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Disparity in Liver Cancer Incidence and Chronic Liver Disease Mortality by Nativity in Hispanics: the Multiethnic Cohort

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Abstract

Background—Hepatocellular carcinoma (HCC) and chronic liver disease (CLD) are major causes of morbidity and mortality in Hispanics. Disparity in HCC incidence and CLD death by nativity in Hispanics has been reported. We assessed whether individual-level risk factors explain this disparity in a prospective study of 36,864 Hispanics (18,485 US-born and 18,379 foreign-born) in the Multiethnic Cohort.

Methods—Risk factors were assessed using baseline questionnaire and Medicare claim files. During a 19.6-year follow up, 189 incident cases of HCC and 298 CLD deaths were identified.

Results—The HCC incidence rate was almost twice as high in US-born as in foreign-born Hispanic men (44.7 vs. 23.1), but comparable in women (14.5 vs. 13.4). The CLD mortality rate was about twice as high in US-born as in foreign-born (66.3 vs. 35.1 in men; 42.2 vs. 19.7 in women). Heavy alcohol consumption was associated with HCC and CLD in foreign-born individuals, while current smoking status, Hepatitis B/C viral infection and diabetes were associated with both HCC and CLD. After adjustment for these risk factors, the hazard rate ratios

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(95% confidence intervals) of HCC and CLD death were 1.58 (1.00, 2.51) and 1.85 (1.25, 2.73), respectively for US-born compared to foreign-born Hispanics.

Conclusion(s)—US-born Hispanics, particularly males, are at greater risk of HCC and CLD death than foreign-born Hispanics. Overall known differences in risk factors do not account for these disparities. Future studies are warranted to identify factors that contribute to the elevated risk of HCC development and CLD death in US-born Hispanics.

Keywords

hepatocellular carcinoma; epidemiology; Latinos; risk factor; minority

Introduction

The Hispanic and Latino (Hispanic) population is the largest racial/ethnic minority population in the United States[1]. While the rates of most cancers in Hispanic populations are declining, the rate of hepatocellular carcinoma (HCC), the most common type of liver cancer, is increasing[2]. During 2006-2010, among individuals aged 50-64 years, Hispanics experienced higher HCC incidence and mortality rates than Asians and non-Hispanic whites[3]. The incidence of HCC in Hispanics in California is among the top three in the US [4]. HCC is one of the most fatal cancers; the 5-year survival rate among Hispanics is 19% for both men and women[5]. Chronic liver disease (CLD) is a major cause of morbidity and mortality in Hispanics[1, 6]. Compared to whites, Hispanics had a 50% greater CLD death rate[1]. In 2009, CLD was the third leading cause of death for Hispanic men aged 55-64[7]. In the Multiethnic Cohort Study (MEC), we observed that Hispanics have the highest rates of HCC incidence and CLD death across five ethnic groups[8, 9].

Nativity (country of birth) has been suggested to play an important role in Hispanic health[10]. Disparity in HCC incidence by nativity in Hispanic populations has been reported[11, 12]. Compared to whites or foreign-born Hispanics, US-born Hispanics have a much higher risk of developing HCC[11]. Very few studies, however, have examined the extent to which detailed individual risk factor data, such as obesity, diabetes, alcohol consumption, smoking, hepatitis B (HBV) and hepatitis C (HCV) infection account for the observed disparity. In this study, we examined whether the risk of incident HCC and CLD mortality differ by birth place among Hispanics in the MEC and whether known risk factors account for the differences.

Materials and Methods

Study population

The details of the MEC and baseline characteristics have been published[13]. Briefly, the MEC is an ongoing population-based prospective cohort study with over 215,000 men and women from Hawaii and California (mainly Los Angeles County), assembled between 1993 and 1996. Potential participants, aged 45 to 75 years at recruitment, were identified primarily through Department of Motor Vehicles drivers' license, voter registration lists, and Health Care Financing Administration data files. All participants returned a self-administered baseline questionnaire that obtained information on demographic, anthropometric measures,

personal history of medical conditions, family history of cancer, and lifestyle factors including diet, physical activity, smoking history, and medication use. The current study only included the California component because almost all Hispanics in the cohort are from California.

Of the 47,438 Hispanic participants, we excluded those with a cancer diagnosis except non-melanoma skin cancer before cohort entry, missing place of birth, education, body mass index, diabetes, smoking status, and alcohol intake information, and those with invalid dietary data based on macronutrient intakes[14] as a marker of quality for the questionnaire. As a result, data on 36,864 Latino participants (18,485 US-born and 18,379 foreign-born) were available for the present analysis. The Institutional Review Boards at the University of Hawaii and at the University of Southern California approved the study protocol.

Endpoint assessment

Incident HCC cases [International Classification of Diseases for Oncology (ICD-O) version 3 topographic (C22.0) and morphology codes (8170-8175)] were identified through annual linkage to the Cancer Surveillance Program for Los Angeles County and the California State Cancer Registry which are part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. CLD deaths (ICD-9=571 and ICD-10=K70-K76) were determined through annual linkage to state death certificate files in California and periodic linkage to the National Death Index. The majority of CLD deaths in the MEC were listed as alcoholic-related diseases (48.7%) or fibrosis/cirrhosis of the liver (38.9%). Participants who died from HCC were not included in the CLD mortality count as the incident cases were already counted. Deaths from other liver cancers were also not included because they were often due to metastasis from another cancer site rather than primary HCC. The endpoint ascertainment was complete through December 31, 2013.

Exposure ascertainment

Data on demographic (education, place of birth, years of living in the US, etc.), medical history, lifestyle and dietary factors including smoking history, alcohol consumption, and vigorous physical activity were obtained from the baseline questionnaire. Dietary information was obtained using a Quantitative FFQ (QFFQ) designed for use in this multiethnic population[13]. A calibration study of the QFFQ was conducted using three 24 hour recalls from a random subsample of participants selected within sex–racial/ethnic groups and revealed a high correlation between the QFFQ and 24 hour recalls for energy-adjusted nutrients[15]. Self-reported body weight and height were used to calculate body mass index (BMI in kg/m^2). HBV and HCV infection status was obtained using ICD-9 codes (HBV: 070.20-23, 070.30-33, V02.61; HCV: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62) in Medicare claim files among the MEC fee-for-service (FFS) participants (n=17,205)[16]. Because the prevalence of HBV infection was low (<1%) in our Hispanic populations, we combined it with the HCV status. The characteristics of FFS participants are shown in Supplemental Table 1; their characteristics were similar to those of the whole cohort (Table 1).

Statistical Analysis

Nativity was categorized into US-born and foreign-born. Hazard rate ratios (HRs) and 95% confidence intervals (CIs) for HCC incidence and CLD deaths associated with nativity were calculated using Cox proportional hazard models. Age (in days) was used as the underlying time variable in the Cox regression starting with a participant's age at entry (baseline questionnaire completion) and ending with the earliest of these endpoints: date of HCC diagnosis, date of death (from CLD or other causes for non-cases), or end of follow up (December 31, 2013). Cox models were adjusted for level of education (high school graduate or less, some college, college graduate or more), BMI (<25, 25-<30, ≥30 kg/m^2), self-reported physician diagnosed type 2 diabetes (yes, no), cigarette smoking status (never, former, current), and alcohol intake (0, <24, ≥24 g ethanol/day; ~24 g ethanol/day was equivalent to ~2 drinks/day). Vigorous physical activity was categorized into none, ≤20 min/day, >20 min/day). Dietary factors (*e.g.* red meat, vegetable and fruit intakes) were categorized using overall tertile distributions in the cohort. We also further adjusted for HBV/HCV infection status in the subset of Medicare FFS population. The proportional hazards assumption was tested by assessing the Schoenfeld residuals and no major violation was observed. Tests for trend were performed by entering the ordinal values representing categories of exposure as continuous variables in the models. All P-values are two sided. Statistical analyses were performed with SAS 9.2 software (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics of Hispanic MEC participants by nativity are shown in Table 1. Among the foreign born, majority of participants were born in Mexico (76.6% men and 71.2% women) and the rest were born in either Central or South America (23.4% men and 28.8% women). Age at cohort entry was slightly higher among US born compared to foreign born Hispanics. The majority of foreign born have lived in the US for 15 years or longer (83.4% men and 80.8% women). The education level was higher in US-born compared to foreign-born Hispanics. In both men and women, there was higher prevalence of heavy alcohol drinking, ever smoking, diabetes and obesity in US-born than in foreign-born Hispanics. The US-born Hispanics consumed lower amounts of total fruit and vegetables than the foreign-born in both men and women, while the intake of saturated fat and red meat were similar. The prevalence of hepatitis infection was higher in US-born than in foreign-born men (4.1% vs. 2.7%) and more similar in women (3.0% vs. 2.6%).

During a median follow up of 19.6 years, 189 Hispanics were diagnosed with HCC and 298 Hispanics died of CLD. The HCC case and CLD death characteristics along with the HCC incidence and CLD mortality rates are shown in Table 2. In men and women, the mean age at HCC diagnosis and stage of disease were comparable between US born and foreign born Hispanics. The age-adjusted HCC incidence rate was almost twice as high in US-born as in foreign-born Hispanic men (44.7 vs. 23.1), but comparable for US- and foreign-born Hispanic women (14.5 vs. 13.4). US-born Hispanic men and women had an 89% to 114% higher CLD mortality rate compared to their foreign-born counterparts, respectively. In men, the majority of CLD deaths were due to alcoholic liver diseases (60.2% US-born and 73.8%

foreign-born), while in women the majority of CLD deaths were due to cirrhosis or fibrosis (55.6% US-born and 64.1% foreign-born). The proportion of alcohol-related CLD death in women were higher in the US- vs. foreign-born. The average age at CLD death was similar between US- and foreign-born Hispanics.

The associations of known and potential risk factors with HCC incidence by nativity are shown in Table 3. The results were similar for men and women; therefore, the results are given for men and women combined. Increasing alcohol consumption was associated with risk of HCC in foreign-born Hispanics (P trend=0.0148). Compared to non-drinkers, those who consumed ≥2 drinks per day had a 3-fold increased risk (HR= 2.96; 95% CI: 1.44, 6.06). Current smoking was associated with HCC in US-born (HR=2.91; 95% CI: 1.75, 4.85) and foreign-born (HR=2.10; 95% CI: 1.13, 3.90) Hispanics. Diabetes was strongly associated with HCC regardless of nativity (HRs ~3.3). BMI was associated with HCC in US-born (P trend=0.0365) and in foreign-born Hispanics (P trend=0.0516). Red meat intake was associated with risk in foreign-born. HBV/HCV was strongly associated with HCC in US-(HR=16.13; 95% CI: 8.73, 29.81) and foreign-born (HR=19.93; 95% CI: 9.44, 42.07) Hispanics. Education levels, vigorous physical activity, saturated fat, and fruit and vegetable intakes were not associated with HCC.

Table 4 shows the associations of known and potential risk factors with CLD mortality by nativity. Alcohol consumption of ≥2 drinks per day, current smoking, diabetes and BMI were significantly associated with risk of CLD death in US- and foreign-born Hispanics. Increasing level of education (P trend=0.006) and vegetable intake (P trend=0.0063) was associated with reduced risk of CLD death in US-born Hispanics. HBV/HCV was a strong risk factor for CLD death in US-born and foreign-born. Vigorous physical activity, saturated fat and red meat and fruit intake were not associated with risk of CLD deaths in this population.

The association between nativity for HCC and CLD death are shown in Table 5. Results were combined for men and women because the numbers of cases were limited and the risk factors associations were similar in men and women. In the age- and sex-adjusted model, US-born Hispanics had a 61% higher risk of developing HCC compared to foreign-born (HR=1.61; 95% CI: 1.20, 2.17). Further adjusting for BMI, smoking status, alcohol intake, and diabetes attenuated the HR but the risk among US-born remained significantly higher (HR=1.45; 95% CI: 1.08, 1.96). Although the sample size of the Medicare sub-cohort was much smaller than in the whole cohort, the elevated risks of HCC incidence (HR=1.58; 95% CI: 1.00, 2.51) was still observed after further adjustment for HBV/HCV infection status in that subset. Similarly, after adjusting for known risk factors (i.e., BMI, smoking status, alcohol intake, diabetes, and HBV/HCV infection status) US-born Hispanics still had a 85% higher risk of CLD death compared to foreign-born (HR=1.85; 95% CI:1.25, 2.73). Coffee intake had previously been associated with HCC and CLD[9], but further adjustment for coffee intake did not change the results substantially (data not shown).

Discussion

After accounting for known risk factors, the risk of developing HCC and dying of CLD among Hispanic differs by place of birth, with US-born Hispanics having 58% higher risk of HCC and 85% higher risk of CLD mortality compared to those born in Mexico or South/Central America. The higher risk of HCC associated with Hispanic nativity was mainly seen in men.

Our results are consistent with results from previous HCC studies in Hispanics[11, 12]. El Serag *et al.* showed that in 1999-2001 the liver cancer mortality rates among US-born Hispanic men in California were more than twice as high than those for foreign-born Hispanic men in California and 65% higher in Texas[11]. Using the California Cancer Registry data, Chang *et al.* showed similar findings; in 1988-2004, US-born Hispanic men in California had 86% higher liver cancer incidence rates than foreign-born Hispanic men[12]. In the MEC which was based in California, we observed 93% higher liver cancer incidence rates in US-born vs. foreign-born Hispanic men. Two other studies showed higher liver cancer incidence rates among Hispanic men in Florida compared to the incidence rates in their country of origin[17] and higher liver cancer incidence rates in US mainland than island Puerto Rican men, but not in women[18].

Acculturation has been associated with increased rates of smoking, alcohol drinking and obesity, in Hispanics[19-22]; consistent with these population-based studies, US-born Hispanics in the MEC had higher rates of smoking, alcohol drinking, and obesity compared to foreign-born Hispanics. It has been suggested that a greater prevalence of risk factors for HCC (*i.e.* HCV infection, greater alcohol consumption, metabolic syndrome, etc.) among the more acculturated US-born Hispanic population causes the disparity in HCC incidence by nativity[11]. The diverging nativity patterns by sex for HCC might be due to a tendency of male immigrants to adopt unhealthy lifestyles (*e.g.* excessive alcohol drinking, weight gain, and illicit drug use, *etc.*) compared with females[17]. In the MEC Hispanic men and women, HBV/HCV infection and diabetes are the strongest risk factors for HCC, and the difference in the prevalence of HBV/HCV (1.4% in men and 0.4% in women) and diabetes (4.2% in men and 2.4% in women) between US-born and foreign-born Hispanics is larger in men than in women. Thus, the greater difference in prevalence of HBV/HCV infection and diabetes between the US- and foreign-born Hispanic men than their female counterparts could be the reasons, at least partially, for the observed HCC incidence difference in men, but not in women, between the two nativity groups. However, even after accounting for these differences and other factors, the risk of HCC among US-born Hispanics remained significantly higher compared to the risk among foreign-born Hispanics.

US-born men and women have much higher rates of CLD death compared to their foreign-born counterparts. The major risk factors for CLD in the MEC Hispanics are excessive alcohol drinking, diabetes, HBV/HCV and smoking. In women, the prevalence of excessive drinking and smoking is higher in US-born compared to foreign-born women which could lead to a much higher rate of CLD death among US-born women. We also observed a higher proportion of alcohol-related CLD deaths among US-born women vs. foreign-born women.

Similar to HCC, accounting for risk factors did not explain the excess risk observed among US-born Hispanics.

Our study has several strengths and weaknesses. The strengths include its prospective design, long follow up, large sample size and detailed information on most HCC risk factors. The major limitations include the ascertainment of HBV/HCV status using Medicare claims as they were only ascertained if there was a medical reason to determine them and thus this information was most likely incomplete. Our analysis was based on exposure collected at baseline based on self-report and thus, exposure misclassification, as well as changes in exposures during follow up, cannot be ruled out. Even in our relatively large cohort, the number of cases within risk factor categories by sex and nativity were small. The limited number of cases might reduce our ability to observe excess risk in any or many of the specific subgroups.

In summary, US-born Hispanics are at greater risk of HCC and CLD death than their foreign-born counterparts. While overall known difference in risk factors do not account for these observed disparities in HCC incidence and CLD mortality risk between US- and foreign-born Hispanics, we observed that HCV/HBV infection, diabetes, excessive alcohol drinking, and current smoking are important risk factors in this population. To reduce and control the development of HCC and death from CLD, public health recommendations should be targeted toward Hispanics, especially among those who are born in the US, such as the identification and treatment of patients with chronic infection with HBV or HCV, the prevention and controls of diabetes, in addition to the recommendations to limit alcohol consumption and quit smoking. Future studies are warranted to identify the unidentified risk factors that contribute to the elevated HCC incidence and CLD deaths in US-born Hispanics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	body mass index
CI	confidence interval
CLD	chronic liver disease
HCC	hepatocellular carcinoma
HR	hazard rate ratio

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Table 1

Characteristics in Hispanic men and women by nativity in the Multiethnic Cohort

	Men		Women	
	US Born	**Foreign Born**	**US Born**	**Foreign Born**
No. at risk cohort	9,176	9,297	9,309	9,082
Mean age at cohort entry (SD)	61.6 (7.5)	59.4 (7.7)	60.9 (7.7)	58.6 (7.5)
Place of birth, n (%)				
USA	9,716 (100%)		9,309 (100%)	
Mexico		7,125 (76.6%)		6,470 (71.2%)
Central or South America		2,172 (23.4%)		2,612 (28.8%)
Years of living in the US, n (%)				
≤10		706 (7.6%)		793 (8.8%)
11-15		771 (8.3%)		845 (9.3%)
15-25		2,311 (24.9%)		2,489 (27.4%)
≥26		5,438 (58.5%)		4,852 (53.4%)
Missing		71 (0.7%)		103 (1.1%)
Level of education, n (%)				
High school or below	5,093 (55.5%)	6,911 (74.3%)	6,264 (67.3%)	7,191 (79.2%)
Some college	2,726 (29.7%)	1,586 (17.1%)	2,232 (24.0%)	1,275 (14.0%)
Completed college or higher	1,357 (14.8%)	800 (8.6%)	813 (8.7%)	616 (6.8%)
Alcohol intake, n (%)				
Non-drinker	3,202 (34.9%)	3,362 (36.2%)	5,541 (59.5%)	6,297 (69.3%)
<2 drink/day	4,288 (46.7%)	4,686 (50.4%)	3,474 (37.3%)	2,661 (29.3%)
≥2 drinks/day	1,686 (18.4%)	1,249 (13.4%)	294 (3.2%)	124 (1.4%)
Smoking status, n (%)				
Never smokers	2,738 (29.8%)	3,147 (33.9%)	5,512 (59.2%)	6,538 (72.0%)
Former smokers	4,807 (52.4%)	4,417 (47.5%)	2,668 (28.7%)	1,779 (19.6%)
Current smokers	1,631 (17.8%)	1,733 (18.6%)	1,129 (12.1%)	765 (8.4%)
Diabetes, n (%)	1,699 (18.5%)	1,332 (14.3%)	1,490 (16.0%)	1,231 (13.6%)
Body mass index, n (%)				
<25 kg/m^2	2,274 (24.8%)	2,323 (25.0%)	2,851 (30.6%)	2,872 (31.6%)
25-<30 kg/m^2	4,793 (52.2%)	5,148 (55.4%)	3,470 (37.3%)	3,890 (42.8%)
≥30 kg/m^2	2,109 (23.0%)	1,826 (19.6%)	2,988 (32.1%)	2,320 (25.6%)
Vigorous physical activity, n (%)				
None	2,829 (30.8%)	2,755 (29.6%)	5,314 (57.1%)	4,853 (53.4%)
≤ 20 min/day	2,067 (22.5%)	1,722 (18.5%)	1,881 (20.2%)	1,545 (17.0%)
> 20 min/day	3,975 (43.3%)	4,267 (45.9%)	1,586 (17.0%)	1,714 (18.9%)
Missing	305 (3.4%)	553 (6.0%)	528 (5.7%)	970 (10.7%)
Dietary intake, mean (SD)				
Calorie intake, kcal/day	2488.2 (1290.0)	2747.3 (1436.9)	2055.3 (1109.8)	2320.6 (1233.8)
% Calories from saturated fat	10.1 (2.5)	9.6 (2.4)	9.8 (2.5)	9.4 (2.5)
Red meat, g/kcal/day	33.3 (18.0)	32.5 (19.2)	27.9 (17.0)	25.9 (17.2)

	Men		Women	
	US Born	**Foreign Born**	**US Born**	**Foreign Born**
Fruit intake, g/kcal/day	143.6 (116.2)	158.3 (119.7)	188.6 (141.7)	214.2 (151.2)
Vegetables intake, g/kcal/day	148.2 (70.6)	175.4 (76.6)	174.3 (85.2)	199.4 (89.3)
Hepatitis B and/or C*, n (%)	157 (4.2%)	133 (2.8%)	118 (3.0%)	123 (2.6%)

SD=standard deviation.

* Based on a subset of MEC participants (N=17,205) linked to fee-for-service (FFS) Part A and B Medicare.

Table 2

Hepatocellular carcinoma incidence and chronic liver disease mortality rates in Hispanics by nativity in the Multiethnic Cohort

	Men		Women	
	US Born	**Foreign Born**	**US Born**	**Foreign Born**
No. HCC cases	85	43	33	28
Mean age at diagnosis (SD)	72.1 (7.9)	73.4 (7.0)	73.9 (6.4)	72.4 (6.7)
HCC stage, n (%)				
Localized	34 (40.0)	19 (44.2)	16 (48.5)	14 (50.0)
Advanced	37 (43.5)	18 (41.9)	13 (39.4)	12 (42.9)
Unknown	14 (16.5)	6 (13.9)	4 (12.1)	2 (7.1)
HCC incidence rates[a]	44.7	23.1	14.5	13.4
No. CLD deaths	113	65	81	39
Alcohol-related disease, n (%)	68 (60.2)	48 (73.9)	23 (28.4)	6 (15.4)
Fibrosis/cirrhosis, n (%)	32 (28.3)	14 (21.5)	45 (55.6)	25 (64.1)
Chronic hepatitis, n (%)	2 (1.8)	0 (0)	1 (1.2)	0 (0)
Other, n (%)	11 (9.7)	3 (4.6)	12 (14.8)	8 (20.5)
Mean age at CLD death (SD)	70.6 (8.2)	70.8 (8.7)	71.9 (7.2)	72.8 (7.6)
CLD mortality rates[a]	66.3	35.1	42.2	19.7

SD=standard deviation.

[a]Per 100,000 an age adjusted to the US 2000 standard population.

Table 3

Association between risk factors and hepatocellular carcinoma incidence in Hispanics by nativity in the Multiethnic Cohort

	US Born		Foreign Born	
	No. of cases	**HR* (95% CI)**	**No. of cases**	**HR* (95% CI)**
Alcohol intake				
Non-drinkers	55	1.00	33	1.00
<2 drinks/day	39	0.78 (0.51, 1.20)	25	1.15 (0.66, 2.00)
≥ 2 drinks/day	24	1.49 (0.89, 2.50)	13	2.96 (1.44, 6.06)
		P trend=0.3732		P trend=0.0148
Smoking status				
Non-smokers	31	1.00	32	1.00
Former	53	1.37 (0.86, 2.17)	21	0.78 (0.43, 1.39)
Current	34	2.91 (1.75, 4.85)	18	2.10 (1.13, 3.90)
Diabetes status				
No	72	1.00	47	1.00
Yes	46	3.32 (2.26, 4.90)	24	3.38 (2.03, 5.62)
Body mass index (kg/m^2)				
<25	18	1.00	16	1.00
25-<30	62	1.75 (1.03, 2.98)	32	1.15 (0.63, 2.11)
≥30	38	1.90 (1.07, 3.39)	23	1.89 (0.99, 3.63)
		P trend=0.0365		P trend=0.0516
Vigorous physical activity				
0	51	1.00	31	1.00
≤20 min/day	26	0.96 (0.59, 1.56)	11	0.96 (0.47, 1.93)
>20 min/day	36	0.78 (0.50, 1.23)	22	0.99 (0.55, 1.79)
		P trend=0.2859		P trend=0.9767
Level of education				
High School or lower	79	1.00	55	1.00
Some college	26	0.75 (0.48, 1.19)	12	1.25 (0.67, 2.36)
Completed college or higher	13	0.90 (0.49, 1.64)	4	0.89 (0.32, 2.48)
		P trend=0.4071		P trend=0.8576
% calories from saturated fat				
Tertile 1	42	1.00	24	1.00
Tertile 2	35	0.78 (0.50, 1.23)	19	0.80 (0.43, 1.47)
Tertile 3	41	0.86 (0.55, 1.35)	28	1.19 (0.68, 2.09)
		P trend=0.5121		P trend=0.5191
Red meat intake, g/kcal/day				
Tertile 1	37	1.00	14	1.00
Tertile 2	39	0.82 (0.52, 1.30)	28	1.99 (1.04, 3.80)
Tertile 3	42	0.76 (0.48, 1.20)	29	1.95 (1.01, 3.78)

	US Born		Foreign Born	
	No. of cases	**HR* (95% CI)**	**No. of cases**	**HR* (95% CI)**
		P trend=0.2407		P trend=0.0622
Fruit intake, g/kcal/day				
Tertile 1	50	1.00	28	1.00
Tertile 2	40	0.93 (0.61, 1.42)	22	0.86 (0.49, 1.53)
Tertile 3	28	0.79 (0.48, 1.28)	21	0.88 (0.49, 1.60)
		P trend=0.3394		P trend=0.6610
Vegetables intake, g/kcal/day				
Tertile 1	49	1.00	31	1.00
Tertile 2	36	0.76 (0.49, 1.17)	23	0.79 (0.46, 1.36)
Tertile 3	33	0.75 (0.48, 1.19)	17	0.55 (0.30, 1.01)
		P trend=0.1987		P trend=0.0523
Hepatitis B and/or C**				
No	29	1.00	19	1.00
Yes	18	16.13 (8.73, 29.81)	12	19.93 (9.44, 42.07)

*Adjusted for age at cohort entry, education, BMI, alcohol intake, smoking status, diabetes, vigorous activity, and sex; dietary factors further adjusted for total calories.

**Based on a subset of MEC participants linked to FFS Medicare (see details in Supplemental Table 1).

Table 4

Association between risk factors and chronic liver disease mortality in Hispanics by nativity in the Multiethnic Cohort

	US Born		Foreign Born	
	No. of cases	**HR* (95% CI)**	**No. of cases**	**HR* (95% CI)**
Alcohol intake				
Non-drinkers	94	1.00	47	1.00
<2 drinks/day	51	0.66 (0.47, 0.94)	37	1.07 (0.68, 1.70)
≥ 2 drinks/day	49	2.23 (1.52, 3.29)	20	2.74 (1.53, 4.91)
		P trend=0.0079		P trend=0.0065
Smoking status				
Non-smokers	70	1.00	41	1.00
Former	71	0.93 (0.66, 1.31)	37	1.12 (0.70, 1.80)
Current	53	1.95 (1.33, 2.84)	26	2.26 (1.33, 3.82)
Diabetes status				
No	136	1.00	79	1.00
Yes	58	2.28 (1.65, 3.15)	25	2.09 (1.32, 3.33)
Body mass index (kg/m^2)				
<25	46	1.00	23	1.00
25-<30	68	0.81 (0.56, 1.19)	46	1.10 (0.66, 1.82)
≥30	80	1.57 (1.08, 2.28)	35	1.90 (1.11, 3.25)
		P trend=0.0086		P trend=0.0156
Vigorous physical activity				
0	94	1.00	41	1.00
≤20 min/day	34	0.74 (0.50, 1.11)	17	1.05 (0.59, 1.87)
>20 min/day	58	0.78 (0.55, 1.11)	35	1.04 (0.64, 1.69)
		P trend=0.1464		P trend=0.8769
Level of education				
High School or lower	135	1.00	90	1.00
Some college	48	0.80 (0.57, 1.12)	9	0.54 (0.27, 1.07)
Completed college or higher	11	0.44 (0.23, 0.81)	5	0.64 (0.26, 1.59)
		P trend=0.0064		P trend=0.0882
% calories from saturated fat				
Tertile 1	63	1.00	38	1.00
Tertile 2	59	0.90 (0.63, 1.29)	26	0.68 (0.41, 1.12)
Tertile 3	72	1.04 (0.73, 1.49)	40	1.06 (0.67, 1.68)
		P trend=0.7984		P trend=0.7749
Red meat intake, g/kcal/day				
Tertile 1	60	1.00	33	1.00
Tertile 2	61	0.83(0.58, 1.19)	30	0.83 (0.50, 1.37)
Tertile	73	0.89 (0.62, 1.27)	41	1.03 (0.63, 1.66)

	US Born		Foreign Born	
	No. of cases	**HR* (95% CI)**	**No. of cases**	**HR* (95% CI)**
		P trend=0.5711		P trend=0.8410
Fruit intake, g/kcal/day				
Tertile 1	77	1.00	42	1.00
Tertile 2	62	1.02 (0.73, 1.44)	38	1.06 (0.68, 1.66)
Tertile 3	55	1.11 (0.76, 1.61)	24	0.74 (0.44, 1.25)
		P trend=0.6026		P trend=0.3004
Vegetables intake, g/kcal/day				
Tertile 1	85	1.00	33	1.00
Tertile 2	66	0.85 (0.61, 1.17)	38	1.23 (0.77, 1.97)
Tertile 3	43	0.59 (0.40, 0.86)	33	1.07 (0.65,1.76)
		P trend=0.0063		P trend=0.7861
Hepatitis B and/or C**				
No	50	1.00	28	1.00
Yes	21	11.25 (6.63, 19.07)	13	17.29 (8.82, 33.88)

*Adjusted for age at cohort entry, education, BMI, alcohol intake, smoking status, diabetes, vigorous activity and sex; dietary factors further adjusted for total calories.

**Based on a subset of MEC participants linked to FFS Medicare.

Table 5

Hazard rate ratios (HRs) for hepatocellular carcinoma incidence and chronic liver disease mortality comparing US born to foreign born Hispanics in the Multiethnic Cohort

	All Participants (N=36,864)		Medicare Fee-for-Service Participants (N=17,205)	
	No. of cases*		No. of cases*	
HCC incidence	118/71		47/31	
HR (95% CI)[a]		1.61 (1.20, 2.17)		1.84 (1.17, 2.91)
HR (95% CI)[b]		1.45 (1.08, 1.96)		1.67 (1.05, 2.64)
HR (95% CI)[c]		--		1.58 (1.00, 2.51)
CLD death	194/104		71/41	
HR (95% CI)[a]		1.90 (1.49, 2.41)		2.13 (1.45, 3.14)
HR (95% CI)[b]		1.69 (1.33, 2.15)		1.91 (1.29, 2.83)
HR (95% CI)[c]		--		1.85 (1.25, 2.73)

[a] Adjusted for age at cohort entry and sex.

[b] Further adjusted for BMI, smoking status, alcohol intake, and diabetes.

[c] Further adjusted for hepatitis B/C infection.

* US Born/Foreign Born