

Epidemiology of Hepatocellular Carcinoma in Florida – Part II: A Socio-economic and Hispanic Report

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ABSTRACT

We recently conducted studies on the incidence of hepatocellular carcinoma (HCC) in Florida for the period from 2004–2008. The incidence in Florida was 6.1 cases/100,000 population. Some recent studies bring age, sex, race/ethnicity along with geographic locales into account. A large Hispanic population lives in the metropolitan areas. The incidence of HCC in these areas is of special concern. Data from Florida Cancer Data Systems was utilized, comprising HCC cases between 2004 and 2008. Whites and Non-Hispanics predominated, although both comprise a larger portion of the state population. Males predominated 3.5 times to 1. The incidence was as follows: Whites, 6.5/100,000 vs. Blacks: 5.3/100,000; Hispanics, 4.6/100,000 vs. Non Hispanics: 6.5/100,000. Eight percent of patients with HCC were uninsured, and 14% of the cases presented with distant disease. Our results showed that more Hispanics and Blacks with HCC were uninsured. Distant staging was more common in the uninsured. Hispanics with HCC were concentrated in the major metropolitan areas where most transplant centers were located. These counties had a high incidence of HCC in Hispanics. HCC cases were not located in rural areas with high proportion of Hispanics. The Hispanic Paradox in HCC in rural south Florida remains unexplained.

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Background

The increasing incidence of hepatocellular carcinoma (HCC) is a burgeoning public health problem in Florida. For this reason, we recently conducted studies on the incidence of HCC in Florida for the period 2004–2008. The incidence in Florida was 6.1 cases/100,000 population. HCC is the fastest growing cause of cancer-related deaths in U.S (National Cancer Institute, 2006) and has the highest mortality in obese (Calle et al., 2003). However, with thorough screening and diagnostic methods, as we discussed, survival can be improved.

Some studies take age, sex, race/ethnicity along with geographic locales into account. Specifically, rates of HCC are more elevated in African American and Hispanics compared to Whites (American Cancer Society, 1998). A greater than two-fold excess in primary liver carcinomas was observed in Mexican Americans compared to Whites (Suarez & Martin, 1987), in Hispanics versus Whites without Spanish surnames in Los Angeles County (Mack et al., 1985), in Hispanic men and women, compared to their non-Hispanic counterparts (Trapido et al., 1995), and in White Hispanics living in primarily Hispanic Miami Dade County (Florida) in the 1980s (Trapido, McCoy, Stein, Engel, Zaverntnik, & Cornerford 1990; McCoy, Stein, Engel, McCoy, & Olejniczak, 1990; Trapido, Chen, Davis, Lewis, MacKinnon, & Strait 1994; Trapido, Chen, Davis, Lewis, & MacKinnon, 1994). A large Hispanic population lives in the metropolitan areas of Tampa, Orlando, and cities in

south Florida. In fact, 72% of Hispanics in Florida live in the south Florida counties of Dade, Palm Beach and Broward, in conjunction with metropolitan areas of Tampa and Orlando. The incidence of HCC in these areas is of special concern.

Available data for liver cancer in Florida come primarily from The Florida Cancer Data System (FCDS), Florida's statewide population based cancer registry. The last report on liver cancer came in 2005, from the Bureau of Epidemiology, Florida Department of Health (DOH) (Florida Department of Health: Bureau of Epidemiology [DOHBOE], 2005) available at: (http://www.doh.state.fl.us/disease_ctrl/epi/cancer/Liver_cancer.pdf) (DOHBOE, 2005). This report includes bile duct cancers, unlike our study, which pertains to HCC exclusively. A Hispanic report for liver cancer in Florida in 2006 was published last year (12). It revealed the following incidences: Hispanic males, 10/100,000; Non-Hispanic males 8/100,000; Hispanic females: 5/100,000; Non-Hispanic females: 2/100,000.

This study aims to study racial and ethnic differences in patients with HCC in cancer variables including stage, diagnostic methods used and whether there is an association to the payer of medical care. We also performed a thorough Hispanic incidence county analysis in the state of Florida. The study hypothesizes that there are differences in diagnostic methods and staging according to race, ethnicity and payers. The study pertains only to

hepatocellular carcinoma and not liver cancer, as usually reported (Hernandez, Fleming, MacKinnon, & Lee 2010).

Methods

Data from FCDS was utilized in this study. Case finding strategies of FCDS for data completeness was previously described. 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 from 2004 to 2008, the most recent time period, as reported in FCDS and our period of interest. Only HCC cases were selected for analysis. Incident cases for each county were reported per 100,000 population / year. Population data was obtained from the U.S. Census Report <http://www.census.gov> and from the FCDS 2010 Hispanic Report (Hernandez et al., 2010). The Stat CD data was transferred to an Excel program and files compressed using statistical program J zip version 1.3. Statistical analysis was performed using Chi square tests for trend and Fisher's exact 2-tailed tests, with p values less than 0.05 deemed significant.

The following variables were analyzed: age, ethnicity, race, tumor grade, marital status, diagnostic methods, morphology (histologic type), sex, stage, insurance payer, and county of origin at time of tumor diagnosis. Non Hispanics likely included blacks and Asians, making ethnicity composition questionable. We followed FCDS ethnicity definitions, as explained in the 2010 FCDS Hispanic report, ["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)] (Hernandez et al., 2010).

Results

The frequencies of study variables are depicted in Table 1. Since 59% of cases had unknown grade, this variable was not further analyzed. We began with 2,296,794 cancer cases, of which 6,474 were liver tumors, including HCC's, adenomas, benign tumors, cholangiocarcinomas, vascular tumors, and other variants. Hepatocellular carcinoma and other HCC variants comprised 68.7% of all liver tumors. Only HCC cases were included in the analysis.

There were 4,449 cases between 2004 and 2008. Seventy (1.5%) of HCC also had features of cholangiocarcinoma (CCA, mixed HCC/CCA), and were included. Thirty one percent (2,025) of cases in the database were non-HCC tumors, of which 627(31%), were CCA. The rest were hepatoblastomas seen in children, sarcomatous tumors, vascular tumors, adenomas, benign tumors and other rare malignant variants. Whites and Non-Hispanics predominated, although both comprise a larger portion of the state population. Males predominated 3.5 times to 1. Eight percent of patients with HCC were uninsured. Overall, 14% of the cases presented with distant disease. The incidence of HCC in the state of Florida was 6.1 cases /100,000 population/year. Male: 9.6/100,000 vs. female: 2.7/100,000; Whites: 6.5/100,000 vs. Blacks: 5.3/100,000; Hispanics: 4.6/100,000 vs. Non Hispanics: 6.5/100,000. HCC cases peaked at age 50-59 (1,435 cases, or 358/year). No difference in staging was observed among different age groups. However, there were more uninsured in the 30-59 age compared to 60-89 (16% vs 2.6%), $p=.0001$.

Socio-Economic Aspects of Study

Insurance Status

Insurance status was unknown in only 3% of cases. More Hispanics with HCC were uninsured (9.8%) vs. Non-Hispanics (7.5%) ($p=0.04$). Fewer Hispanics had Tricare, VA, Indian or Public Health Service (0.9%) vs. Non-Hispanics (2.4%) ($p=.01$). There was no difference in rates of Private or Medicare/Medicaid coverage by ethnicity. More Blacks with HCC were uninsured (13%) vs. Whites (6.7%) ($p=.0001$), and more Blacks had Tricare, VA, Indian or Public Health Service (3.1%) vs. Whites (2%) ($p=.04$). However, fewer Blacks (49%) had Medicare/Medicaid vs. Whites (59%) ($p=.0001$). There were no differences in rates of private insurance.

Diagnostic Methods

Hispanics with HCC had less radiographic method of diagnosis (9%) vs. Non-Hispanics (12%) ($p=.03$). Similarly, Blacks with HCC were less likely to be diagnosed by radiology (9%) vs. Whites (12%) ($p=.03$). There was no difference in rates of histologic confirmation of HCC by ethnicity or race. Patients with Medicaid had lowest rate of histologic confirmation of HCC (72%), vs. Medicare (79%) ($p=.002$), vs. Private (81%) ($p=.003$), and vs. Tricare, VA, Indian or Public Health Service (83%) ($p=.02$). For the uninsured (77%) HCC patients, no difference vs. other payers was found. Tricare, VA, Indian or Public Health Service was higher than Medicaid (see above), but not others. Medicaid patients had the highest radiographic confirmation as their diagnostic method (16%), vs. Medicare (11%) ($p=.001$), Private (11%) ($p=.008$), and Tricare, VA, Indian or Public Health Service (6%) ($p=.004$), but not the Unin-

sured (11%) ($p=.053$). Tricare, VA, Indian or Public Health Service was lower than Medicaid, but not others.

Staging

About 21% of cases of HCC had unknown stage. Hispanics presented with more local stage (Hispanic 47% vs. Non-Hispanic 42.6%) ($p=.01$). There was no difference in rates of regional or distant stage by ethnicity. Blacks had more distant disease than Whites, 17% vs. 12% ($p=.0003$), whereas Whites had more local disease than Blacks, 44% vs 38% ($p=.006$). There were no differences of regional stage by race. Medicaid patients had less local staging (32%) vs. Medicare (43%) ($p=.0001$) and Private (46%) ($p=.0001$). There was no difference in local staging between Tricare, VA, Indian or Public Health Service and the other payers. Also, the uninsured had less local staging (38%) vs. private (46%) ($p=.009$) but not vs. other payers. No difference in regional staging was observed. Medicaid had more distant staging (16%) vs. Medicare (11%) ($p=.002$). The Uninsured also had more distant staging (21%) vs. Medicare (11%) ($p=0.0001$) and Private (14%) ($p=.0006$). Counties with the largest proportion of uninsured HCC cases are depicted in Table 2. Table 3 depicts counties with largest proportion of Blacks. HCC cases peaked at age 50-59 (1,435 cases or 358/year). No differences in stage were observed among different age groups. However, there were more uninsured in the 30-59 age group compared to 60-89 (16% vs. 2.6%) ($p=.0001$).

County Analysis

The overall HCC incidence for Hispanics was 4.6 cases and for Non-Hispanics 6.5 cases/100,000 population. We performed two county analyses. The first consisted of counties with the largest proportion of Hispanics comprising total number of HCC cases: Dade (58%), Osceola (32%), Hillsborough (23%), Orange (23%), and Broward (14%). These are also 4 of the 6 counties where liver transplant centers are located in Florida. Among transplant centers, the largest proportion of Hispanics comprising total number of HCC cases was in Dade (58%), Hillsborough (23%), Orange (29%), vs Alachua (4%), Duval (3.4%), and Broward, (14%) ($p=.0001$, Fisher's 2-tailed test). The incidence of HCC in the above counties, with the largest proportion of Hispanics comprising the total number of HCC cases (cases/100,000 population/year) was as follows: Osceola 12.5; Hillsborough 29; Orange 21 and Broward 15.8. Dade County was an anomaly. With a large total Hispanic population (888,025) comprising 60% of the entire county population, the incidence was

Table 1. Study Variables

	Percent of HCC Cases	X ² 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	

only 4.4/100,000 population/year. These five counties also had the highest proportion of Hispanics as a proportion of the entire county population – top five counties: Dade (60%), Osceola (38%), Hillsborough (22%), Orange (23%), and Broward (23%). The second county analysis determined the incidence of HCC in the remaining six Florida counties where the percentage of Hispanics as a proportion of the total county population (expressed below in parenthesis), was greater than 20% (counties 6 to 11). These included Collier (24%), incidence 9.2, and four large rural counties in south Florida, with large proportion of Hispanics: DeSoto (35%), Hardee (43%), Hendry (48%), and Okeechobee (23%). There were fewer than 10 HCC cases in these counties combined over a four-year period. The data were suppressed per FCDS guidelines, to maintain confidentiality.

Table 2. Payer County Analysis: Counties with Largest Percentage of Uninsured HCC Cases

Alachua	17%
Broward	14%
Collier	14%
Dade	10%
Escambia	13%
Hillsborough	8%
Brevard	7%
Orange	6%
Polk	6%

* Expressed a percentage of total cases

Table 3. Counties with Largest Proportion of Blacks as a Percentage of Total HCC Cases

Union	51%
Gadsden	*
Duval	31%
Leon	*
Alachua	28%
Dade	21%
Orange	20%
Collier	18%
Broward	17%
Hillsborough	16%
Palm Beach	16%
Escambia	16%
Seminole	16%

* Data suppressed

Discussion

Florida has the third largest number of Hispanics (3.7 million in 2007) in the US, comprising 21% of the state population (Pew Hispanic Center, 2009). The Hispanic population in the U.S. has shown overall decrease in cancer rates and mortality (Markides & Coreil, 1989; Francini et al., 2001; O'Brien et al., 2003). There are many factors that affect variable cancer rates among Hispanics. Among these are acculturation to U.S. lifestyles, positive and negative behaviors (obesity, substance abuse, diet, exercise), and the heterogeneity of the Hispanic population (O'Brien et al., 2003; Lara et al., 2005; Pinheiro et al., 2009).

Despite lower rates of health insurance and lower socioeconomic status, U.S. Hispanics have had better health outcomes, including mortality from major cancers. This so-called Hispanic Paradox exists as a result of interplay of several factors, including culture, family support, health immigration effects (selection), diet, genetics, census undercounting, emigration and misclassification of deaths (Markides & Coreil, 1986; Francini et al., 2001; American Cancer Society, 2007; Morales et al., 2002). The paradox is found mostly in Mexican-Americans and those of lower socio-economic status (Turra & Goldman, 2007). However, in the 2010 FCDS Hispanic Report, Hispanics had lower overall rates of cancer, relative to non-Hispanics (Hernandez et al., 2010). The paradox appears to exist in Florida also. However, there were certain types of cancer that had increased incidence and mortality in Hispanics, including liver, stomach, cervix, gallbladder and acute lymphocytic leukemia (El-Serag et al., 2007; Howe et al., 2006; Trapido et al., 1995; Wikinson, Wohler-Torres, Trapido, Fleming, MacKinnon, & Peace, 2002; Wilkinson, Wohler-Torres, Trapido, Fleming, MacKinnon, Voti, & Peace, 2002).

In general, Hispanics smoke less than Non Hispanics (American Cancer Society, 2007; Howe et al., 2006). They participate in less cancer prevention screening, have less insurance, less education, lower socioeconomic status and more cultural barriers (American Cancer Society, 2007; Vidal et al., 2009). Of the 2.7 million Hispanics in Florida in 2000, 33% were of Cuban ancestry, 19% were Puerto Rican, 14% were Mexican, and 34% were other (U.S. Census Bureau, 2001). Cubans have the highest rates of cancer than other Hispanic groups (Pinheiro et al., 2009), but they also are the oldest group (Pew Hispanic Center, 2009), with a median age of those with cancer of 70 years. They dominate in liver and gallbladder cancers for both males and females, as well as other forms (lung, bladder, head and neck, prostate and ovaries). Mexican and Puerto Ricans have a small percentage of Hispanic cancers, with the exception of liver cancer in Puerto Ricans (21%).

Our results showed that more Hispanics and Blacks with HCC were uninsured. Higher mortality in Blacks and Hispanics has been observed in HCC (Mathur et al., 2010). They were also more likely to have the diagnosis of HCC made radiologically, but not less likely to have histologic confirmation of HCC. Medicaid recipients were also more likely to have a radiographic only diagnosis, but less likely to have histologic confirmation. Hepatocellular carcinoma is increasingly more diagnosed by radiologic methods, based on Practice Guidelines, most recently updated in July 2010 by the AASLD (Bruix & Sherman, 2011). We pursued the diagnosis of HCC analysis to compare this old methodology (5 years ago) to most recent ones. We expect a major shift to radiologic diagnosis, particularly with development of multidisciplinary liver cancer programs at the transplant centers in Florida, including ours. It will be important to demonstrate this shift to oncologists, whom traditionally do not follow the established HCC guidelines for diagnosis. Delay in treatment and stage migration is definitely a concern. Distant staging was more common in the uninsured, possibly related to late access to medical services.

Dade, Hendry and Hardee counties have the highest proportion of Hispanics (60%, 48%, and 43%, respectively) of the total county population. Furthermore, 57% of the Hispanics in the state of Florida live on Dade, Palm Beach and Broward counties alone, whereas 15% live in Hillsborough and Orange counties. The south Florida counties of Dade, Hendry, and Palm Beach, as well as the more central counties of Hillsborough and Orange were in the first or second lowest quartile of age adjusted overall cancer incidence rates in Florida for 2000-2006 (Hernandez et al., 2010). Overall, the counties with the largest proportion of Hispanics with HCC as a proportion of all HCC cases had fairly high incidence rates of HCC in Hispanics, except Dade county (4.4/100,000 population). The highest incidence was noted in Hillsborough and Orange counties (29/100,000 and 21/100,000 population respectively). The low incidence of HCC in Dade County, despite a large population of Hispanics, deserves further study. The rural central counties in south Florida (DeSoto, Hendry, Hardy, and Okeechobee), with large proportions of Hispanics comprising the total county population had relatively few HCC cases. Their data were suppressed (per FCDS). It appears that the incidence of HCC in Hispanics in these counties is low. Interestingly, Hispanics with HCC were concentrated in the major metropolitan areas where most transplant centers were located. They were not located in rural areas with high proportion of Hispanics. It is not known whether the Hispanic paradox in HCC truly occurs in these rural counties nor are the factors associated with it.

The overall liver cancer incidence in Florida, per the FCDS report, has continued to increase (BOEDOH, 2010). The rates were higher in Hispanics, both males (10/100,000 population) and females (5/100,000 population) vs. Non-Hispanics (males 8/100,000 population and females 2/100,000 population). The FCDS report on liver cancer contains non-HCC tumors, including bile duct cancers (627 cases) that could account for the discrepancy with our study. Our study revealed a lower incidence of HCC in Hispanics during the period of 2004 to 2008, the latest period available. It also revealed that Hispanics with HCC were concentrated in the large metropolitan counties, not in rural ones, despite the large proportion of Hispanics in all these rural counties studied. The HCC incidence in Hispanics in 4 of 5 of these large metropolitan counties was relatively high. The low incidence of HCC in Hispanics in Dade County and rural south Florida deserves further study. Efforts on screening, diagnosis, education of HCC may need to be concentrated in high population areas.

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