during 1988–2010 according to ICD-O-3 histology codes 8170–8175, and resided in California at the time of their diagnosis. Age was categorized into three groups: 20–49 years, 50–64 years, and 65+ years. Race and ethnicity were collected from medical records and categorized into four mutually exclusive racial/ethnic groups: non-Hispanic White, Hispanic, non-Hispanic Black, and non-Hispanic Asian/Pacific Islander. An additional analysis included the following Asian subgroups: Chinese, Japanese, Filipino, Korean, South Asian (Asian Indian/Pakistani), Vietnamese, Cambodian, Thai, and Laotian/Hmong. Socioeconomic status (SES) was determined using the summary Yost index which utilizes US Census characteristics [11] and categorized as low, middle-low, middle, middle-high, and high. Stage at diagnosis was defined based on SEER summary staging categorized as follows: localized, regional, distant, and unknown, and in this analysis, early HCC was defined as localized.

All data were analyzed using SEER*Stat version 8.1.15 and Joinpoint Regression Program version 4.1.0, and a p value of <0.05 was considered statistically significant. Joinpoint regression is a program of SEER that defines trends during a defined time period. The primary endpoint in this analysis was the average annual percent change (AAPC) of the proportion of early-stage HCC. The AAPC was calculated for age, race, sex, and SES to determine any trends during this time period.

Lastly, a 2- and 5-year cause-specific survival analysis was performed with follow-up through 2011. Estimates were calculated using the Kaplan–Meier method and the standard life table approach. Only individuals with one primary cancer and with the cause of death being liver cancer were used in this analysis. Survival trends were calculated for age, sex, race, SES, and stage.

Results

During the years 1988–2010, 35,190 patients were diagnosed with HCC. Of these cases, 13,855 (39 %) were localized cancers or early HCC. The proportion of early HCC was 42.6 % in women and 38.3 % in men. The proportion of early HCC was 35.7 % in 20–49 year olds, 40.4 % in 50–65 year olds, and 39.5 % in patients 65 years and older. There were slight differences among the proportion of early HCC in the racial/ethnic groups: non-Hispanic Whites (39.3 %), non-Hispanic Blacks (35.0 %), Hispanics (40.8 %), and non-Hispanic Asian/Pacific Islanders (39.5 %).

In Asian subgroups, the proportion of early HCC was 43.1 % in Vietnamese, Japanese (39.4 %), Chinese (39.0 %), Filipino (37.9 %), Korean (37.6 %), Cambodian (37.4 %), South Asian (37.0 %), Thai (33.0 %), and Laotian/Hmong (29.4 %) (Table 1).

The proportion of cases diagnosed with early HCC increased in all age, race, sex, and SES groups between 1988 and 2010. The overall proportion of patients diagnosed with early HCC increased from 19.2 to 49.2 %

Table 1 Proportion early HCC by age, sex, race, and SES, California 1988–2010

	All HCC	(%)	Proportion early-stage HCC (%)
Total	35,190	100	39.4
Age			
20–49	4,292	12.2	35.7
50–64	14,168	40.3	40.4
65+	16,730	47.5	39.5
Sex			
Male	26,156	74.3	38.3
Female	9,034	25.7	42.6
Race			
NH White	14,144	40.2	39.3
NH Black	2,773	7.9	35.0
Hispanic	8,666	24.6	40.8
NH Asian/PI[a]	9,607	27.3	39.5
Chinese	2,826	29.4	39.0
Japanese	698	7.3	39.4
Filipino	1,460	15.2	37.9
Korean	1,144	11.9	37.6
South Asian	165	1.7	37.0
Vietnamese	2,087	21.7	43.1
Cambodian	227	2.4	37.4
Thai	81	0.8	33.0
Laotian/Hmong	262	2.7	29.4
SES			
Low SES	7,381	21.0	36.8
Middle-low SES	7,603	21.6	39.1
Middle SES	7,375	21.0	39.3
Middle-high SES	6,888	19.6	40.5
High SES	5,943	16.9	41.6

Early stage is defined as localized

HCC hepatocellular carcinoma, *SES* socioeconomic status, *NH* non-Hispanic, *PI* Pacific Islander

[a] Not all Asian subgroups were available

during this period, with an AAPC of 4.3 %. The increase in proportion diagnosed early was seen in all age groups: 20–49 years (4.5 %), 50–64 years (4.6 %), and 65+ years (4.6 %). Women had an AAPC of 5.1 % and men 4.3 %. The increase was greatest among non-Hispanic Asian/Pacific Islander patients and among patients residing in low and middle-low SES neighborhoods (Table 2).

Both the 2- and 5-year cause-specific survival analyses showed that survival among HCC patients has been increasing since 1988 across all categories; 2-year survival for all HCC cases increased from 14.5 % for patients diagnosed in 1998 to 45.9 % for those diagnosed in 2010 with an AAPC of 5.4 %, and 5-year survival increased from 8.0 to 31.9 % for patients diagnosed in 1988–2007 with an AAPC of 7.9 %. In all categories, the increase in 5-year survival was greater than the increase in 2-year survival. The overall and stratified trends were statistically significant at a p value <0.05 except for patients diagnosed with tumors diagnosed at distant summary stage. Younger patients generally had higher survival, but patients 65 years and older had the highest AAPC in both the 2- and 5-year cause-specific survival trends (5.9 and 8.0 %, respectively). The 20–49 years old and 50–64 years old age groups had similar AAPCs in both 2- and 5-year survival trends. Non-Hispanic Blacks had the lowest survival, but the greatest increase in 5-year survival with an AAPC of 20.4 %. Non-Hispanic Asian/Pacific Islanders had the highest survival starting in about 1994 and the second greatest increase in 5-year survival with an AAPC of 8.1 %. Females had overall better survival than males, but the two groups had similar AAPCs. Although survival was generally lower in the lowest SES group and higher in the highest group, all groups had a similar increase in survival over time (Table 3).

Table 2 Proportion of early HCC, AAPC by age, sex, race, California 1988–2010

	1988 (%)	1990 (%)	1992 (%)	1994 (%)	1996 (%)	1998 (%)	2000 (%)	2002 (%)	2004 (%)	2006 (%)	2008 (%)	2010 (%)	AAPC (%)
Total	19.2	21.1	25.7	28.3	31.6	35.3	36.7	40.1	43.5	45.8	46.8	49.2	4.3^
Age													
20–49	18.9	21.0	28.2	27.1	31.0	32.6	40.9	36.4	44.0	40.8	36.2	50.5	4.5^
50–64	19.0	20.9	24.1	24.0	29.2	34.6	35.8	39.6	43.5	45.2	46.2	48.8	4.6^
65+	19.5	21.3	26.0	30.8	33.3	36.6	36.1	41.5	43.5	47.6	49.5	49.5	4.6^
Sex													
Male	19.3	20.3	24.8	26.0	30.5	35.9	35.7	39.1	42.8	44.2	44.8	47.7	4.3^
Female	19.1	23.2	27.9	35.0	34.5	33.4	39.7	42.6	46.0	50.5	53.1	54.0	5.1^
Race													
NH White	21.5	21.6	23.9	28.2	30.2	38.3	37.5	38.0	43.3	45.3	47.9	49.6	4.4^
NH Black	15.7	28.0	23.0	23.5	27.1	17.2	31.3	32.8	38.1	44.1	40.6	51.3	4.6^
Hispanic	20.5	19.2	26.8	25.2	33.3	37.4	35.4	40.0	45.1	46.9	44.7	49.0	4.4^
NH Asian/PI	15.8	19.9	28.0	31.5	33.6	33.8	38.3	44.7	44.2	45.7	49.2	48.2	5.4^
SES													
Low SES	16.8	21.2	24.9	29.4	25.5	34.2	33.7	38.0	38.7	41.3	45.4	49.4	5.0^
Middle-low SES	13.2	23.7	21.2	27.8	27.2	35.2	35.1	38.5	43.9	45.5	44.4	48.0	6.0^
Middle SES	23.4	17.7	23.3	22.1	34.2	31.5	37.8	40.2	44.5	44.5	47.3	50.8	3.5^
Middle-high SES	24.0	24.8	34.1	32.3	36.5	32.8	38.0	46.6	46.1	49.8	45.1	48.2	4.3^
High SES	20.7	18.4	24.3	29.1	33.2	42.3	40.0	48.8	46.1	48.5	53.9	49.8	4.3^

HCC hepatocellular carcinoma, *SES* socioeconomic status, *NH* non-Hispanic, *PI* Pacific Islander

^ The AAPC is significantly different from zero at alpha = 0.05

Discussion

The proportion of HCC cases diagnosed early, as well as the proportion of patients surviving 2 and 5 years, have increased in California since 1988 over all and across all demographic groups. These findings may be influenced by improvements in screening and surveillance of patients with known risk factors for HCC as well as advances in curative therapies [4, 12, 13].

Our study, as well as other studies, has seen the proportion of early-stage HCC increasing steadily. Altekruse et al. [9] suggested that there is more awareness to HCC now increasing the number of patients diagnosed at an early stage. In a summary of HCC diagnosis and treatment, El-Serag et al. indicated that the screening of HCC has manifested recently with the combination of screenings such as serum alpha-fetoprotein testing, abdominal ultrasound, and diagnostic testing [9, 14–16]. More so, special attention to high-risk groups has increased the number of patients diagnosed at an early stage [9, 15, 16]. Although not drastically different, in our study non-Hispanic Asian/Pacific Islanders, known to be a high-risk group, had the highest increase in the proportion of early HCC diagnosis [2, 15].

While all age, sex, race, and SES groups demonstrated increasing survival trends, notable disparities were apparent among certain racial, SES, and age groups. Although not statistically comparable, overall, non-Hispanic Blacks and non-Hispanic Asian/Pacific Islanders had the highest 2 and 5 years average annual percent increase in survival between 1988 and 2010. Non-Hispanic Blacks consistently had the lowest 2-year survival across all racial groups during the entire period examined and generally the lowest 5-year survival. However, this group had the greatest increase in survival. In previous studies, low income, education, employment, and lack of access to health care among non-Hispanic Blacks have been linked to this racial disparity in survival [17–20]. It is possible that the dramatic increase in survival for non-Hispanic Blacks reflects that this disparity gap is decreasing. The survival advantage among non-Hispanic Asian/Pacific Islanders, especially after surgical resection, may be related to a lower prevalence of cirrhosis in hepatitis B-associated HCC and better hepatic reserve after treatment as compared to cases of hepatitis C-associated HCC cases [21]. In addition, practitioners are advised to perform more stringent HCC surveillance in high-risk groups.

Table 3 2- and 5-year cause-specific survival, all HCC, California 1988–2010

	1988 (%)	1990 (%)	1992 (%)	1994 (%)	1996 (%)	1998 (%)	2000 (%)	2002 (%)	2004 (%)	2006 (%)	2008 (%)	2010 (%)	AAPC (%)
Total	14.5[a]	16.4	18.5	20.9	23.6	26.7	30.1	34.0	38.4	43.3	44.6	45.9	5.4^
	8.0[b]	9.2	10.7	12.4	14.3	15.6	19.2	22.2	25.7	29.7			7.9^
Age													
20–49	20.3[a]	22.1	24.2	26.5	28.9	31.6	34.5	37.8	41.3	45.1	49.3	53.9	4.6^
	11.7[b]	13.4	15.3	17.4	19.8	22.6	25.8	29.4	33.6	38.3			6.8^
50–64	16.3[a]	18.3	20.6	23.2	26.0	29.2	32.9	36.9	41.5	46.6	48.0	49.3	5.2^
	10.6[b]	12.1	13.9	15.8	18.0	20.6	23.5	26.8	30.6	34.9			6.8^
65+	11.9[a]	13.7	15.7	18.1	20.8	23.9	27.5	31.6	33.9	36.4	39.1	41.9	5.9^
	5.3[b]	6.1	7.3	8.5	9.8	11.5	13.4	15.6	18.2	21.1			8.0^
Sex													
Male	12.8[a]	14.7	16.8	19.3	22.1	25.3	29.1	33.3	38.2	43.8	44.1	44.3	5.8^
	7.4[b]	8.6	10.1	11.8	13.7	16.0	18.7	21.8	25.4	27.5			8.0^
Female	19.5[a]	21.3	23.2	25.3	27.6	30.1	32.9	35.6	39.1	42.7	46.6	50.8	4.4^
	9.9[b]	11.2	12.7	14.4	16.3	18.4	20.9	23.6	26.7	30.3			6.4^
Race													
NH White	15.9[a]	17.5	19.4	21.4	23.6	26.1	28.8	31.8	35.2	38.8	42.9	47.4	5.1^
	8.4[b]	9.6	11.0	12.5	14.4	16.4	18.8	21.5	24.6	28.2			7.0^
NH Black	11.3[a]	12.8	14.5	16.3	18.5	20.9	23.7	26.8	30.3	34.2	38.7	43.8	6.4^
	1.0[b]	1.4	2.03	2.9	4.3	6.2	8.9	12.9	18.7	27.1			20.4^
Hispanic	17.2[a]	18.9	20.7	22.8	25.0	27.5	30.2	33.1	36.4	40.0	43.9	48.3	4.8^
	9.6[b]	10.4	12.3	13.9	15.8	17.9	20.2	22.9	26.0	29.4			6.4^
NH Asian/PI	14.9[a]	17.1	19.6	22.4	25.7	29.5	33.9	38.8	44.5	48.3	49.5	50.8	5.7^
	8.3[b]	9.8	11.4	13.3	15.6	18.2	21.3	24.8	29.0	33.9			8.1^
SES													
Low	13.0[a]	14.5	16.2	18.2	20.3	22.7	25.4	28.5	31.9	35.7	39.9	44.6	5.8^
	7.2[b]	8.2	9.4	10.7	12.2	14.0	15.9	18.2	20.8	23.7			6.9^
Middle-low	11.7[a]	13.5	15.6	17.9	20.6	23.8	27.4	31.5	36.3	41.8	42.3	42.8	6.1^
	6.3[b]	7.4	8.7	10.2	11.9	14.0	16.4	19.3	22.6	26.6			8.4^
Middle	13.9[a]	15.6	17.6	19.8	22.4	25.2	28.4	32.0	36.1	40.7	45.8	51.6	6.2^
	6.4[b]	7.5	8.9	10.5	12.3	15.5	17.1	20.1	23.7	27.9			8.5^
Middle-high	16.5[a]	18.5	20.8	23.3	26.2	29.3	32.9	36.9	41.4	46.5	46.1	45.8	4.8^
	9.2[b]	10.7	12.3	14.2	16.5	19.1	22.0	25.5	29.5	34.1			7.5^
High	23.1[a]	25.1	27.1	29.4	32.0	34.7	37.6	40.8	44.2	48.0	52.1	56.5	4.2^
	12.2[b]	14.4	16.3	18.4	20.8	23.5	26.6	30.0	34.0	33.4			6.3^
Stage													
Localized	33.5[a]	35.7	37.9	40.3	42.9	45.6	48.5	51.5	54.8	58.3	62.0	65.9	3.1^
	19.3[b]	21.1	23.2	25.6	28.1	30.9	33.9	37.3	40.9	45.0			4.8^
Regional	13.4[a]	14.8	16.2	17.8	19.6	21.5	23.6	26.0	28.5	31.4	34.4	37.8	4.8^
	7.5[b]	8.3	9.2	10.3	11.5	12.8	14.2	15.8	16.7	18.6			5.5^
Distant	7.9[a]	9.1	10.3	11.8	13.5	15.4	17.5	11.4	9.7	11.0	12.5	14.2	2.7
	4.7[b]	5.0	5.3	5.7	6.0	6.4	6.8	7.2	7.6	8.1			3.0
Unknown	12.3[a]	13.3	14.3	15.5	16.7	18.0	19.4	20.9	22.5	24.3	26.2	28.3	3.8^
	5.2[b]	5.6	6.2	6.8	7.4	8.1	8.9	9.7	10.6	11.7			4.6^

HCC hepatocellular carcinoma, *SES* socioeconomic status, *NH* non-Hispanic, *PI* Pacific Islander

^ The AAPC is significantly different from zero at alpha = 0.05

[a] 2-year cause-specific survival

[b] 5-year cause-specific survival

Although patients residing in higher SES neighborhoods had better survival overall, no dramatic differences in regard to the average annual percent changes in the 2- and 5-year survival trends were seen among the SES groups. Presumably, patients with more economic resources have better access to healthcare as well as improved healthcare literacy. Although there may still be disparities among socioeconomic status, the similar AAPCs indicate that survival is increasing in all groups at a similar rate despite historical disparities. Lastly, it appears patients 65 years and older had poorer 2- and 5-year survival outcomes than other age groups. This may be due to increased concomitant co-morbidities at later stages in life as well as more advanced fibrosis in an older population. However, survival appears to be increasing at a greater rate in this age group, indicating that treatment of co-morbidities may be improving.

Altekruse et al. [9] found similar results in which the survival has been increasing which can be attributed to the increase in diagnosis at such an early-stage and more advanced treatments, such as transplantation and tumor resection. Although increase in survival has been seen by utilizing transplants, there is controversy on how long patients should wait on the transplant list before trying other forms of treatment [16]. Nathan et al. [22] found a fivefold increase in surgical treatment of HCC, which may be attributable to the increase in diagnosis and proportion of early HCC.

Having access to data since 1988 from the largest cancer registry in the USA gave our study tremendous power allowing trends and interpretations to be made. The population in this study represented the diverse population of California which allowed analysis of diagnosis and survival by race/ethnicity, SES, and age. Limitations of the study include lack of information about infection with hepatitis B and C, and lack of information on screening, and limited information on treatment.

Our study found that despite the increasing incidence of HCC, the proportion of patients diagnosed early is continuing to climb, and the overall survival of HCC is improving across all demographics. This increase in survival among patients with HCC may be correlated with the innovation of new treatments and most importantly that patients are being diagnosed at an earlier stage to receive such treatments. Future studies looking at these individual treatments to see which may be having the most impact on survival could help translate the findings in this study. It may be a combination of treatment and diagnosis that are having the most impact on overall survival of patients with HCC. With continued surveillance and improved primary prevention of HCC, we can expect to observe declining incidence and mortality in future years.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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