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Epidemiology of Hepatocellular Carcinoma in Florida – Part I: A Statewide Report

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ABSTRACT

The increasing incidence of hepatocellular carcinoma (HCC) has become a burgeoning public health problem. The effect has been most notable at liver transplant centers. Traditional reports of liver cancer include many non-HCC variants. This study aims at determining the incidence of HCC in the state of Florida, utilizing data from Florida Cancer Data Systems. This study pertains exclusively to HCC. Of 2,296,794 cancer cases, 4,447 HCC and variants were identified (68.7%). Incidence rates were as follows. The incidence of HCC in the state of Florida was 6.1 cases /100,000 population/year; Male: 9.6/100,000 population/year vs. Female: 2.7; Whites: 6.5/100,000 population/year vs. Blacks: 5.3; Hispanics: 4.6/100,000 population/year vs. Non-Hispanics: 6.5. Limitations of the study included lack of etiology of liver disease, treatments and survival. The classification of tumors and under-reporting in the database are also concerns. The study elaborates on guidelines for screening and diagnosis of HCC. The incidence of HCC in Florida in this study was three times higher than previous reports from 2 decades ago. This is the most updated study reporting the incidence of HCC in Florida, although data was 5 years old. The incidence of this cancer is expected to continue to increase over the next decade. The study is a preamble to socioeconomic and county studies currently being performed at this liver transplant center.
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Background

Hepatocellular carcinoma (HCC), a primary malignancy of the liver and one of the most common malignancies worldwide accounts for more than 1 million deaths annually. The increasing incidence of HCC has started to become a burgeoning public health problem. Recent publications during the past 40 years have noted a significant rise in the incidence of HCC within the United States (Altekruse, McGlynn, & Reichman, 2009).

The geographic distribution of HCC has been linked to a multitude of risk factors: Hepatitis B virus and Hepatitis C virus being the two most implicated factors. It has been shown that the distribution of HCC is closely related to the incidence of hepatitis B/C virus infection. Therefore, not surprisingly, because the high rates of horizontal transmission of hepatitis B, the highest incidences of HCC are found in Southeast Asia and Africa (greater than 10 to 20 per 100,000), whilst the lowest incidence is found in Australia, North America and Europe (1-3 per 100,000).

HCC has been demonstrated to be the third leading cause of cancer mortality worldwide (Altekruse et al., 2009). It has also been shown that approximately 90% of primary liver carcinomas within the United States are HCC, while the remaining 10 percent are cholangiocarcinomas. It has been established throughout literature that a large percent of HCC is significantly associated with hepatitis viral infection, while other factors include alcohol use, smoking, genetic metabolic disease, cirrhosis, environmental exposure, chronic infections and family history of liver cancer.

Over the past 20 years, the age adjusted incidence of HCC has nearly tripled in the United States, ignited by the unforeseen incidence of chronic Hepatitis C and Hepatitis B. At present there are 4 million US citizens afflicted with chronic Hepatitis C and 1.2 million afflicted with chronic hepatitis B. Like the rest of the U.S., the incidence of liver cancer has increased significantly within the state of Florida. Whether the increased incidence is related to immigration, increased screening, increased rate of hepatitis B or hepatitis C infection, cirrhosis, obesity/diabetes mellitus or a combination has yet to be determined. HCC is the fastest growing cause of cancer-related deaths in the U.S. (National Cancer Institute [NCI], 2006) and has the highest mortality in the obese population (Calle, Rodriguez, Thun & Walker-Thurmond 2003).

Previous reports of liver cancer in Florida come from two recent sources. In 2001, from the Department of Epidemiology and Public Health, the overall incidence between 1985 and 1995 was 2.01/100,000 population; 3.29/100,000 in Hispanics; 1.82/100,000 in white males; 3.86/100,000 in Black males; 1.23/100,000 and 1.18/100,000 in Hispanic and Black females, respectively; and 0.6/100,000 in White females (Shea, Fleming, Wilkinson, Wohler-Torres, & McKinnon, 2001). The second study was from the Bureau of Epidemiology, Florida Department of Health (DOH) (Florida Department of Health: Bureau of Epidemiology [DOHBOE],

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2005). In this 2005 study, 1,127 new cases of liver cancer were diagnosed that year. The age adjusted incidence was 5.1 per 100,000 population. This rate was below the national incident rate of 6.8% and 2.5 times higher than the incident rate in 1981. Mortality was 3.9 per 100,000 population (below national rate of 5.3), and 45% higher than in 1981, with 890 Floridians dying of liver cancer in 2005.

This study aims at determining the incidence of HCC in the state of Florida, utilizing data from FCDS which contains all liver cancer types. Different from the 2005 DOH report on Epidemiology of Liver Cancer, this study pertains exclusively to hepatocellular carcinoma and its variants. Therefore, our study has the most updated incidence data and characteristics of HCC in Florida. It is unique in this respect. The study is a preamble to socioeconomic studies of HCC and transplant center studies on HCC performed by our liver transplant center.

Methods

Available data for liver cancer in Florida comes primarily from The Florida Cancer Data System (FCDS), Florida's statewide population based cancer registry (DOHBOE, 2005). The system has collected cancer incidence data since 1981. The last report on liver cancer came in 2005, collected by FCDS under contract by the DOH. The data does not include cancers diagnosed before a person became a Florida resident. The FCDS has achieved the highest standard and received "Gold Certification" for quality, completeness, and timeliness for the data collected for each year from 2000 to 2005.

The FCDS implemented case-finding strategies to ensure a complete database. Mortality follow-back was implemented to identify unreported cancer cases from death data. Death certificates were checked annually. A process implemented by the FCDS uses hospital discharge data from the Florida Agency of Health Care Administration (AHCA) to identify missed cases and compared to the FCDS database. Cancer cases that are identified in the AHCA data and that are missing in the FCDS database are "followed back" to the hospital to obtain complete reports. This procedure has also been employed to ascertain new cancer cases from ambulatory surgical centers.

The STAT CD from FCDS, containing data for the years 1983 to 2010, with a total of 2,296,794 cancer cases was decoded using the Data Acquisition Manual, 2009. The site code 2627 actually included both liver (HCC) and intrahepatic bile duct cancer, or cholangiocarcinomas (CCA) (ICCD-9 155, 155.2, and 155.1; ICD-03 is C22 and C22.1), and other liver tumors. We included only data for the 2004-2008 period, the most recent time period, as reported in FCDS and our period of interest. All age ranges were included. Only HCC cases were selected for analysis. Incident cases for each county were reported per 100,000 population per year. Population data were obtained from the U.S. Census Report (U.S. Census Bureau [USCB]) and from the FCDS 2010 Hispanic Report (Fleming 2001, 2010; Hernandez, 2010; Lee, 2010; MacKinnon, 2001, 2010). The Stat CD data was transferred to an Excel program and files compressed using statistical program J zip version 1.3. Fisher's exact 2-tailed tests were utilized, with p values less than 0.05 deemed significant. Permission from FCDS to conduct the research and approval from the University of South Florida Institutional Review Board was obtained.

The following variables were analyzed: age, ethnicity, race, tumor grade, marital status, diagnostic methods, morphology (histologic type), sex, stage (local, regional, distant), insurance payer, and county of origin at time of tumor diagnosis. Since 59% of cases had unknown grade, this variable was not further analyzed. Non-Hispanics likely included Blacks and Asians, making ethnicity composition questionable. This is explained in the 2010 FCDS Hispanic report (Hernandez, et al. 2010), as follows: ["Hispanics" include both Blacks and Whites in part because this follows the patterns of Hispanic race-ethnic self-identification (i.e., Black Hispanics often identify as "Hispanics" rather than "Black"), and because the numbers of identified Black Hispanics in the FCDS database are quite small. These analyses do not include non-Hispanic Blacks who are a mixture of African Americans and Blacks from other countries (particularly the Caribbean)]. Stepwise case-finding of HCC cases is described below.

Results

Originally, the study began with 2,296,794 cancer cases. Of these cases, 6,474 were classified as liver tumors. Among the liver tumors, there were 2,025 (31.3%) non-HCC and 4,447 (68.7 %) HCC. The non-HCC tumors included adenomas, benign tumors, cholangiocarcinomas, vascular tumors, and many other variants. Cholangiocarcinomas accounted for 9.6% of all tumors. HCC and variants are depicted in Table 1. Only the tumors in Table 1 were included in the incidence study and comprised all HCC cases. Incidence rates were as follows. The incidence of HCC in the state of Florida was 6.1 cases /100,000 population/year; Male: 9.6/100,000 population/year vs. Female: 2.7/100,000 population/year; Whites: 6.5/100,000 population/year vs. Blacks: 5.3/100,000 population/year; Hispanics: 4.6/100,000 population/year vs. Non-Hispanics: 6.5/100,000 population/year.

Table 2 displays percentages of all study variables. Males, Whites and Non-Hispanics were the predominated variables. Uninsured HCC patients comprised 7.9 % of all HCC cases. Tumor grade was not recorded in 59% of HCC cases. Only 43% of the

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Table 1. HCC Cases 2004–2008

	No.	% HCC
Mixed HCC/CCA	70	1.5
Clear cell	29	0.6
Fibrolamellar	16	0.3
HCC NOS	4320	97
Pleomorphic	1	< 0.001
Spindle cell	13	0.2
Total	4,447	

NOS = Not otherwise specified

cases presented with local disease. HCC cases peaked at age 50-59 (1,435 cases, or 358/yr) (Table3). No difference in staging was observed among different age groups. However, there were more uninsured cases in the 30-59 age compared to 60-89 (16% vs. 2.6%, p=.0001).

A detailed county incidence study has been conducted and will be reported separately. The frequency of counties at incidence range of 0-4/100,000 population was 20%; at 5-6/100,000 was 44%; at 6-7/100,000 was 24% and at 7-9/100,000 was 22%. Union County was an outlier, with 33 HCC cases for an incidence of 56.8/100,000 population. It also contained the largest proportion of Blacks as percentage of total HCC cases (51%).

Discussion

Our study updates the incidence of HCC in Florida for the period between 2004 and 2008. The incidence was 6.1 cases/100,000 population. Although data used for this study is almost 5 years old, the incidence of HCC in Florida has continued to increase. This is based on previous state reports which estimated the incidence at 5.1/100,000 population, a study that also included bile duct cancers (DOHBOE, 2005). As we expected, the incidence was similar to previous national reports on HCC (Altekruse et al., 2009; El-Serag et al., 2003). Compared to a 1985-1995 incident HCC report, the incidence tripled during the time period we examined (DOHBOE, 2005). Whites and Non-Hispanics comprised the majority of HCC cases. The incidence was lower in Blacks vs. Non-Blacks and lower in Hispanics vs. Non-Hispanics. This finding is contrary to what would be expected, based on

Table 2. Study Variables

	Percent of HCC Cases	χ2 trend
Race		p < .0001
Black	14.1	
White	85.9	
Ethnicity		p < .0001
Hispanic	16.1	
Non-Hispanic	83.9	
Payer		p < .0001
Medicaid	10.2	
Medicare	46.2	
Not Insured	7.9	
Private	30.4	
Tricare, Military, VA, Indian/Public Health Service	2.3	
Unknown	3.0	
Grade		p < .0001
Well diff.	18.0	
Mod	14.4	
Poor	7.8	
Undiff	0.7	
Unknown	59.0	
Diagnostic Method		p < .0001
Pos. Cytology	4.6	
Pos Histology	82.5	
Pos Micros conf	0.2	
Radiography	12.0	
Unknown	0.7	
Stage		p < .0001
Local	43.0	
Regional	21.1	
Distant	14.0	
Unknown	21.3	
Sex		p < .0001
Female	22.6	
Male	77.4	

previous data (Altekruse et al., 2009; El-Serag et al., 2003). The FCDS database has limitations in the racial and ethnicity composition and we recognize this as a limitation in our study. Asians, who have a known

Table 3. Age Distribution HCC

Decade	HCC Percent
<10	0.04
10-19	0.2
20-29	0.5
30-39	1.3
40-49	8.3
50-59	32.3
60-69	22.0
70-79	22.7
80-89	12.5

high incidence of HCC, are not categorized. Inclusion of liver cancers other than HCC in previous Florida reports may account for these differences as well. Characteristics of the Hispanic population in Florida and corresponding HCC incidence are the subjects of our current research. As expected, males predominated 3.5 to 1. Many tumors have androgen receptors (Nagasue et al., 2005). The preponderance of risk factors for HCC in males is well known.

HCC were the tumors of interest, based on rising incidence. These tumors have accounted for as many as 20-30% of liver transplant indications at some centers, including ours. These are also cancers that arise from risk factors that are well known and we can control. In contrast, cholangiocarcinomas, which in this database comprised 9.6% of all tumors similar to previous reports of 8% (Goodman, 2007), have poorly defined risk factors and occur frequently in absence of cirrhosis. There is some concern in the data about the histologic classification of the tumors according to well established nomenclature, such as the WHO Histological Classification (Enjoji, 2008). Epithelial tumors comprise a large segment of liver tumors. There are benign variants, which include hepatocellular adenomas, focal nodular hyperplasia, intrahepatic bile duct adenomas and cystadenomas, and biliary papillomatosis. Several malignant variants are also included within the epithelial tumors, including HCC, intrahepatic Cholangiocarcinoma, bile duct Cystadenocarcinoma, mixed HCC/Cholangiocarcinoma, Hepatoblastomas, and other undifferentiated tumors. There were 202 epithelial tumors in the database (3.1% of all total tumors, or 10% of non-HCC tumors), that were unclassified as above, some of which were malignant per degree of grade reported. Some of these may have been HCC, possibly underscoring the true incidence of HCC.

In this report, 14% of patients with HCC were reported as having distant metastases and in 21% of the cases the staging was unknown. This is certainly concerning. Our liver transplant center, which specializes in HCC, has concentrated on education related to screening for liver cancer in patients that are at risk, based on the presence of chronic liver disease, cirrhosis, a positive family history and infectious hepatitis, particularly chronic hepatitis B and C, among other risk factors. This information has to be spread through the oncology and gastroenterology medical communities, but most importantly, through the primary care and internal medicine specialties. Guidelines for the screening, diagnosis and treatment of hepatocellular carcinoma came from published reports, most recently updated in July 2010, and endorsed by the American Association for the Study of Liver Diseases (AASLD) (Bruix & Sherman, 2011). It consists of liver ultrasonography every 6 months. Patients at risk for HCC need to be entered into surveillance programs. There is Level 1 evidence for this and specific cut-offs of HCC incidence at which screening becomes cost effective (Keefe, Lin, Keefe, Sanders & Owens, 2004). There is concern that ultrasonography will miss tumors, particularly in the obese, advanced cirrhotic livers and those with ascites. Computerized tomography or magnetic resonance imaging is routinely utilized in specialized clinics to screen at risk patients for HCC.

Our study likely underestimates the true incidence of HCC. It is our belief that many HCC cases go underreported in cancer databases and cancer registries. HCC is one of very few tumors that are frequently diagnosed without tissue confirmation, possibly making reporting the carcinomas difficult. HCC can be diagnosed radiologically without need for tissue confirmation, as long as findings on contrast enhanced CT scan or MRI are typical for HCC (Former et al., 2008). Diagnosis guidelines by imaging are elaborated in the HCC Guidelines (Bruix & Sherman, 2011). We want to strongly emphasize that radiologic guidelines for HCC are to be applied only to patients with cirrhosis and risk factors for liver cancer, and not in any other circumstance. It should also be understood that biopsy confirmation of HCC presents several challenges. Not only it can be risky in patients with cirrhosis and portal hypertension, but it can be also difficult to interpret, which can result in delay of diagnosis and treatment, and may also result in stage migration. At liver cancer programs and transplant centers such as ours, HCC is frequently diagnosed, treated with locoregional therapy, resection, liver transplantation and systemic therapy, without tissue confirmation. Another limitation of the study was the lack of important variables, including the etiologies of liver disease, treatments and survival. The creation of multidisciplinary liver cancer programs in the state of Florida, particularly at most of the 6 liver transplant centers, should be improving the overall survival of HCC.

This study is a preamble to upcoming prospective studies on HCC. The diagnosis of HCC should

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no longer be a death sentence. It should be recognized by all those treating patients at risk for HCC, that the disease can be prevented (vaccination of Hepatitis B, treatment of hepatitis B and C), that careful screening can detect early disease, and that treatments are available for early, intermediate and advanced stages of the disease. Cure can be achieved with locoregional therapy and resection, long term disease free survival can be achieved with liver transplantation, and improved survival can now be achieved with transarterial chemoembolization and systemic therapy (Llovet et al., 2008).

Healthy People 2020, the nation's new 10-year goals for health promotion and disease prevention, have cancer objectives that support monitoring trends in cancer incidence, mortality, and survival. The recommendations for screening come from the U.S. Preventive Services Task Force (United States Preventative Task Force [USPSTF]). The Agency for Healthcare Research and Quality's Prevention and Care Management Portfolio administers the USPSTF (United States Department and Health and Human Services: The Agency for Health Care Research and Quality [HHSTAFHCRAQ]). Surprisingly, the U.S. Preventive Services Task Force does not have screening recommendations for liver cancer.

Conclusions

The incidence of hepatocellular carcinoma in Florida in this study was three times higher than previous reports from 2 decades ago (DOHBOE, 2005). This is the most updated study reporting the incidence of HCC in Florida. The study utilized data that, on average, was 5 years old. It is not an ethnic and racial composition report. We expect the incidence of this cancer to continue to increase over the next decade. HCC remains the fastest growing cancer in the U.S. In our next study, we would like to report socioeconomic variables and perform group and county studies of HCC.

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