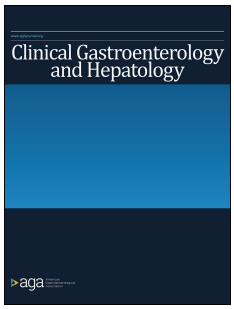
Journal Pre-proof



Incidence of Etiology-specific Hepatocellular Carcinoma: diverging trends and significant heterogeneity by race and ethnicity

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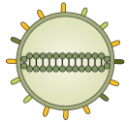
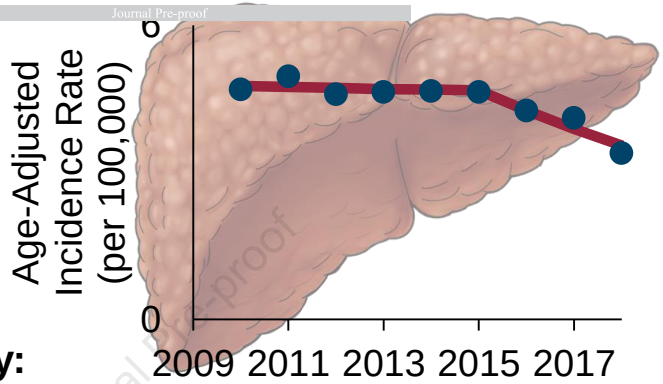
HCV

NAFLD

ALD



HBV



Population-based trends in HCV-HCC rates are decreasing (while NAFLD-HCC and ALD-HCC are increasing).

Leading cause of HCC by race-ethnicity:

	WHITE	BLACK	BLACK		HISPANIC			HISPANIC				ASIAN	ASIAN						
			US-born	Haiti-born		Central and South American	Cuban	Mexican	Mexican		Puerto Rican		Chinese	Filipino	Japanese	Korean	South Asian	Southeast Asian	Vietnamese
									Foreign-born	US-born									
Men	HCV	HCV	HCV	HBV	HCV	NAFLD	HCV	ALD	ALD	HCV	HCV	HBV	HBV	NAFLD	HCV	HBV	HCV/ HBV	HBV	HCV
Women	HCV	HCV	HCV	HCV	NAFLD	NAFLD	NAFLD	NAFLD	NAFLD	HCV	HCV	HCV							

Clinical Gastroenterology and Hepatology

Title

Incidence of Etiology-specific Hepatocellular Carcinoma: diverging trends and significant heterogeneity by race and ethnicity

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Keywords (4-5 words): etiology; liver cancer; race; ethnicity; trends

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Data Availability: The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDS), the statewide cancer registry funded by the Florida Department of Health (FDOH) and the Centers for Disease Control and Prevention's National Program of Cancer Registries (CDC-NPCR). The views expressed herein are solely those of the author(s) and not necessarily reflect those of the FDOH or CDC-NPC. This study was approved by the University of Miami and the Florida Department of Health Institutional Review Boards. The datasets are available by request with required approvals from the Florida Department of Health Cancer Registry Program and Florida Department of Health Institutional Review Board. Applications for data request are available from the FCDS Webpage (http://fcds.med.miami.edu/inc/datarequest.shtml).

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Abstract

Background & Aims: The main causes of hepatocellular carcinoma (HCC) include chronic hepatitis C and B viral infections (HCV, HBV), NAFLD, alcohol-related disease (ALD). Etiology-specific HCC incidence rates and temporal trends on a population-basis are needed to improve HCC control and prevention.

Methods: All 14,420 HCC cases from the Florida statewide cancer registry were individually linked to data from the hospital discharge agency and the viral hepatitis department to determine the predominant etiology of each case diagnosed during 2010–2018. Age-adjusted incidence rates (AAIR) were used to assess the intersection between etiology and detailed race-ethnicity. Etiology-specific temporal trends based on diagnosis year were assessed using Joinpoint regression.

Results: HCV remains the leading cause of HCC among men, but since 2017 NAFLD-HCC is the leading cause among women. HCV-HCC AAIRs are particularly high among US-born minority men, including Puerto Rican (10.9 per 100,000), African American (8.0 per 100,000), and US-born Mexican American men (7.6 per 100,000). NAFLD is more common among all Hispanics and Filipinos, HBV-HCC among Asian and Haitian Black men. HCV-HCC surpasses HBV-HCC in Asian women. ALD-HCC is high among specific Hispanic male groups. Population-based HCV-HCC rates experienced a rapid decline since 2015 (-9.6% annually), while ALD-HCC (+6.0%) and NAFLD-HCC (+4.3%) are rising ($p<0.05$).

Conclusions: New directly acting anti-viral drugs have impacted rates of HCV-HCC, offsetting important increases in both ALD- and NAFLD-HCC. Hispanics may be a group of concern due to higher rates for ALD- and NAFLD-HCC. HCC etiology varies remarkably and may warrant specific interventions by detailed race-ethnicity.

Introduction

Hepatocellular carcinoma (HCC), representing 78% of liver cancers in the United States (US), is highly fatal with only 18% of patients surviving 5 years [1]. Approximately 25,000 new HCC cases are diagnosed annually and incidence rates have increased 48% since 2000 [2]. Clinician reports have shown that over 90% of HCC cases can be attributed to a particular etiology, with the most prevalent causes being chronic hepatitis C infection (HCV), chronic hepatitis B infection (HBV), alcohol-related liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD) [3,4]. Yet, the respective burden of each distinct cause of HCC in the diverse US population is poorly understood, a knowledge gap that hinders our ability to develop effective prevention and control efforts, especially for the non-infectious causes of HCC.

To date, studies describing the relative burden of HCC causal factors have primarily been hospital-based series [3]. Often, these studies utilize only proportions without considering the size of the underlying population at risk, limiting resultant epidemiological information. Moreover, hospital-based series are subject to selection biases, rooted in referral and health insurance coverage patterns, which can perpetuate data limitations for marginalized subpopulations. HCC is a cancer that disproportionately affects those of low socioeconomic status, as well as immigrant, Veteran, and incarcerated populations [4], all of whom are difficult to capture in clinical research studies because they often diverge from typical healthcare pathways. Establishing etiology-specific HCC patterns and trends based on truly inclusive (population-based) data is critical to develop effective prevention and control efforts, especially for those most vulnerable.

In this study, we use individual-level data from three independent population-based data sources in novel statewide linkages to estimate incidence rates and trends by etiology. Moreover, we leverage the remarkable diversity of Florida's population to examine these patterns in detailed race-ethnicity groups: Central Americans, Cubans, Dominicans, Mexican—including US-born Mexican and Foreign-born Mexican—Puerto Ricans, and South Americans instead of Hispanic/Latino(x) only, and African American, Haitian and West Indian instead of Non-Hispanic (NH) Black only. We expand and deepen the findings of our previous study [5] by including more years of data (2010–2018) instead of 2014–2015 only, computing population-based rates accounting for all

HCC cases, adding data from a new linkage with chronic viral hepatitis biomarkers, performing trend analyses, and including a more refined subgroup analysis for Black, Hispanic, and Asian populations.

Materials and Methods

All liver cancer cases reported to the statewide cancer registry, the Florida Cancer Data System (FCDS), diagnosed during 2010–2018, were studied. The FCDS has been recognized for its quality/completeness and has maintained Gold Certification status from the North American Association of Central Cancer Registries for 20 years [6]. Eligible cases for this report included all ICD-O-3 HCC morphologies 8170–8180 (n=12,992). In addition, and because American clinical practice guidelines allow for HCC diagnosis without biopsy, based on imaging alone, cancer cases coded C22.0 (liver) with morphologies 8000-8010 (n=1,428) were also included unless any other primary cancer (e.g., breast, colon, etc.) had occurred prior to the corresponding HCC diagnosis which could cause misclassification of the liver as the primary cancer site.

All HCC cases were individually linked with two data sources: firstly, with the statewide hospital and discharge data provided by Florida's Agency for Healthcare Administration (AHCA), a database including diagnosis codes for every medical episode in any hospital setting in Florida and secondly the viral hepatitis data from the Florida Department of Health's Department of Sexually Transmitted Diseases and Viral Hepatitis surveillance. Linkages were deterministic based on first and last name, sex, birth date, social security number, when available, and county of residence. For the viral hepatitis data, all HCV-RNA positive and/or anti-HCV positive cases and HBV-DNA positive and/or HBs Ag positive cases were considered chronic HCV and chronic HBV cases respectively. For discharge data, relevant diagnosis codes for the etiology of HCC were extracted using established ICD-9-CM and ICD-10-CM codes [7,8] (Table S1).

Based on these two linkages, we assessed seven types of causes including HCV, HBV, ALD, NAFLD, and rarer causes such as autoimmune diseases, genetic causes (e.g., hemochromatosis), and cryptogenic (defined as cases matched with discharge data, but without any code of the remaining six causes, and non-matched to viral hepatitis). To select a predominant-cause category in cases with multiple causes, we used Beste's hierarchical approach [9], largely based on decreasing strength of association (from past research) for each

HCC etiology. Because this is a population-based study, to avoid underestimating etiology-specific counts which would distort rates and trends we performed multiple imputations (MI) with 20 iterations based on sex, racial/ethnicity group, age group, region of residence, and year of diagnosis for cases that did not initially match with any of the data sources (n=1,795 or 12.4%) and placed each into the mentioned 7 cause groups.

We computed proportions of cases by etiology for each racial/ethnic group, sex, and by age groups. We also analyzed etiology of HCC by stage at diagnosis, level of poverty defined by the prevalence of poverty in the respective census tract of residence (0% to < 5%, very low; 5% to < 10%, low; 10% to < 20%, intermediate; 20% to < 100%, high), and US or foreign birth, in addition to race-ethnicity level I (broad racial-ethnic groups comprising non-Hispanic (NH) White (White), NH-Black (Black), and NH-Asian/Pacific Islander (API), as well as Hispanic of all races) and level II (detailed groups including those among the Hispanic population: Central Americans, Cubans, Dominicans, Mexican—including US-born Mexican and Foreign-born Mexican—Puerto Ricans, and South Americans, and among the Black population: African American/US-born Black, Haiti-born Black and West Indies-born Black). We compared prevalence proportions for each of these characteristics using Chi-square tests. Technical aspects of the definition of race-ethnicity Levels I and II can be found in supplemental Annex 1. Level II group identification was possible for 87.5% of Hispanic and 91.2% of NH-Black persons. For the missing cases we used the combined MI procedure with imputation of etiology into a specific group based on age, sex, county of residence, and HCC etiology (when available).

To demonstrate population-level differences, we calculated annualized, sex-stratified, etiology-specific age-adjusted incidence rates (AAIR) for HCC for each Level I and II race and ethnicity groups using the 2000 US population standard and 18 age group bands. Population denominators corresponding to each age group, race-ethnicity, and sex came from the American Community Survey (ACS) 2010-2018 [10]. Finally, we used Joinpoint regression to assess annual rate trends of the predominant cause by sex, race, and race-ethnicity level I [11]. For Asian level II groups such as Chinese or Filipino, we were unable to calculate detailed rates because of their relatively low numbers and the imprecision of their denominator ACS data available for Florida. However, to depict unstudied heterogeneity among Asian persons regarding HCC, we collected and linked data as far back as 2005 to attain informative proportions for this important population. In this study, we

only report on cases and rates for the four most common HCC causes: HCV, HBV, ALD, and NAFLD. All numbers presented in tables are post-imputation.

Data were analyzed using SAS 9.4 and SPSS V22.0.

Results

All 14,420 cases of HCC diagnosed during 2010–2018 and identified through the population-based cancer registry constituted our analytical dataset. Table 1 shows the distribution of general demographics and predominant HCC etiologies. The most prevalent etiology was HCV (n=6,714; 46.6%), followed by 3,927 NAFLD-HCC (27.2%), 1,879 ALD-HCC (13.0%), and 633 HBV-HCC (4.4%). The remaining were cryptogenic (7.3%) and other causes (1.5%) including hemochromatosis, auto-immune hepatitis, among others. When considering all overlapping causes rather than only the predominant cause, two important combinations were HCV with NAFLD (24.6% of all cases) and HCV with ALD (13.9% of all cases) (Table S2).

Demographic and clinical characteristics by cause of HCC

HCV-HCC proportions were significantly higher among males, US-born, and residents of high poverty areas. The median age at diagnosis for HCV-HCC was 60 years; however, among those with NAFLD-HCC, the median age was 71. The proportion of those residing in high poverty areas for NAFLD-HCC was lower than for HCV-HCC ($p<0.05$). HBV-HCC was more prevalent among persons not born in the US and had the lowest median age (59 years). There were no marked differences in stage at diagnosis by etiology. However, Black populations showed a poorer distribution of stage at diagnosis, with the lowest percentage of localized HCC (38.9%) of all racial-ethnic groups (Table S3).

Leading causes of HCC by race and ethnicity

Puerto Rican men had the highest HCC rates at 19.6 per 100,000, largely due to a high rate of HCV-HCC (Table 2, Figure S1)**.** In contrast, West-Indies born Black men had the lowest HCC rates of all groups (3.0). Among women, foreign-born Mexican women showed the highest rates (5.9), principally attributable to high rates of NAFLD-HCV, and West-Indies born Black women had the lowest rate (1.6). Overall, while HCV-HCC

was the main cause of HCC in most populations, HBV-HCC was the leading cause among Haitian-born Black men and Asian men. NAFLD-HCC was the leading cause among foreign-born Mexican (men and women), Central American (men and women), South American (men and women), and Cuban women (Table S4). NH-White, Cuban, and West Indian Black groups were the three with significantly lower HCC rates than the all-races combined rate. NH-White and Cuban persons account for 62% of the Florida population and their relatively lower rates bring the Florida HCC overall rates below the US average masking the high risk detected for some Florida populations [5,10].

Cause-specific incidence rates by sex

The overall HCC AAIR for Florida was 9.3 per 100,000 (95%CI:9.2-9.5) for men which is 3.8-fold higher than the AAIR in women at 2.4 (95%CI:2.4-2.5) (Table 2). By etiology, male-to-female sex ratios for HBV-HCC and ALD-HCC were 5.6 (4.5-7.1) and 5.6 (4.9-6.4), respectively. For HCV-HCC the ratio was 4.4 (4.2-4.7) while for NAFLD-HCC the ratio was 2.7 (2.5-2.9).

HCV-HCC rates

Among men HCC rates were dominated by HCV-HCC rates, which were highest among US-born populations other than NH-White persons. AAIRs for Puerto Rican, African American, and US-born Mexican American males were 10.9, 8.0, and 7.6, respectively, all significantly above 4.4 seen among NH-White men. For women, HCV-HCC rates were high among the same ethnic groups with rates of 2.2, 2.1, and 2.6, respectively, all significantly higher than the rate among NH-White women (1.0). The lowest rates of HCV-HCC were found among foreign-born Hispanic and foreign-born NH-Black populations.

NAFLD-, ALD-, and HBV-HCC rates

NAFLD-HCC incidence rates were significantly higher among Hispanic persons compared to NH-White persons (50% higher in males and double for females) (Figure S1). When sexes were combined, NAFLD-HCC incidence rate ratios using NH-White persons as reference were 1.53 (1.41-1.65) for Hispanic, 0.90 (0.69-1.15) for Asian, and 0.81 (0.71-1.91) for NH-Black persons. AAIRs of NAFLD-HCC among NH-Black men and women and NH-White women were the lowest of all groups. ALD-HCC rates were low among women of all

ethnicities but high among Puerto Rican, Central American, and Mexican males. HBV-HCC AAIRs were high among Asian (4.9/100,000) and Haitian Black males (4.6/100,000), which were four-fold higher than among the next ranked group, African American males (1.1/100,000). Among women, HBV-HCC rates were low (<0.2/100,000) in all groups, apart from Asian women (1.2/100,000).

Cause-specific incidence trends 2010-2018

Trends for all racial-ethnic groups presented by etiology and sex can be seen in Figures 1 and 2 and Table S5. Overall HCC rates were stable for males over the 2010–2018 period but increased in women, 2.7% annually. However, there were substantial differences by cause. After a continuous increase, there was a sharp reduction in HCV-HCC trends (all races combined) during 2015–2018 (-8.7% annually in men and -11.9% in women). In 2010-2018, ALD-HCC increased for both sexes (6.0% annually), although, among women, the increase is based on very low baseline rates (0.2/100,000). Overall, the NAFLD-HCC AAIR increased 4.3% annually. While HCV-HCC continued to have the highest rates in all male populations, in women, NAFLD-HCC surpassed HCV-HCC rates in 2017. In 2018, the NAFLD-HCC AAIR for all women combined was 1.2 per 100,000 compared to HCV-HCC, 0.8 per 100,000 in women. In 2018 alone, for men and women combined, HCV and NAFLD accounted for 36% and 35% of all HCC cases respectively.

Leading causes of HCC among Asian Americans

Lastly, proportions dating back to 2005 were pooled for Asian Populations (Table 3) and significant differences were observed by sex, with HBV-HCC being the most common etiology in Asian men and HCV-HCC, the most common among Asian women.

Discussion

In this population-based analysis we document, for the first time, etiology-specific HCC trends based on one state's entire population. We observed a recent but substantial decline in HCV-HCC rates (-9.6% annually since 2014 in all groups combined) and substantial increasing trends for ALD-HCC (+6.0%) and NAFLD-HCC (+4.3%) during 2010–2018.

HCV-HCC was the most common etiology, with the highest rates among persons aged 50-69 years. The primary cause of chronic HCV infection is historical use of HCV-infected blood transfusions, while additional suggested potential causes include risky practices in tattoo parlors and/or IV drug use during 1960–1990 [12].

HCV-HCC rates were higher among specific US-born populations including Puerto Ricans, African Americans, and Mexicans, compared to NH-Whites. Higher rates in the Puerto Rican population are supported by the higher HCV prevalence reported by the Latino SOL study [13]. Moreover, US-born non-White people such as Puerto Ricans, African Americans, and Mexicans, exhibit higher rates of incarceration [14], a group among whom the HCV prevalence is as high as 23% [15,16]. High rates in these populations, approximately double those of other populations residing in the US during the same period (i.e., NH-White and Cuban persons), may be related to complex social environments of specific Hispanic groups and African American persons, especially among males.

The second most common form of HCC was NAFLD-HCC. NAFLD is the most common chronic liver disease in the US affecting up to 100 million Americans [17] and particularly Hispanic persons, among whom a genetic predisposition among other risk factors has been suggested [18]. In this study, rates of NAFLD-HCC among Hispanic persons were at least 40% higher than among NH-White and NH-Black populations. Unlike HCV-HCC, the difference between US-born and foreign-born populations was not marked. NAFLD is typically associated with obesity and diabetes, both of which are more prevalent among African Americans than Hispanics [19]. However, among Black persons the association between obesity and NAFLD is not so evident [20], and, in agreement, we found lower rates of NAFLD-HCC among NH-Black persons than would otherwise be expected.

ALD-HCC rates were higher among males, particularly among Puerto Rican, Central American, and Mexican persons. While it is known that consumption of alcohol and binge drinking is more prevalent in these groups [21,22], the pathways for these behaviors may be different according to each group's distinct historical trajectory and/or recency of immigration to the US.

HBV-HCC rates were high among male Asian and Haitian Black persons. While the high prevalence of HBV is known among Asian groups, HBV characterization among Haitian persons, particularly in Florida, is less well reported. Previous work has shown Haiti to be a high prevalence HBV country with ongoing vertical transmission [23]. Haiti was the last country in the Americas to introduce hepatitis B vaccination in 2012, and as of 2019, the birth dose of hepatitis B vaccine had yet to be included in their vaccination schedule [23].

Except for the Japanese population, it is generally assumed that HBV is the cause of most HCCs among Asian persons [4]. However, our study suggests a more nuanced etiologic distribution in this heterogeneous population. For instance, among Asian women (all groups combined) HCV superseded HBV as the first cause of HCC. While HBV-HCC was the most prevalent cause among Chinese, Korean, and Southeast Asian Americans, an important proportion of cases among Asian persons were due to HCV. HCV was the leading cause among Japanese persons, while among those South Asian and Vietnamese, the proportions of cases due to HBV-HCC and HCV-HCC were nearly equivalent. Lastly, and similarly to Hispanic populations, NAFLD-HCC was the leading cause among Filipino persons, which could be a result of socio-environmental factors such as diet and cooking habits.

Our study shows that on a population-basis HCV-HCC started to decline after 2014, coinciding with the discovery of DAAs. This decline contrasts with increases in both NAFLD-HCC and ALD-HCC in both sexes. The increase in ALD-HCC aligns with increasing mortality rates from alcoholic cirrhosis observed in the US [24]. Overall, given the higher incidence of HCV-HCC in men and the favorable recent trends in HCV-HCC, it is logical that more favorable HCC trends of all causes combined are also recorded in men. Future HCC trends will depend on the success and speed of HCV treatment and the prevention and control of the rising trend in NAFLD-HCC and ALD-HCC.

The major strengths of our study are first, the unique presentation of etiology-specific HCC rates on a population basis (i.e., all HCC cases for an entire state) with no restriction on ages by leveraging existing individual-level surveillance data, and second, the novel characterization of HCC profiles specific for each detailed race-ethnicity. Because population-based incidence rates measure risk, they facilitate accurate

comparisons for each etiology-specific HCC, which is advantageous when compared to hospital-based series or simple proportions. For instance, while NAFLD-HCC accounts for as many as 36% of all HCC cases among females and 25% in males, the actual AAIR is higher in males 2.3/100,000 compared to 0.8/100,000 in females (IRR 2.7; 95%CI:2.5-2.9).

Importantly, the incidence rates presented here result not only from variation in the prevalence of each risk factor for each population, but also, from differences in treatment for underlying liver diseases that can progress to HCC. Therefore, HCC disparities are a consequence of risk factors, but also, the result of access to quality healthcare, which aggravates existing disparities. For example, differential rates of antiviral therapy and/or transplantation directly impact the development of HCC.

There are several limitations to the current study. Aflatoxin exposure, an established risk factor for HCC, common in Africa, Asia, and parts of Central Americans, could not be studied; however, existing data suggests low prevalence of aflatoxin in the US. Another limitation is that up to 50% of people with an anti-HCV positive result do not have detectable HCV RNA [25]. However, we were unable to distinguish the two scenarios and all patients with positive HCV antibody were considered to have HCV-related HCC. However, of all HCV-HCC cases in our analysis, only 0.4% were identified based on this test alone. A third limitation, similar to other population-based studies [7,8], is the reliance upon NAFLD-related condition codes [7-9] such as diabetes, obesity, and metabolic syndrome; NAFLD historically has not been captured by discharge data and it was impossible to distinguish between NAFLD and NASH. The hierarchical classification of HCC causes may, to a limited degree, result in an underestimation of etiologies ranked lower than HCV, such as ALD and NAFLD. Lastly, the Florida Department of Health does not release individual-level data on Viral Hepatitis matches from VA institutions because of existing legal agreements. This limitation is not extended to veterans who received care at any given point in non-VA institutions and its overall impact was small (see sensitivity analysis for Multiple Imputation procedure in Annex S2 and Table S6).

Our study shows disparate HCC incidence in specific groups and provides important data about which groups could benefit from enhanced HCC screening, treatment, and surveillance of underlying liver disease.

Knowledge of etiology-specific HCC is also important to anticipate the future HCC burden and develop targeted outreach and intervention programs. Further, these causes are not specific to HCC, and primary and secondary prevention efforts will impact chronic liver disease outcomes in general. The current challenges are to ensure that populations at risk are tested for viral hepatitis infection, that all persons with chronic HCV and/or HBV infection receive appropriate medication. In this respect, we are developing a continuing medical education effort to highlight the need for following the current screening recommendations, which will be preferentially targeting medical practitioners in areas serving the most affected racial-ethnic groups in Florida. Other options could include targeted mailings, radio show announcements, educational programs, or health fairs in specific ethnic enclaves. Even more challenging will be to find ways to target the rising incidence of ALD-HCC and NAFLD-HCC, as well as clarifying the origins or causes of the Hispanic population's vulnerability to these two exposures. In this regard, while ALD-HCC patterns are sex-specific, which does not suggest genetic susceptibility among Hispanic persons, NAFLD-HCC rates are significantly higher in both Hispanic men and women compared to both NH-Whites and NH-Blacks. In conclusion, HCC patterns and trends are highly complex and their surveillance by etiology is fundamental to better control and prevent this challenging disease.

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Table 1. Sociodemographic and clinical characteristics by predominant cause of HCC cases. Florida 2010–2018.						
	Total[a] N (%)	**HCV-HCC N (%)**	**HBV-HCC N (%)**	**ALD-HCC N (%)**	**NAFLD-HCC N (%)**	**p-value[b]**
Total Cases	14,420	6714	632	1879	3927	
Median Age	64	60	59	66	71	
Sex						<0.0001
Male	11,082 (76.9%)	5,348 (79.7%)	530 (83.9%)	1,568 (83.4%)	2,723 (69.3%)	
Female	3,338 (23.1%)	1,365 (20.3%)	102 (16.1%)	312 (16.6%)	1,204 (30.7%)	
Race/Ethnicity						<0.0001
Whites	9,412 (65.3%)	4,367 (65.0%)	153 (24.2%)	1,337 (71.2%)	2,691 (68.5%)	
Blacks	1,878 (13.0%)	1,076 (16.0%)	215 (34.0%)	148 (7.9%)	294 (7.5%)	
Asians	427 (3.0%)	130 (1.9%)	172 (27.2%)	19 (1.0%)	69 (1.8%)	
Hispanics	2,703 (18.7%)	1,141 (17.0%)	93 (14.7%)	375 (20.0%)	873 (22.2%)	
Age Group						<0.0001
<49	609 (4.2%)	225 (3.4%)	146 (23.1%)	73 (3.9%)	80 (2.0%)	
50-69	9,106 (63.1%)	5,612 (83.6%)	345 (54.6%)	1,053 (56.0%)	1,463 (37.3%)	
70+	4,705 (32.6%)	877 (13.1%)	141 (22.3%)	753 (40.1%)	2,383 (60.7%)	
Stage at Diagnosis						<0.0001
Localized	6,441 (44.7%)	3,075 (45.8%)	284 (44.9%)	836 (44.5%)	1,815 (46.2%)	
Regional	3,702 (25.7%)	1749 (26.1%)	152 (24.1%)	483 (25.7%)	898 (22.9%)	
Distant	2,156 (15.0%)	912 (13.6%)	109 (17.2%)	237 (12.6%)	615 (15.7%)	
Unknown	2,121 (14.7%)	978 (14.6%)	87 (13.8%)	323 (17.2%)	599 (15.3%)	
Poverty Level						<0.0001
Very low poverty	1,189 (8.2%)	450 (6.7%)	58 (9.2%)	156 (8.3%)	401 (10.2%)	
Low poverty	3,269 (22.7%)	1,354 (20.2%)	141 (22.3%)	471 (25.1%)	995 (25.3%)	
Medium poverty	5,438 (37.7%)	2,498 (37.2%)	225 (35.6%)	714 (38.0%)	1,530 (39.0%)	
High poverty	4,386 (30.4%)	2,353 (35.0%)	203 (32.1%)	514 (27.4%)	958 (24.4%)	
Unknown	138 (1.0%)	59 (0.9%)	4 (0.6%)	23 (1.2%)	42 (1.1%)	
Nativity Status						<0.0001
US birth	10,211 (70.8%)	5,014 (74.7%)	249 (39.4%)	1,346 (71.6%)	2,662 (67.8%)	
Foreign birth	2,331 (16.2%)	756 (11.3%)	310 (49.1%)	286 (15.2%)	731 (18.6%)	
Unknown birth	1,878 (13.0%)	945 (14.1%)	72 (11.4%)	248 (13.2%)	534 (13.6%)	
Detailed Black Subgroups						<0.0001
African American/US-born Black[c]	1,600 (11.1%)	1,003 (14.9%)	112 (17.7%)	13 (7.1%)	238 (6.1%)	
Haiti-born Black	165 (1.1%)	37 (0.6%)	84 (13.3%)	--	23 (0.6%)	
West Indies-born Black	84 (0.6%)	30 (0.4%)	12 (1.9%)	10 (0.5%)	27 (0.7%)	
Detailed Hispanic Subgroups						<0.0001
Central American	231 (1.6%)	--	14 (2.2%)	46 (2.4%)	89 (2.3%)	
Cuban	809 (5.6%)	309 (4.6%)	27 (4.3%)	90 (4.8%)	324 (8.3%)	
Dominican	81 (0.6%)	33 (0.5%)	12 (1.9%)	8 (0.4%)	23 (0.6%)	
Mexican	226 (1.6%)	82 (1.2%)	--	61 (3.2%)	56 (1.4%)	
Foreign-born Mexican	113 (0.8%)	24 (0.4%)	--	37 (2.0%)	36 (0.9%)	
US-born Mexican	113 (0.8%)	58 (0.9%)	--	24 (1.3%)	20 (0.5%)	
Puerto Rican	982 (6.8%)	558 (8.3%)	20 (3.2%)	108 (5.7%)	228 (5.8%)	
South American	346 (2.4%)	87 (1.3%)	15 (2.4%)	60 (3.2%)	144 (3.7%)	

-- Note: Not reported; observations fewer than 10.

a. Includes all listed as well as Cryptogenic and Others (e.g. genetic, auto-immune); b. p-value from chi-square test of independence, computed on 4 categories of etiology-specific HCC; c. African American is exclusively reserved to US-born Black persons in this report.

Abbreviations: ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.

Table 2. Age-adjusted[a] incidence rates (AAIR) per 100,000 by detailed race/ethnicity. Florida 2010–2018.							
Level I Race/ethnicity	**Level II Race/ethnicity**	**n**	**Total[b]**	**HCV-HCC**	**HBV-HCC**	**ALD-HCC**	**NAFLD-HCC**
			Rate (95% CI)	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**
MALES COMBINED[d]		11,082	9.3 (9.2-9.5)	4.4 (4.3-4.6)	0.5 (0.5-0.5)	1.3 (1.3-1.4)	2.3 (2.2-2.4)
White		7,419	8.8 (8.6-9.1)	4.4 (4.3-4.6)	0.2 (0.1-0.2)	1.3 (1.2-1.4)	2.2 (2.1-2.3)
Black[c]		1,387	10.7 (10.1-11.3)	5.9 (5.5-6.3)	1.5 (1.3-1.7)	0.9 (0.7-1.1)	1.5 (1.3-1.8)
	African American/US-born Black[e]	1,188	13.1 (12.3-13.8)	8.0 (7.5-8.6)	1.1 (0.9-1.3)	1.2 (0.9-1.4)	1.8 (1.5-2.2)
	Haiti-born Black	129	8.0 (6.6-9.7)	1.6 (1.0-2.6)	4.6 (3.6-5.9)	--	0.8 (0.4-1.7)
	West Indies-born Black	50	3.0 (2.2-4.4)	0.9 (0.5-2.1)	--	--	0.9 (0.5-2.1)
Asian		290	11.0 (9.7-12.4)	3.1 (2.5-3.9)	4.9 (4.0-5.8)	0.6 (0.4-1.0)	1.6 (1.1-2.2)
Hispanic[c]		1,986	10.4 (10.0-10.9)	4.3 (4.0-4.6)	0.4 (0.3-0.5)	1.7 (1.5-1.9)	3.2 (2.9-3.5)
	Central American	147	10.8 (8.9-12.9)	2.6 (1.8-3.5)	0.6 (0.3-1.1)	2.8 (1.9-4.0)	4.1 (2.8-5.6)
	Cuban	596	7.4 (6.8-8.1)	2.8 (2.5-3.2)	0.3 (0.2-0.5)	1.0 (0.8-1.3)	2.8 (2.4-3.2)
	Dominican	60	9.4 (7.0-12.4)	3.5 (2.1-5.3)	--	--	2.7 (1.5-4.5)
	Mexican	168	11.8 (9.8-14.1)	3.6 (2.7-4.7)	--	3.9 (2.8-5.2)	2.8 (1.8-4.3)
	Foreign-born Mexican	80	9.2 (6.9-12.2)	1.6 (0.9-3.1)	--	3.5 (2.2-5.4)	3.0 (1.6-5.3)
	US-born Mexican	88	17.1 (13.5-21.4)	7.6 (5.4-10.2)	--	4.5 (2.7-6.9)	2.6 (1.2-4.9)
	Puerto Rican	762	19.4 (18.0-20.8)	10.9 (10.0-12.0)	0.4 (0.3-0.7)	2.4 (1.9-2.9)	4.1 (3.4-4.9)
	South American	233	8.1 (7.1-9.3)	1.8 (1.3-2.3)	0.4 (0.2-0.7)	1.5 (1.1-2.1)	3.6 (2.8-4.4)
FEMALES COMBINED[d]		3,338	2.4 (2.4-2.5)	1.0 (1.0-1.1)	0.1 (0.1-0.1)	0.2 (0.2-0.3)	0.8 (0.8-0.9)
White		1,993	2.2 (2.1-2.3)	0.9 (0.8-1.0)	0.03 (0.02-0.05)	0.3 (0.2-0.3)	0.7 (0.7-0.8)
Black[c]		491	3.2 (2.9-3.5)	1.7 (1.5-2.0)	0.2 (0.1-0.3)	0.3 (0.2-0.3)	0.8 (0.7-1.0)
	African American/US-born Black[e]	412	3.9 (3.5-4.3)	2.2 (1.9-2.5)	0.2 (0.1-0.3)	0.3 (0.2-0.5)	0.9 (0.7-1.1)
	Haiti-born Black	37	2.2 (1.5-3.2)	0.9 (0.5-1.7)	--	--	0.7 (0.3-1.4)
	West Indies-born Black	34	1.6 (1.1-2.6)	0.7 (0.4-1.6)	--	--	0.5 (0.3-1.5)
Asian		137	4.3 (3.6-5.1)	1.4 (1.0-1.8)	1.2 (0.9-1.7)	0.1 (0.0-0.2)	1.1 (0.7-1.5)
Hispanic[c]		717	3.1 (2.8-3.3)	1.1 (0.9-1.2)	0.1 (0.0-0.1)	0.2 (0.2-0.3)	1.4 (1.2-1.5)
	Central American	84	4.4 (3.5-5.5)	0.7 (0.4-1.2)	--	--	2.7 (2.0-3.6)
	Cuban	213	2.1 (1.8-2.4)	0.8 (0.7-1.0)	--	--	1.0 (0.8-1.2)
	Dominican	21	2.2 (1.3-3.4)	--	--	--	--
	Mexican	58	5.4 (4.0-7.0)	1.7 (1.0-2.7)	--	--	2.5 (1.6-3.7)
	Foreign-born Mexican	33	5.9 (3.9-8.6)	--	--	--	3.2 (1.8-5.4)
	US-born Mexican	25	5.0 (3.1-7.4)	2.6 (1.3-4.4)	--	--	--
	Puerto Rican	220	4.8 (4.2-5.5)	2.1 (1.7-2.5)	--	0.4 (0.2-0.6)	1.9 (1.5-2.4)
	South American	113	2.9 (2.4-3.5)	0.6 (0.4-0.9)	--	0.4 (0.2-0.6)	1.4 (1.1-1.9)

--Note: Rates based on fewer than 10 observations are not reported because of possibility of identification.

a. Age-adjusted to the 2000 US standard population; b. Includes all listed as well as Cryptogenic and Others (e.g. genetic, auto-immune); c. Includes all cases of this race and/or ethnicity; not just listed groups; d. All race-ethnicities combined only includes those listed here (excludes multiracial, other, and unknown race); e. African American is exclusively reserved to US-born Black persons in this report.

Abbreviations: ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.

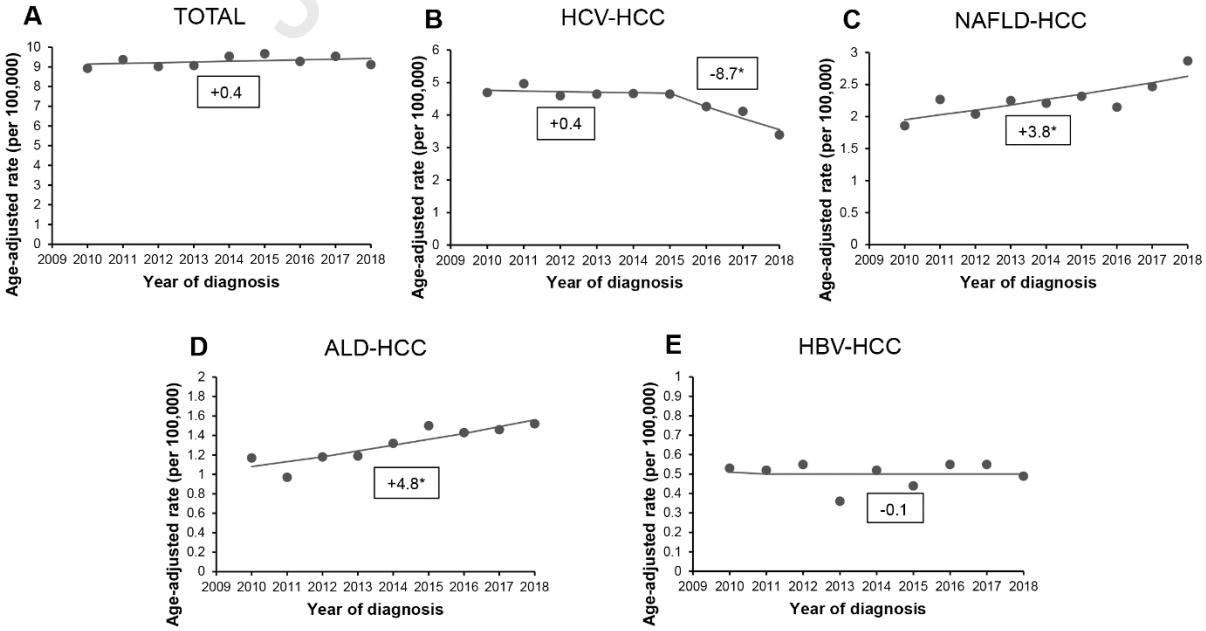
Table 3. Distribution of HCC cases by etiology among Non-Hispanic Asian Americans. Florida, 2005–2018.						
	Total[a] N (%)	HCV-HCC n (%)	HBV-HCC n (%)	ALD-HCC n (%)	NAFLD-HCC n (%)	p-value[c]
Detailed Subgroup						<0.0001
All Asians Combined[b]	600	190 (31.7%)	228 (38.0%)	30 (5.0%)	98 (16.3%)	
Chinese	99	21 (21.2%)	53 (53.5%)	--	17 (17.2%)	
Filipino	80	16 (20.0%)	17 (21.3%)	--	29 (36.3%)	
Japanese	32	14 (43.8%)	--	--	--	
Korean	48	13 (27.1%)	22 (45.8%)	--	--	
South Asian	89	29 (32.6%)	29 (32.6%)	--	16 (18.0%)	
Southeast Asian	34	--	16 (47.1%)	--	--	
Vietnamese	184	79 (42.9%)	71 (38.6%)	--	16 (8.7%)	
Sex						0.004
Men	411	124 (30.2%)	172 (41.8%)	26 (6.3%)	59 (14.4%)	
Women	189	66 (34.9%)	57 (30.2%)	--	39 (20.6%)	

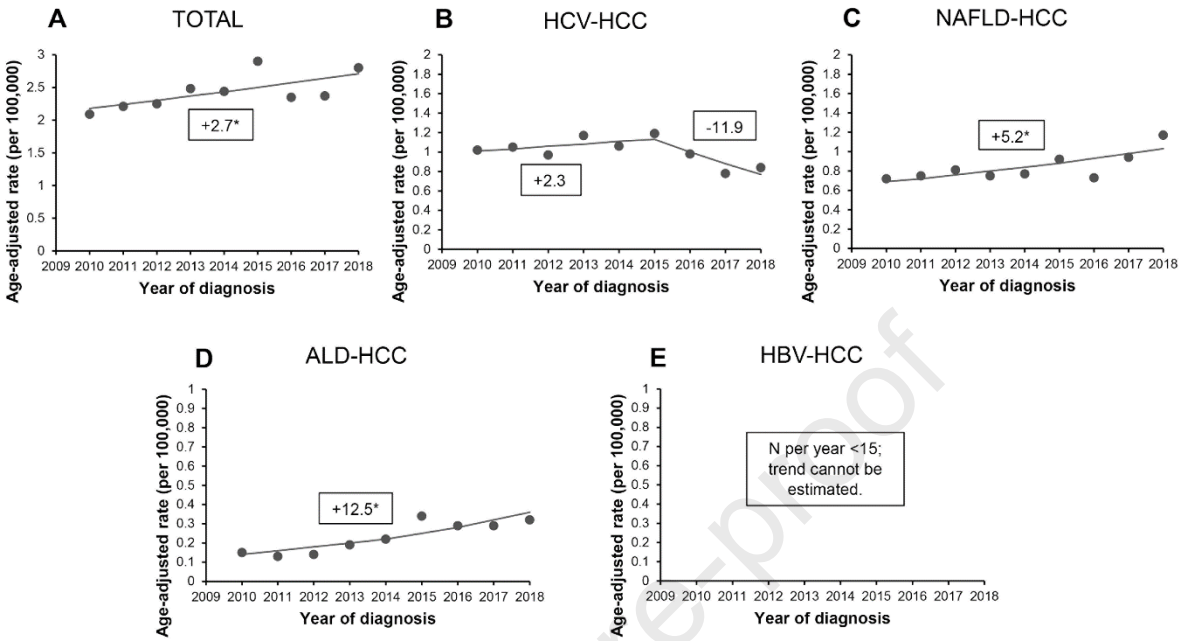
-- Note: Not reported; observations fewer than 10.
a. Includes all listed as well as Cryptogenic category, Other causes category (e.g. genetic, auto-immune); b. Includes all cases of this race-ethnicity; not just listed groups; c. p-value from chi-square test.
Abbreviations: ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.

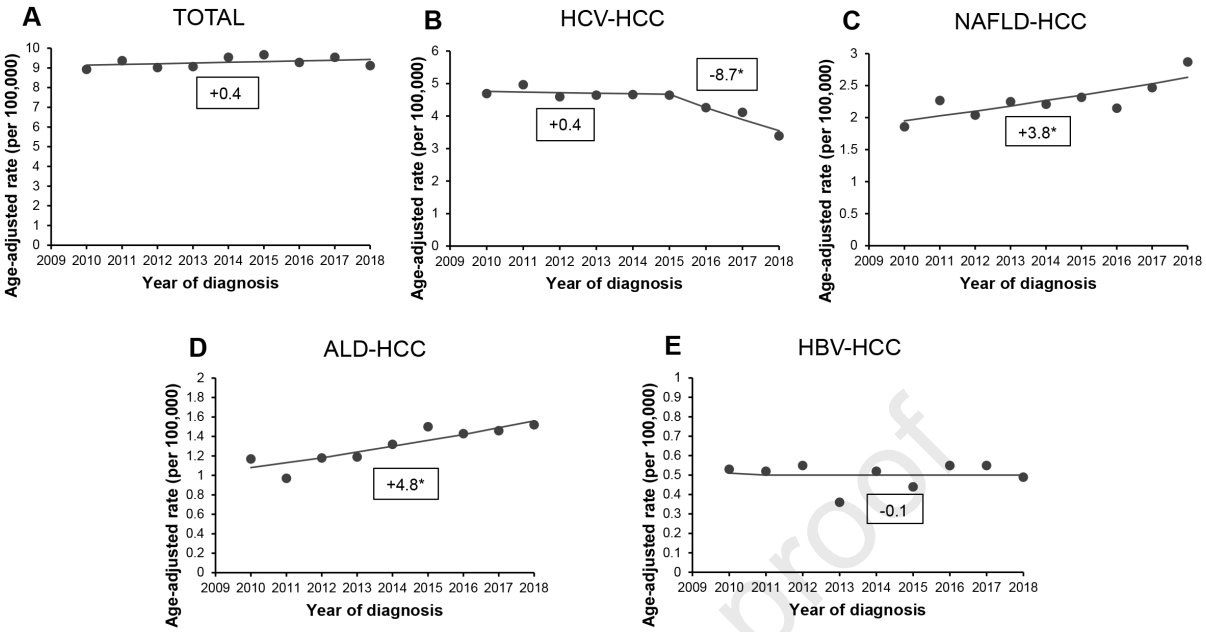
Figure Legends

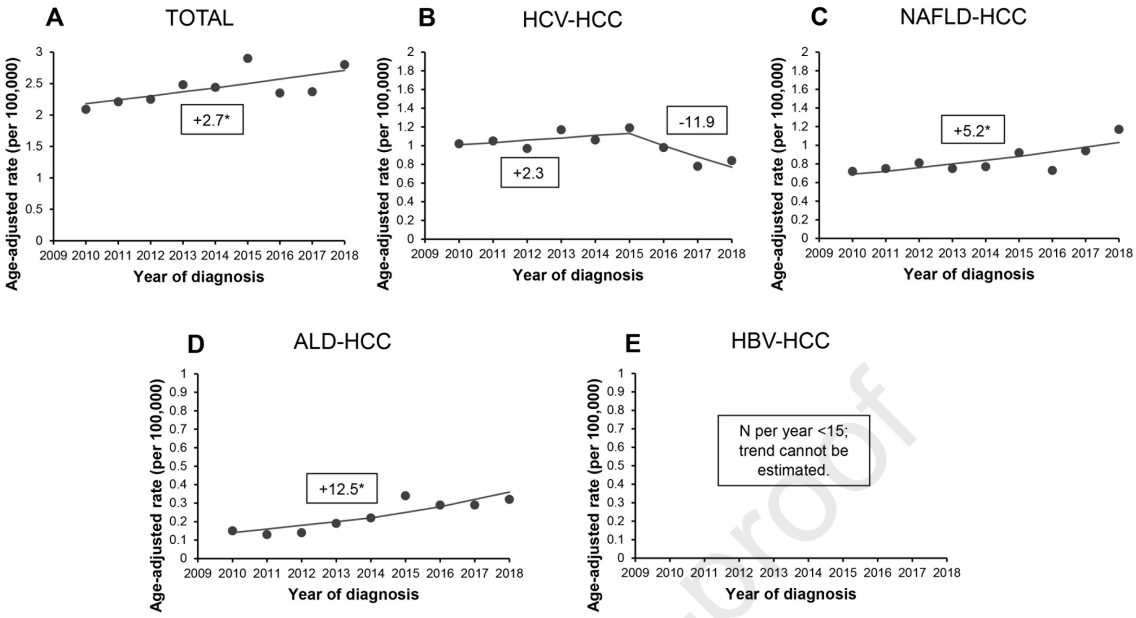
Figure 1 (Males) and Figure 2 (Females). Trends in HCC age-adjusted incidence rates for all race/ethnicities combined. Florida 2010–2018. Rates are shown by select HCC etiologies: Total, HCV, NAFLD, ALD, HBV. Annual percentage change (AAPC) estimates shown next to each respective curve. *Trend significantly different than zero at $P < .05$.

Figures







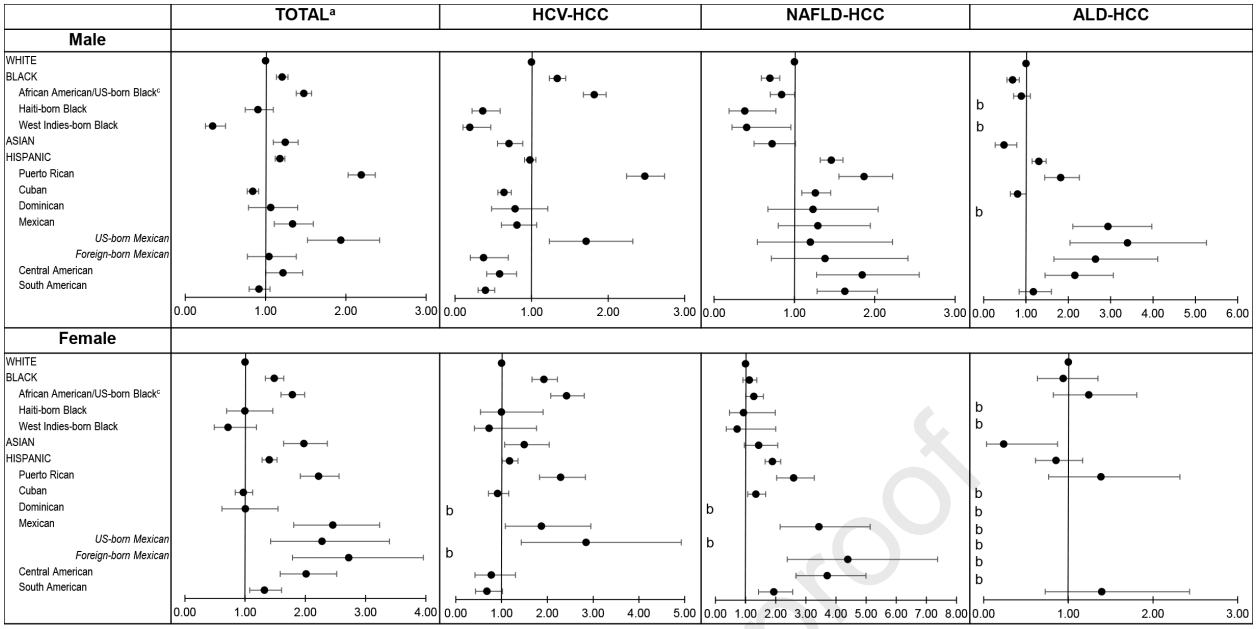


What You Need to Know:

BACKGROUND: Incidence rates and trends of hepatocellular carcinoma (HCC) by etiology, including alcohol-related disease, NAFLD, HCV, HBV, are unknown in the US. Heterogeneity by detailed racial-ethnic groups has been largely ignored.

FINDINGS: HCV-HCC is declining while alcohol and NAFLD-HCC are increasing. HCV-HCC is the leading etiology among Puerto Rican, African American, and US-born Mexican men. NAFLD-HCC leads among women, Hispanics and Filipinos.

IMPLICATIONS FOR PATIENT CARE: Remarkable variation in HCC etiology warrants tailored awareness and interventions by detailed race-ethnicity. Of concern are Hispanics, due to higher rates for alcohol- and NAFLD-HCC, two rising disease entities.



Supplementary Annex 1:

For all 14,420 cases of HCC, level I race-ethnicity data (comprising non-Hispanic (NH) White, NH-Black, and NH-Asian/Pacific Islander (API), as well as Hispanic of all races) was readily available from Florida Cancer Data System (FCDS).

Level II race-ethnicity was available for 87.5% of Hispanics and 91.2% of NH-Blacks, after linkage with FCDS and death certificate data. Those with level II missing group were dealt with via Multiple Imputation as described.

Hispanic level II race-ethnicity comprised Cubans, Puerto Ricans, Dominicans, Central Americans, South Americans, and Mexicans, including delineations by nativity with US-born Mexican and foreign-born Mexican. The need to separate Mexican populations between foreign-born and US-born is due to their nationally demographic importance and their distinct HCC patterns (1,2).

NH-Black level II race-ethnicity comprised the following groups based on nativity: US-born NH-Blacks, Haiti-born NH-Blacks, and West Indies-born NH-Blacks. West Indies comprise all non-Spanish speaking islands and territories in the Caribbean region except for Haiti, thus comprising Florida residing Black individuals born in the following countries and territories: Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Cayman Islands, Dominica, Grenada, Guadeloupe, Jamaica, Martinique, Montserrat, Saint Kitts and Nevis, Saint Barthelemy, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, the Netherlands Antilles, the British Virgin Islands, Trinidad and Tobago, Turks and Caicos, and West Indies not otherwise specified (3).

Other Hispanic groups such as those from Spain or other countries and other NH-Black groups such as those African-born are included in the respective total data for their Level I racial-ethnic group, though not analyzed in detail at level II race-ethnicity due to low numbers.

Among NH-Black persons, those born in Haiti and the West Indies do not always identify as African American, thus this denomination was exclusively reserved to US-born persons in this report.

NH-Asian and Pacific Islander (API) rates were calculated in combination of all groups for purposes of being all inclusive. The Pacific Islander population is very small in Florida, as well as some of the Level II Asian groups, and thus, only proportions (not rates) for etiology of HCC were calculated. Etiologic-specific HCC proportions were assessed for a larger period, 2005–2018, and were displayed for Level II API groups with more than 30 cases of HCC.

Supplementary Annex Table 1: Average Annual Population of Florida by Level I and Level II racial-ethnic group. Source: ACS 2010–2018.

Level I race-ethnicity	Level II race-ethnicity	Annual Population
Non-Hispanic White		11,059,250
Non-Hispanic Black		3,254,810
	African American/US-born Black	2,575,797
	Haiti-born Black	318,509
	West Indies-born Black	289,615
	Others	70,889
Hispanic		4,887,550
	Central American	556,189
	Cuban	1,435,005

	Dominican	220,368
	Mexican	704,417
	Foreign-born Mexican	288,349
	Us-born Mexican	416,068
	Puerto Rican	1,041,912
	South American	864,548
	Others	65,111
Non-Hispanic Asian and Pacific Islander		677,640
	Chinese	97,827
	Filipino	121,434
	Japanese	24,430
	Korean	34,686
	Pacific Islander	18,077
	South Asian (includes Indian subcontinent)	177,857
	Southeast Asian (Cambodian, Laotian, Thai)	25,268
	Vietnamese	79,660
	Others	98,041

References:

1.Pinheiro, P.; Callahan, K.; Jones, P.; et al. Liver Cancer: A Leading Cause of Cancer Death in the United States and the Role of the 1945-1965 Birth Cohort by Race/Ethnicity. Journal of Hepatology 2019, 1(3):162-169.

2.Pinheiro, P.S.; Callahan, K.E.; Stern, M.C.; de Vries, E. Migration from Mexico to the United States: A high-speed cancer transition. Int J Cancer 2018, 142, 477-488, doi:10.1002/ijc.31068.

3.Pinheiro, P.S.; Callahan, K.E.; Ragin, C.; et al. Black Heterogeneity in Cancer Mortality: US-Blacks, Haitians, and Jamaicans. Cancer Control 2016, 23, 347-358, doi:10.1177/107327481602300406.

Supplementary Annex 2:

Because there were multiple disease entities considered in hierarchical order we performed a sensitivity analysis on HCV-HCC (the most common HCC etiology) to assess the result of the multiple imputation procedure. We considered the following two extreme, plausible scenarios in the context of the non-release of matched VA data by the Florida Department of Health:

Scenario 1) proportional allocation of etiology among cases with missing etiology based on the proportion of known (non-imputed) cases by age, sex, race, and ethnicity, and

Scenario 2) the assumption of a 2*higher proportion of HCV matched in the data of those with missing etiology (non-released cases from the VA) compared to the known, non-VA released data.

The imputed rates reported in this study fell between Scenarios 1 and 2, not revealing any major departure from these two scenarios (Please see Table S5).

Table S1. Discharge Data Codes for causes of Hepatocellular Carcinoma.†	
Etiology Categories	**ICD-9 CM Codes***
Chronic Hepatitis C Virus Infection	070.41, 070.44, 070.51, 070.54, 070.70, V02.62
Chronic Hepatitis B Virus Infection	070.2, 070.22, 070.23, 070.3, 070.32, 070.33, 070.42, 070.52, V02.61
Alcohol-Related Liver Conditions	571.0 (alcohol-induced fatty liver disease); 571.1 (Alcohol-induced hepatitis); 571.2 (alcohol-induced cirrhosis); 571.3 (alcohol-induced liver damage) 291, 291.0-291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303, 303.0, 303.00-303.03, 303.9, 303.90-303.93, 305.0, 305.00-305.03, 357.5, 425.5, 535.3, 535.30, 535. 31, 571.5, 571.6, 790.3, 980, 980.0, 980.8, 980.9, E86.0, E86.00, E86.01, E86.08, E86.09, V11.3, V79.1 (alcohol-related disorders)
Metabolic	277.7 (metabolic syndrome); 278, 278.0, 278.00-278.03, 278.1, 278.8, 783.1, V45. 86, V77.8, V85.4, V85.30-V85.45 (obesity); 272.0, 272.1, 272.2, 272.4, 272.5, 272.7, 272.9 (dyslipidemia); 401, 402, 403, 404 (hypertension); 790.2, 790.21, 790.22, 790.29 (impaired glucose metabolism); 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 571.8 (non-alcoholic fatty liver disease), 790.2 (type 2 diabetes/impaired fasting glucose)
Biliary Conditions	751.61 (Caroli Disease); 571.6 (primary biliary cholangitis); 576.1 (primary sclerosing cholangitis); 51.2, 576.0 (cholecystectomy); 751.69 (choledochal cysts); 574.00, 574.01, 574.10, 574.11, 574.20, 574.21 (cholelithiasis); 574.30, 574.31, 574.40, 574.41, 574.50, 574.51 (choledocholithiasis)
Autoimmune Conditions	571.42 (autoimmune hepatitis); 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 (type 1 diabetes)
Genetic Conditions	270.2 (tyrosinemia); 277.1 (porphyrias); 275.0, 275.01 (hemochromatosis); 275.1 (Wilson disease); 273.4 (alpha-1 antitrypsin deficiency); 271 (glycogen storage disease)
*Equivalent ICD-10-CM codes inclusive of specific NAFLD code K76.0 in effect since October 2015 were also used. †Makarova-Rusher, O.V.; Altekruse, S.F.; McNeel, T.S.; et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer 2016, 122, 1757-1765, doi:10.1002/cncr.29971.	

Table S2. Frequencies of HCC causes statewide for 14,420 cases (pre-imputation), based on linkages with discharge data and viral hepatitis data.		
Cryptogenic	875	6.1%
HCV	1,563	10.8%
HBV	189	1.3%
HCV,HBV	68	0.5%
ALD	525	3.6%
ALD,HCV	706	4.9%
ALD,HBV	42	0.3%
ALD,HBV,HCV	32	0.2%
OC	76	0.5%
OC,HCV	54	0.4%
OC,HBV	2	0.0%
OC,ALD	16	0.1%
OC,ALD,HCV	47	0.3%
OC,ALD,HBV	3	0.0%
OC,HBV,HCV	3	0.0%
OC,ALD,HBV,HCV	5	0.0%
Met	3,163	21.9%
Met,HCV	2,063	14.3%
Met,HBV	221	1.5%
Met,HBV,HCV	107	0.7%
Met,ALD	1,012	7.0%
Met,ALD,HCV	1,063	7.4%
Met,ALD,HBV	53	0.4%
Met,ALD,HBV,HCV	59	0.4%
Met,OC	298	2.1%
Met,OC,HCV	151	1.0%
Met,OC,HBV	15	0.1%
Met,OC,ALD	100	0.7%
Met,OC,ALD,HCV	89	0.6%
Met,OC,HBV,HCV	12	0.1%
Met,OC,ALD,HBV	3	0.0%
Met,OC,ALD,HBV,HCV	10	0.1%
Missing	1,795	12.4%
Total	14,420	100%
Abbreviations: ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Met: metabolic causes - obesity, diabetes, metabolic syndrome; OC: other causes , genetic and/or auto-immune.		

Table S3. Distribution of HCC cases by stage at diagnosis and race and ethnicity. Florida, 2010–2018.

		Stage at Diagnosis				
Level I Race/ethnicity	**Level II Race/ethnicity**	**Localized n (%)**	**Regional n (%)**	**Distant n (%)**	**Unknown n (%)**	**Total N**
White		4,298 (45.7%)	2,411 (25.6%)	1,376 (14.6%)	1,327 (14.1%)	9,412
Black[a]		730 (38.9%)	501 (26.7%)	351 (18.7%)	296 (15.8%)	1,878
	African American/ US-born Black[b]	622 (38.9%)	445 (27.8%)	291 (18.2%)	242 (15.1%)	1,600
	Haiti-born Black	57 (34.3%)	29 (17.5%)	40 (24.1%)	40 (24.1%)	166
	West Indies-born Black	34 (40.5%)	21 (25.0%)	16 (19.0%)	13 (15.5%)	84
Asian		207 (48.5%)	93 (21.8%)	79 (18.5%)	48 (11.2%)	427
Hispanic[a]		1,206 (44.6%)	697 (25.8%)	350 (12.9%)	450 (16.6%)	2,703
	Central American	96 (41.6%)	64 (27.7%)	40 (17.3%)	31 (13.4%)	231
	Cuban	363 (44.9%)	198 (24.5%)	115 (14.2%)	133 (16.4%)	809
	Dominican	37 (45.7%)	22 (27.2%)	11 (13.6%)	11 (13.6%)	81
	Mexican	99 (43.8%)	48 (21.2%)	28 (12.4%)	51 (22.6%)	226
	Foreign-born Mexican	48 (42.5%)	27 (23.9%)	11 (9.7%)	27 (23.9%)	113
	US-born Mexican	51 (45.1%)	21 (18.6%)	17 (15.0%)	24 (21.2%)	113
	Puerto Rican	447 (45.5%)	268 (27.3%)	118 (12.0%)	149 (15.2%)	982
	South American	153 (44.2%)	90 (26.0%)	38 (11.0%)	65 (18.8%)	346

a. Includes all cases of this race and/or ethnicity; not just listed groups; b. African American is exclusively reserved to US-born Black persons in this report.

Abbreviations: HCC, hepatocellular carcinoma.

Table S4. HCC leading cause by race, ethnicity, and sex. Florida, 2010–2018.			
Level I Race/ethnicity	**Level II Race/ethnicity**	**Males**	**Females**
White		HCV	HCV
Black[a]		HCV	HCV
	African American/ US-born Black[b]	HCV	HCV
	Haiti-born Black	HBV	HCV
	West Indies-born Black	HCV	HCV
Asian[a]		HBV	HCV
	Chinese	HBV	
	Filipino	NAFLD	
	Japanese	HCV	
	Korean	HBV	
	South Asian	HBV/HCV	
	Southeast Asian	HBV	
	Vietnamese	HCV	
Hispanic[a]		HCV	NAFLD
	Central American	NAFLD	NAFLD
	Cuban	HCV	NAFLD
	Mexican	ALD	NAFLD
	Foreign-born Mexican	ALD	NAFLD
	US-born Mexican	HCV	HCV
	Puerto Rican	HCV	HCV
	South American	NAFLD	NAFLD

a. Includes all cases of this race and/or ethnicity; not just listed groups; b. African American is exclusively reserved to US-born Black persons in this report.

Abbreviations: ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.

Table S5. Incidence trends for HCC cases by race, ethnicity, and sex . Florida, 2010–2018.

	All HCC		Cause-specific HCC							
	Total[a]		HCV-HCC		HBV-HCC		ALD-HCC		NAFLD-HCC	
	AAPC[b]	p-value	AAPC[b]	p-value	AAPC[b]	p-value	AAPC[b]	p-value	AAPC[b]	p-value
MALE										
White	+0.7	0.31	+1.4 (2010-2015); -9.6 (2015-2018)	0.53; 0.09	-1.9	0.64	+4.0	<0.01	+4.0	0.01
Black	-0.9	0.59	-4.4	0.04	+0.6	0.84	+9.3	0.04	+6.3	0.09
Asian	-1.2	0.64	-0.7	0.86	-0.9	0.85	+8.8	0.25	-4.3	0.39
Hispanic	-0.3	0.82	-5.8	<0.01	-5.4	0.33	+5.0	0.15	+2.5	0.19
All Combined[c]	+0.4	0.32	+0.4 (2010-2015); -8.7 (2015-2018)	0.79; 0.04	-0.1	0.97	+4.8	<0.01	+3.8	<0.01
FEMALE										
White	+3.4	0.05	+9.6 (2010-2014); -11.1 (2014-2018)	0.09; 0.04	--	--	+13.4	0.02	+5.8	0.02
Black	+1.6	0.38	-2.7	0.36	+4.6	0.48	+8.6	0.15	+3.8	0.16
Asian	-2.2	0.54	+1.9	0.76	-2.4	0.65	--	--	-3.4	0.64
Hispanic	+0.9	0.59	-8.0	<0.01	--	--	+9.2	0.09	+4.4	0.05
All Combined[c]	+2.7	0.05	+2.3 (2010-2015); -11.9 (2015-2018)	0.45; 0.11	--	--	+12.5	<0.01	+5.2	0.01
BOTH SEXES										
White	+1.2	0.13	+3.9 (2010-2014); -8.1 (2014-2018)	0.16; 0.02	-1.0	0.80	+5.6	<0.01	+4.6	<0.01
Black	-0.3	0.80	-4.1	0.04	+1.2	0.62	+9.2	0.03	+5.6	<0.01
Asian	-2.3	0.06	-0.5	0.86	-2.1	0.44	+8.3	0.23	-5.6	0.29
Hispanic	0.0	0.99	-6.3	<0.01	-2.8	0.45	+5.9	0.07	+3.2	0.08
All Combined[c]	+0.9	0.09	0.0 (2010-2014); -9.6 (2014-2018)	0.96; <0.01	+0.8	0.51	+6.0	<0.01	+4.3	<0.01

--Note: Trends of annual rates of less than 0.02 per 100,000 are not reported.

a. Includes all listed as well as Cryptogenic and Others (e.g. genetic, auto-immune); b. AAPC is the average annual percent change and is a weighted average of the AAPCs over the fixed interval 2010-2018 using the underlying Joinpoint model; c. All race-ethnicities combined includes only those listed here (excludes multiracial, other, and unknown race).

Abbreviations: ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.

Table S6. Sensitivity analysis of population-based rates for HCV-HCC by race and ethnicity. Florida, 2010–2018.

	Imputed Results	Proportional allocation of missing cause into different causes	Assuming proportion of unreleased viral data would yield same as released data
		Lower bound scenario	Higher bound scenario
Race and ethnicity			
	MALE		
White	4.4 (4.3-4.6)	4.2 (4.1-4.4)	4.6 (4.4-4.7)
Black	5.9 (5.5-6.3)	5.7 (5.3-6.1)	6.1 (5.6-6.5)
API	3.1 (2.5-3.9)	3.3 (2.7-4.2)	3.2 (2.5-4.0)
Hispanic	4.3 (4.0-4.6)	4.3 (4.0-4.6)	4.5 (4.2-4.8)
Total	4.4 (4.3-4.6)	4.3 (4.1-4.4)	4.6 (4.5-4.7)
	FEMALE		
White	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.9-1.0)
Black	1.7 (1.5-2.0)	1.7 (1.5-1.9)	1.8 (1.6-2.0)
API	1.4 (1.0-1.8)	1.4 (1.0-1.9)	1.4 (1.0-1.9)
Hispanic	1.1 (0.9-1.2)	1.0 (0.9-1.2)	1.1 (1.0-1.3)
Total	1.0 (1.0-1.1)	1.0 (0.9-1.0)	1.0 (1.0-1.1)

a. Assumption: unreleased data on viral hepatitis biomarkers by FCDS follow the same pattern of the released linked data.

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; API, Asian and Pacific Islander.