

Liver cancer: A leading cause of cancer death in the United States and the role of the 1945–1965 birth cohort by ethnicity

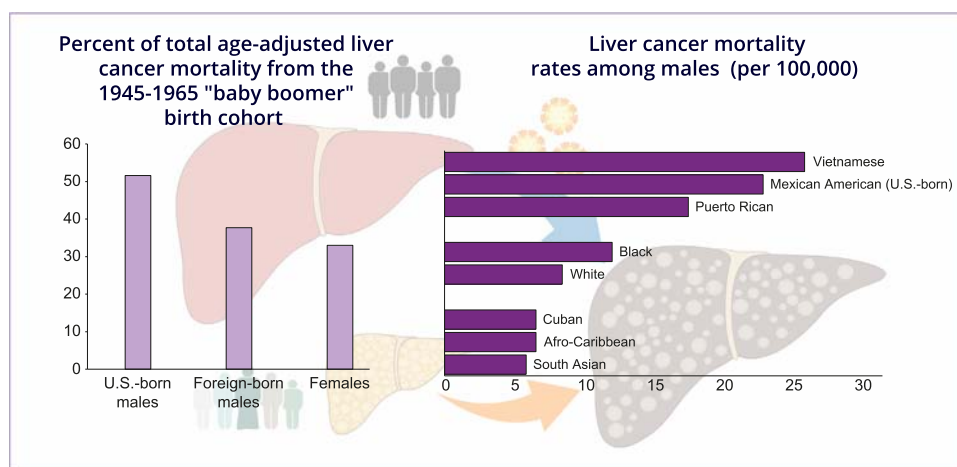
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Graphical abstract



Highlights

- Liver cancer is now the leading cause of cancer death among Mexican American males.
- Rates vary intra- racially: *e.g.* Vietnamese have high rates; South Asians have low.
- US-born male "baby boomers" of any race/ethnicity have the highest liver cancer mortality.
- Foreign-born men and all women have higher mortality at older ages, 70 or more.
- In the "baby boomer" cohort, US Whites have higher liver cancer mortality than Europeans.

Lay summary

Liver cancer, a major cause of cancer death among US males, is increasing. The causes of liver cancer are varied, including hepatitis C, hepatitis B, alcohol-related liver disease, and non-alcoholic fatty liver disease. Racial/ethnic groups are impacted differently, but the highest rates are seen among US-born men born between 1945–1965, the so-called "baby boomers", whether White, Black, or Hispanic, likely linked to the known high prevalence of hepatitis C infection among this cohort.



Liver cancer: A leading cause of cancer death in the United States and the role of the 1945–1965 birth cohort by ethnicity

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Background & Aims: Liver cancer is highly fatal and the most rapidly increasing cancer in the US, where chronic hepatitis C (HCV) infection is the leading etiology. HCV is particularly prevalent among the 1945–1965 birth cohort, the so-called “baby boomers”. Focusing on this cohort-etiology link, we aim to characterize liver cancer patterns for 15 unique US populations: White, African American, Mexican Immigrant, Mexican American, Cuban and Chinese, among others.

Methods: Individual-level mortality data from 2012–2016 from the health departments of 3 large states – California, Florida, New York – were pooled to compute liver cancer mortality rates for each racial/ethnic group and for 2 birth cohorts of interest: “1945–1965 cohort” and “older cohort”.

Results: Liver cancer is a major cause of cancer death among all US male groups and the leading cause in Mexican American men. Over 50% of the age-adjusted liver cancer mortality of White, African American, Mexican American, and Puerto Rican males came from the 1945–1965 birth cohort. In contrast, foreign-born male and all female populations had higher liver cancer mortality originating from the older cohort. Internationally, US White male baby boomers had a 49% higher liver cancer mortality rate than their counterparts in Europe (mortality rate ratio 1.49; 95% CI 1.43–1.56).

Conclusions: Populations burdened disproportionately by liver cancer in the 1945–1965 cohort include US-born males who were all present in the US during the 1960s–1990s when significant HCV transmission took place; these individuals will benefit most from HCV screening and treatment. For the others, including all women, Asian subgroups, and especially burgeoning Hispanic immigrant populations, comprehensive liver cancer prevention efforts will require detailed study of the distribution of etiologies.

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Introduction

Liver cancer (LC) is the fastest growing cancer in the US, with increasing incidence and mortality and dismal survival.^{1,2} Major causes include chronic hepatitis C (HCV) infection, hepatitis B (HBV), alcohol-related liver disease (ALD), and metabolic conditions including non-alcoholic fatty liver disease (NAFLD), as well as obesity and type 2 diabetes. These diseases have profiles that vary by racial/ethnic group, sex, and birthplace, which contribute to the unique epidemiological patterns of LC observed across diverse populations.^{3–6}

In the US, increases in incidence and mortality from LC and its main type, hepatocellular carcinoma (HCC), have largely been driven by chronic HCV infection,⁷ which, while affecting all age

groups to some extent, primarily impacts the birth cohort of 1945–1965.⁸ Due to the particularly high HCV prevalence, up to 5-fold greater than average, in this cohort of so-called “baby boomers” in the US, the Centers for Disease Control and Prevention recommends one-time HCV screening for this group.⁸

Previously, using mortality data from New York State, we reported how LC rates are being impacted among baby boomers⁹ in what is becoming evident as a typical cohort effect.¹⁰ Puerto Rican and African American (US-born) males in this cohort had very high age-specific rates (ages 50–69) compared to all other analyzed population groups, including non-Hispanic whites and Asians. Remarkably, these baby boomer groups had higher rates than their own older age counterparts (ages 70–74), presenting a counterintuitive “hump and dip” pattern rather than the incremental increases in LC mortality typically seen with increasing age.⁹ These significant differences in LC risk likely associated with HCV, however, would have been missed had the usual broad categories of “Hispanic” and “Black” been used.

Nonetheless, on a national scale, this heterogeneity in LC patterns among these and other detailed racial/ethnic groups (e.g. Mexican American, Puerto Rican, Afro-Caribbean, Chinese, etc.) has been largely overlooked, despite evidence suggesting

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that the prevalence of precursor conditions for LC, including HCV, differs widely by population group.^{2,11} Unfortunately, LC incidence data in cancer registries is not detailed enough on racial/ethnic subgroups, and birthplace is incomplete in nearly 50% of cases, preventing accurate analyses of patterns for disaggregated race/ethnicity groups.¹² In contrast, mortality data provide comprehensive and complete information on race/ethnicity and birthplace. Given the uniformly high fatality of LC, with average observed 5-year survival rates of less than 15%,¹³ it is defensible to infer that LC mortality broadly reflects LC incidence patterns. In this study, we aim to assess current patterns in LC as a primary cause of death among detailed races/ethnicities in the US, correcting the oversimplification arising from studying Black, Asian and Hispanic populations in single aggregated groups, using the most recently available mortality data from 3 large and diverse US states: California, Florida and New York. Our baseline rationale is that the LC burden of the 1945-1965 cohort is the best proxy, on a population basis, for HCV-related LC, while for older cohorts (born before 1945), the relative weight of LCs will be more evenly distributed between HCV, ALD, NAFLD, etc. Thus, we will shed light into unique population patterns, particularly in relation to HCV, providing critical information needed to prepare for and, wherever possible, stem the increasing LC burden in the US.

Materials and methods

Data sources

Individual-level cancer mortality data from death certificates for California and Florida (2012-2016) and New York (2012-2014) were obtained from the Department of Public Health in California and the Departments of Health in Florida and New York. Cases with LC as the primary cause of death, ICD-10 code C.22 (includes C22.0 liver; C22.1 intra-hepatic bile duct; and C22.9 liver-not-otherwise-specified), were selected. Choice of states was driven by availability and by their detailed race/ethnicity profiles; mortality data with the birthplace detail required are not procurable in national death data sources,¹² but only through direct data requests on a state-by-state basis. Pooled (3 states) LC data were highly complete for race/ethnicity (99.5%) and birthplace (98.7%); Hispanic subgroup was ascertainable for 95.2% of Hispanics.

Detailed population denominators for each analyzed race/ethnicity for each state corresponding to the death data were obtained from the US Census Bureau, using 2012 to 2016 single-year American Community Survey data, the standard source for US demographic data for intercensal years.¹⁴

Classification of race/ethnicity

Four mutually exclusive major race/ethnicity groups were analyzed: non-Hispanic white (hereafter; White); non-Hispanic black (Black); Asian, including Pacific Islander (Asian); and Hispanic. Additionally, we disaggregated to obtain 15 distinct groups, each with a minimum population over 400,000 for the 3 states.¹⁴

Within the Black group, 2 distinct populations were analyzed: African American, born in the US, and Afro-Caribbean, born in Jamaica, Haiti or the West Indies (country/territory list detailed elsewhere).¹⁵ Other foreign-born (e.g., Africa) Black decedents were included in the aggregate Black category but not analyzed separately due to their relatively small size. Six unique Asian groups were identified from race codes in the mortality data: Chinese, Vietnamese, Japanese, Filipino, Korean, and South Asian (India, Nepal, Pakistan, Bangladesh, Sri Lanka). For Hispanics, all

race and ethnicity codes, including text fields and birthplace, were examined to obtain 5 unique Hispanic groups: Mexican, Puerto Rican, Cuban, Dominican, and South/Central American. For Mexicans, with previously documented distinct mortality rates by nativity,^{16,17} we formed 2 groups for analysis: Mexican American (born in the US) and Mexican Immigrant (born abroad, regardless of citizenship). LC deaths among Native American/Alaskan Natives as well as individuals with unknown race-ethnicity or more than 2 races reported were excluded from analyses.

Data analyses

After careful data assembly, approximately 4.8% of all Hispanic decedents (US-born, mostly Californian) remained of unknown Hispanic subgroup. For mortality rate calculations, these were proportionally assigned to specific groups based on age and sex, using methodology described elsewhere.¹⁸

For each race/ethnicity group, LC age-specific mortality rates (ASMRs) and age-adjusted mortality rates (AAMRs) stratified by sex were calculated per 100,000 persons, annualized and age-standardized to the 2000 US Standard Population using 18 age group bands, each of 5-year increments except for the last group which was 85 and older. Gamma intervals modification was used to calculate all 95% CIs, presented in Tables S2 and S3.

To examine age- and cohort-specific LC mortality patterns within the US, data were pooled across the 3 states. Sex-stratified AAMRs for each race/ethnicity group were computed for all ages as well as for 2 distinct birth cohorts: baby boomers, or decedents born between 1945-1965, and decedents who were born before 1945, here called the older cohort.

For each race/ethnicity group, cause of cancer death rank was calculated by computing and ranking the proportion of total cancer-specific deaths (e.g. liver, lung, breast) out of all cancer deaths.

To assess inferentially the extent to which HCV may be differentially impacting the overall LC burden for each race/ethnicity group, we partitioned the total AAMR into 3 cohorts according to birth year: younger (born after 1966); baby boomer (born 1945-1965); and older (born before 1944). Because each of the 3 birth cohorts spans several 5-year age groups, and to avoid within-cohort confounding by age, we computed independent AAMRs for each cohort. While most 5-year age groups fell into 1 distinct birth cohort (making AAMR calculation straightforward: sum of age-specific rates multiplied by their corresponding US population standard weights), for some age groups (specifically: 45-49, 50-54, 65-69, 70-74), 2 birth cohorts overlapped. For these overlapping age groups only, the US standard population relative weights were partitioned proportionally into the 2 cohorts using the corresponding observed proportion of underlying population by race/ethnicity and age group. Partitioned weights from overlapping age groups and standard weights from non-overlapping age groups were used to compute final AAMRs for each birth cohort. Importantly, for each race/ethnicity, the sum of the 3 AAMRs, younger (not shown; available by subtraction), baby boomer, and older, equates exactly to the total AAMR, which enabled us to divide the baby boomer AAMR by the overall AAMR and use these proportions to compare the relative weight of age-adjusted LC mortality among baby boomers for each race/ethnicity group.

Lastly, previous studies have shown that LC mortality disparities among baby boomers are most pronounced in minority groups;⁹ the excess is normally assessed in comparison to

Whites, the largest race/ethnicity in the US. However, excess LC mortality among US White baby boomers themselves is likely. To assess this, we compared LC ASMRs of US Whites with overwhelmingly Caucasian countries in Europe, including all 17 countries defined as Northern and Western Europe by the United Nations¹⁹, based on available cancer mortality and population data from the World Health Organization mortality database (2012–2015).²⁰ Unlike US data, LC mortality counts from the World Health Organization mortality database are presented only in aggregate 5-year age groups; thus, decedents between the ages of 45–49 overlap between the 1945–1965 cohort and those born earlier; likewise, decedents ages 65–69 overlap between the 1945–1965 cohort and the older cohort. Therefore, age groups were combined to approximate the baby boomer and older cohort, 50–64 and 70+ respectively. Negative binomial regression was used to obtain LC age-adjusted mortality rate ratios (MRR) between Northern and Western Europe (used as reference) and Whites in the US.

SAS 9.3 and SPSS 25 were used for data analyses. Ethical review was undertaken by the Institutional Review Boards of the University of Miami School of Medicine, New York Department of Health and the California Health and Human Services Agency.

Results

A total of 29,470 LC deaths from the 3 states were analyzed (Table 1). For every race/ethnicity group in each state, LC mortality among males was consistently higher than their female counterparts, over 3 times higher for Mexican American and Puerto Rican males (Table 2). All minority groups analyzed had higher LC AAMRs than Whites, except Japanese and Cuban males, and South Asian and Afro-Caribbean males and females. Comparing states, LC AAMRs for Hispanic, Asian and Black males and for Hispanic females were lowest in Florida, while for Whites, the lowest AAMR was in New York. However, by disaggregated race/ethnicity group, patterns across states were not markedly different (Table 2 and Table S2). When rates were pooled across the 3 states, 3 racial/ethnic groups emerged with the highest overall LC mortality among both men and women: Mexican Americans (23.0 and 7.3 per 100,000 among men and women, respectively), Koreans (20.9 and 8.4), and Vietnamese (26.0 and 8.2) (Table 2 and Table S3).

The relative importance of LC as a cause of cancer death is shown by the ranks. LC is currently the first cause of cancer death for Mexican American men and second for Puerto Rican, Vietnamese, Korean and Chinese men as well as Asian men in aggregate. Among women, LC is a less prominent cause of cancer death, positioned between fourth among Vietnamese women and twelfth among Afro-Caribbean women (Table 2).

Patterns varied when examining cohort-specific AAMRs. Mexican American men had high LC AAMRs in both the 1945–1965 cohort as well as the older cohort, 11.9 and 10.4 per 100,000, respectively, while Korean and Vietnamese men showed the highest overall AAMRs. White, African American, Mexican American and Puerto Rican men had higher LC AAMRs in the 1945–1965 cohort than in the older cohort. In direct contrast, all other male groups (Cubans, South Americans, Mexican Immigrants, Chinese, etc.), each majority foreign-born, had higher AAMRs in the older cohort. Among women, AAMRs were higher in the older cohort for all race/ethnicities (Table 2 and Table S3).

Table 1. Liver cancer deaths and population, pooled from California (2012–2016), Florida (2012–2016), and New York (2012–2014).

	Decedents		Annualized population denominators ^b
	Number	Born in US ^a	
All-populations-combined ^c	29,479	65%	78,345,481
White	15,612	89%	36,934,576
Black ^d	2,870	81%	8,741,874
African American	2,312	100%	7,055,257
Afro-Caribbean	314	0%	1,215,360
Hispanic ^e	6,887	45%	23,557,515
Mexican	4,141	54%	13,961,287
Mexican American	2,228	100%	8,936,430
Mexican Immigrant	1,913	0%	5,024,857
Puerto Rican	927	100%	2,374,111
Cuban	563	4%	1,602,625
South/Central American	1,025	3%	4,251,481
Dominican	165	3%	1,092,798
Asian ^f	3,766	6%	8,584,583
Chinese	1,159	4%	2,299,776
Filipino	636	7%	1,641,903
South Asian	181	2%	1,522,727
Vietnamese	599	0%	805,566
Korean	420	2%	680,540
Japanese	191	44%	446,190

^aIncludes Puerto Rico; ^bRef.14; ^cIncludes Multiracial and American Indians/Alaskan Natives; ^dIncludes Blacks born in other countries, e.g. Africa; ^eIncludes Spaniards; ^fIncludes all Asian/Pacific Islanders.

The proportion of the overall AAMR that came from the 1945–1965 birth cohort was highest in the same 4 US-born groups among not only men, but also women. African American men and women had the highest relative 1945–1965 cohort-associated LC AAMR, at 59% for men and 46% for women. Conversely, all populations that were majority foreign-born had relatively low contributions from the 1945–1965 cohort except for South Asian women. South Asian men (24%) and Japanese women (19%) had the lowest contributions from the 1945–1965 cohort (Table 2).

ASMRs (unlike AAMRs, these are not dependent on population weights for age adjustment) of LC by racial/ethnic group are shown in Fig. 1. As expected, for most groups age-specific rates increase with age. However, for African American and Puerto Rican men, rates dip or level off uncharacteristically to a relatively lower rate among the older cohort. For other males, including Mexican Immigrant, South/Central American and Asian, rates increase with age. For females, the age-specific rates increase with age for all racial/ethnic groups except for African Americans (Fig. 1).

Lastly, compared with Northern and Western Europeans (n = 96,001), US Whites (n = 15,612) showed different age-specific patterns by the approximated birth cohorts. Among ages 50–64, US men had a 49% higher LC mortality risk than Northern and Western European men (MRR 1.49; 95% CI 1.43–1.56), while the MRR for women was 1.29 (95% CI 1.21–1.37). Conversely, US White males and females aged 70+ had a significantly lower LC mortality than their European counterparts (MRR 0.68; 95% CI 0.66–0.70 and MRR 0.82; 95% CI 0.79–0.85, respectively) (Fig. 2).

Table 2. Liver cancer age-adjusted^a mortality rates per 100,000 by detailed race/ethnicity in California, Florida, New York (2012-2016).

	AAMR ^b by State			Pooled 3 States			Cause of cancer death rank	
	California	Florida	New York	Total AAMR ^b	1945-1965 birth cohort AAMR ^b	Older ^c cohort AAMR ^b		1945-1965 birth cohort AAMR/Total AAMR ^b
Male								
All-populations-combined ^d	11.3	9.1	9.2	10.6	5.0	5.2	47%	5
White	8.6	9.0	7.5	8.5	4.2	4.0	50%	5
Black ^e	13.8	10.3	12.5	12.1	6.7	4.8	55%	4
African American	14.0	11.7	13.0	12.9	7.7	4.9	59%	4
Afro-Caribbean		6.8	7.0	6.6	2.3	3.4	35%	6
Hispanic ^f	14.9	9.1	13.0	13.0	5.9	6.7	46%	4
Mexican	15.6	13.5	10.2	15.4	7.0	8.0	46%	2
Mexican American	23.1	24.2		23.0	11.9	10.4	52%	1
Mexican Immigrant	11.0			10.9	4.3	6.3	39%	4
Puerto Rican		16.2	20.6	17.6	9.6	7.6	54%	2
Cuban		6.4		6.6	2.9	3.5	44%	5
South/Central American	13.5	9.1	9.2	10.9	3.6	7.0	33%	4
Dominican			8.5	7.9	3.3	4.5	42%	4
Asian ^g	14.9	8.9	14.0	14.3	5.5	7.8	38%	2
Chinese	15.2		17.3	15.3	5.4	8.4	35%	2
Filipino	12.1			11.9	4.5	6.6	38%	3
South Asian	5.7			5.9	1.4	4.2	24%	4
Vietnamese	25.7			26.0	11.3	13.4	44%	2
Korean	22.5			20.9	7.4	12.3	35%	2
Japanese	6.5			6.6	2.4	4.2	36%	6
Female								
All-populations-combined ^d	4.8	3.6	3.6	4.5	1.5	2.8	33%	8
White	3.7	3.4	3.0	3.4	1.3	2.0	37%	10
Black ^e	5.5	4.2	4.0	4.6	1.9	2.4	42%	8
African American	5.6	4.7	3.7	4.8	2.2	2.4	46%	8
Afro-Caribbean		3.2	3.3	3.1	0.8	2.3	25%	12
Hispanic ^f	6.8	4.1	5.9	5.9	1.9	3.8	32%	6
Mexican	7.1	5.9	4.4	7.0	2.3	4.5	32%	5
Mexican American	7.4	5.2		7.3	2.7	4.3	37%	5
Mexican Immigrant	7.0			6.9	2.0	4.8	29%	5
Puerto Rican		4.8	6.3	5.6	2.1	3.3	38%	5
Cuban		3.6		3.6	0.9	2.5	26%	8
South/Central American	6.3	4.9	5.7	5.7	1.6	3.9	29%	7
Dominican			5.8	5.0	1.1	3.8	21%	6
Asian ^g	5.9	4.2	5.0	5.7	1.5	4.0	25%	5
Chinese	5.4		6.1	5.4	1.2	4.0	21%	5
Filipino	5.4			5.2	1.3	3.7	24%	6
South Asian	2.8			3.2	1.6	1.5	50%	6
Vietnamese	8.7			8.2	1.6	6.3	20%	4
Korean	8.6			8.4	2.2	5.7	26%	6
Japanese	4.9			5.2	1.0	4.0	19%	6

Data presented are pooled total and birth cohort AAMRs; weight of 1945–1965 birth cohort on total AAMR; cause of cancer death rank.
^aAge-adjusted to the 2000 US Standard; ^b95% CIs in Table S2 and S3; ^cBorn before 1945; ^dIncludes Multiracial and American Indians/Alaskan Natives; ^eIncludes non-Hispanic blacks born in other countries, e.g. Africa; ^fIncludes Spaniards; ^gIncludes all Asian and Pacific Islanders.
AAMR, age-adjusted mortality rates.

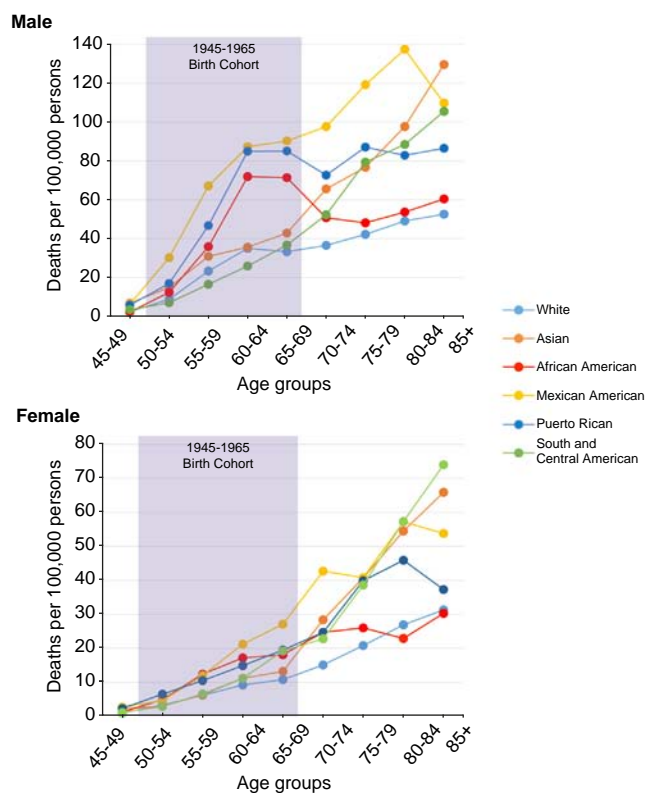


Fig. 1. Age-specific, sex-stratified LC mortality rates by selected racial/ethnic groups, California, Florida, and New York, 2012–2016. Lavander region highlights the 1945–1965 birth cohort. LC, liver cancer.

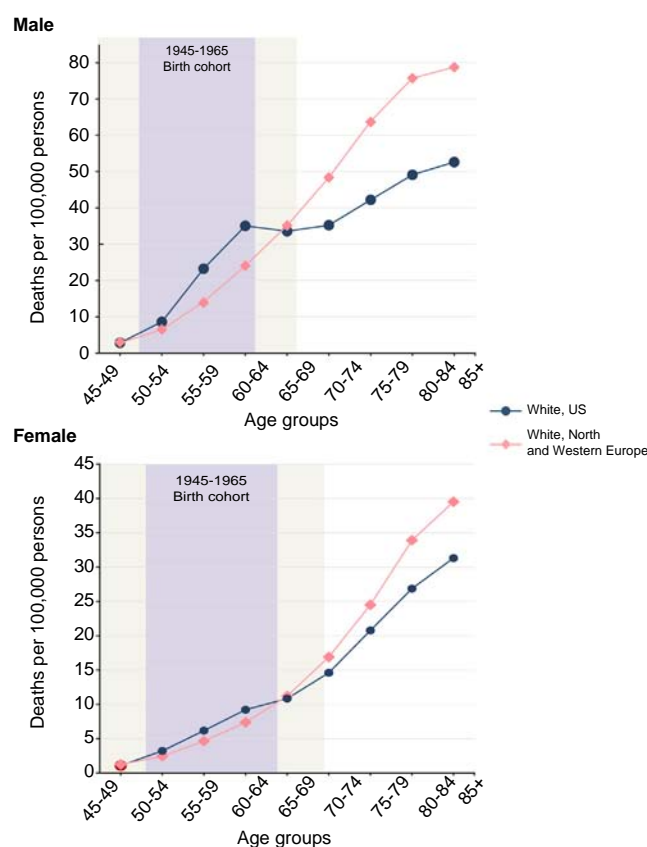


Fig. 2. Age-specific, sex-stratified LC mortality rates, US Whites and Northern & Western Europeans. US Whites, includes California, Florida, and New York, 2012–2016; Northern & Western Europeans, 2012–2015. Lavander region highlights the 1945–1965 birth cohort. Tan regions highlight areas where the 1945–1965 birth cohort overlaps with younger or older cohorts. MRR calculated for US Whites, with Europe as reference. 1945–1965 cohort: Male MRR 1.49 (95% CI 1.43–1.56); Female MRR 1.29 (95% CI 1.21–1.37); Older Cohort: Male MRR 0.68 (95% CI 0.66–0.70); Female MRR 0.82 (95% CI 0.79–0.85). LC, liver cancer; MRR, mortality rate ratios.

Discussion

Liver cancer, the fastest growing cancer in the US, increased 43% between 2000 and 2016.^{1,21} As our study shows, LC is now the leading cause of cancer death among Mexican American men and the second among Puerto Rican men living in the continental US; for White men, it is fifth.

Chronic infection with HCV has been the primary driver of the increasing trends in LC over these past 2 decades and is now the number one risk factor for HCC in the US.^{2,7} While the absolute impact of HCV on LC has never been directly calculated (via the calculation of etiology specific HCV-LC rates) on a population basis, its relative impact has been demonstrated by several studies.^{22,23} Notably, these studies present results only by major race/ethnicity groups, such as Black, Hispanic, and Asian, thus missing important details visible only when groups are disaggregated.

The current study addresses this gap in knowledge and examines the specific effect of the 1945–1965 birth cohort, previously shown to have high levels of HCV infection.⁸ In contrast to the baby boomers, LC among the older cohort likely reflects higher proportions of ALD-associated and metabolic disease-associated LC, including NAFLD rather than HCV-associated LC.^{11,24} In this context, we found complex mortality patterns by sex, birth cohort and specific race/ethnicity group, with important implications for cancer control and prevention.

First, by sex, we found that LC is a leading cause of cancer death among men of all racial/ethnic groups. However, while Asian male

rates reflect overwhelmingly foreign-born populations, the Hispanic male groups most afflicted by LC are US-born, a sharp contrast that suggests salient differences in LC etiology between these groups. LC is also an important cause of death among female groups, although their mortality rates are consistently lower than males, as shown in previous research.^{1,2,11} Ranks for cause of cancer death among women are also lower but follow similar patterns as their male counterparts. Additionally, when all populations are assessed in combination, the proportion of overall AAMR that originates from the 1945–1965 birth cohort is much higher among men (47%) than women (33%), setting the tone for significantly distinct patterns by sex. Collectively, these findings likely reflect the previously documented lower prevalence of chronic HCV infection among women than men.²⁵

Analyzing birth cohort patterns added a second level of complexity. For both males and females, LC that occurs in the 1945–1965 birth cohort has a larger weight in the overall LC mortality of Whites, African Americans, Mexican Americans and Puerto Ricans, as evidenced by their proportions of AAMRs from the 1945–1965 birth cohort being universally higher than the all-populations-combined proportions. The single commonality between these 4 large groups is their presence in the US when

significant HCV transmission occurred in the 1970s–1990s primarily through needle-sharing among intravenous drug users, but also via less common transmission routes, including blood transfusions before routine HCV screening was implemented in July 1992,²⁶ or through nosocomial infection even earlier (1940–1960).²⁷ Accordingly, in all other race/ethnicity groups whose decedents are overwhelmingly foreign-born, e.g. Asians in general, Mexican Immigrants, South/Central Americans, *etc.*, proportions are lower than the all-populations-combined, indicating a higher AAMR weight among the older cohort and lower among the 1945–1965 birth cohort.

Lastly, we see substantial variation in LC mortality patterns by detailed race/ethnicity. Within Hispanics, both Mexican American and Puerto Rican baby boomer males have exceedingly high LC mortality, not entirely surprising given their known high prevalence of chronic HCV infection.²⁸ In the Hispanic Community Health Study,²⁸ HCV prevalence among Puerto Ricans and US-born Latinos (largely Mexican American) was higher than HCV prevalence among Blacks and Whites in the US.²⁹ Conversely, but consistent with their lower HCV prevalence,²⁸ South/Central American, Cuban and Dominican males primarily foreign-born, have relatively lower LC mortality rates in the 1945–1965 cohort.

Thus, while historically the high LC burden among Hispanics in aggregate has been correlated with the burden of infectious disease-related cancers among immigrants,³⁰ the granular data presented here point in a different direction. In the older cohort, all Hispanic groups except Cubans had uniformly high rates, more likely driven by non-infectious causes, consistent with the relatively low prevalence of HCV and HBV infection in Central and South America.^{31,32} Thus, NAFLD, for which Hispanics are more susceptible,^{33–35} and ALD may be more important etiological factors for LC than previously thought among Hispanics, given the higher prevalence of metabolic disorders, including diabetes, and heavy drinking in some Hispanic groups.³⁶ These non-infectious LC causes merit closer scrutiny among detailed Hispanic populations, as they will continue to drive the LC burden even after the HCV-cohort effect eases up, as predicted.³⁷

Vietnamese and Korean male and female populations have the highest overall LC mortality rates, despite recent research documenting a decreasing trend in LC mortality for Asians in aggregate.^{2,37} Our results further confirm previous findings of LC as the second leading cause of cancer death for Vietnamese men;³⁸ for the first time, we show this for Korean and Chinese men as well. Interestingly, Vietnamese and Korean AAMRs in the 1945–1965 birth cohort are similarly high as the US-born populations. Yet, their lower AAMR proportion originating from that cohort suggest a predominantly non-HCV cause of LC. Previous research has documented a high prevalence of HBV infection driving LC rates among Asian and Pacific Islander populations in the US,^{2,32} resulting in the highest LC rates in the past decades.³⁸ However, there is likely significant heterogeneity of HBV and HCV prevalence which has not been studied thus far.

Among Whites, rates are relatively low, especially compared to the other US-born populations: African American, Mexican American and Puerto Rican. However, the effect of the 1945–1965 birth cohort is quantitatively evident not only by the high LC AAMR proportion originating from that cohort, but also by comparison with Northern and Western Europe where medically reviewed cases in France, Germany and the UK show a higher proportion of LCs to be alcohol-related and/or due to metabolic causes.^{39–42} Moreover, published HCV prevalence data show higher HCV prevalence in the White population in

the US⁴³ (even excluding many populations with high prevalence including homeless, incarcerated, and nursing homes⁴⁴) than in countries in Northern and Western Europe.⁴⁵ Combined, these data suggest HCV-associated LC excess as an important factor driving LC mortality among US Whites, similar to US-born minorities. From a public health and health care systems standpoint, this HCV-related excess among Whites is crucial since in absolute numbers, due to their demographic weight in older US populations, Whites remain the main source of LC cases in the US.^{5,9,16}

One limitation of this study is that rather than incidence data, which would directly assess the LC burden, we analyze mortality. Due to a lack of medical record information, disparities in stage at diagnosis as well as in access to health care and curative therapies, which could potentially account for some of the observed differences in mortality by race/ethnicity, could not be analyzed. Also, we were unable to accurately separate intrahepatic cholangiocarcinoma (ICC) and HCC due to the large proportion (39%) of deaths coded “*liver-cancer-not-specified*”; these can represent either HCC or ICC.¹² Nonetheless, national incidence data show ICC only accounting for about 1 in 10 LC cases while HCC accounts for 78%, suggesting that variation in LC mortality rates is primarily driven by variation in HCC.²¹ Moreover, while distinct diseases, HCC and ICC share similarly low survival²¹ as well as some overlapping causes, including HCV.^{11,24,46} While cause of death coding on death certificates has been assessed as useful for population-based mortality studies, inevitably some LC deaths may correspond to metastasized rather than primary liver cancers.⁴⁷ However, this portion is unlikely to differ by race/ethnicity and is likely small due to poor LC survival and the proximity between LC incidence and mortality. Finally, specific etiology from the LC mortality data was not available for analyses; undoubtedly, other causes including ALD and NAFLD account for some LC deaths among the 1945–1965 cohort.

As strengths of this study, we used 3 large states whose combined population comprises almost one-quarter of all Americans and whose pooled demographic composition uniquely enabled analysis of every major racial/ethnic minority group in the US, except Pacific Islander, Hawaiian and Native American/Alaskan Native. Also, the death certificate data were highly complete for race/ethnicity and birthplace, previously assessed for quality and deemed highly accurate,⁴⁸ which enabled our detailed race/ethnicity classification.

In conclusion, the analyzed data showed that LC among baby boomers is very prominent in US-born male populations, suggesting a high impact of HCV, corroborated by documented higher HCV prevalence in these populations. However, the LC burden among Asian subgroups, foreign-born Hispanics, and, to some extent, among women of all races/ethnicities, is likely much more balanced between different LC etiologies. The contrast found here between Mexican Americans and Mexican Immigrants in the 1945–1965 cohort supports the likely nexus of HCV with this birth cohort. Importantly, the current study reveals for the first time that LC is now the leading cause of cancer death in Mexican American males, who account for over 11 million Americans.¹⁴

Understanding etiological differences by detailed race-ethnicity (NAFLD among Hispanics, HCV among US-born male baby boomers, *etc.*) may reveal opportunities for better assessment, prevention, and treatment strategies. Moreover, it may provide critical information both to healthcare providers and researchers, such as transplant needs in specific subpopulations, or analysis of the

potential of direct-acting antivirals introduced in 2014 to reduce LC in the general population.⁴⁹ For HCV, the main focus of this study, uptake of the recommended HCV screening of asymptomatic baby boomers, currently only at 10%,⁵⁰ could be increased through wider information dissemination among all medical practitioners, including updates on the scope and seriousness of the LC problem. Correspondingly, funding for treatment of HCV infected

people, many of them minorities, should be secured irrespective of insurance status. The current study provides direct evidence that race/ethnicity itself should raise the index of suspicion among clinicians for heightened risk and the possibility of underlying liver disease. Over 30,000 LC deaths are estimated for 2019 in the US; our current state of knowledge about the variation in LC etiology leaves us underprepared to meet this challenge.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Pinheiro was involved in all aspects, including study supervision; conception and design of the study; generation, collection, assembly, analysis and interpretation of data; drafting and revision of the manuscript; and approval of the final version of the manuscript. Callahan was involved in study concept and design; analysis and interpretation of data; drafting of the manuscript; administrative, technical, and material support; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Jones was involved in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Morris was involved in acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Ransdell was involved in administrative, technical, and material support; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Kwon was involved in statistical analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Brown was involved in analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Kobetz was involved in study supervision; analysis and interpretation of data; critical revision of the manuscript for important intellectual content, approval of the final version of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jhepr.2019.05.008>.

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