Research Article

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Birth cohort-specific disparities in hepatocellular carcinoma stage at diagnosis, treatment, and long-term survival

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Background & Aims: Individuals born between 1945 and 1965 account for nearly 75% of hepatitis C virus (HCV) infections in the United States. As this cohort ages, progressive HCV-related liver disease leading to cirrhosis and hepatocellular carcinoma (HCC) will place a significant burden on the healthcare system. We aim to evaluate birth cohort-specific disparities in HCC stage at diagnosis, treatment rates, and overall survival with a focus on the 1945–1965 birth cohort.

Methods: A population-based retrospective cohort study of adult patients with HCC identified in the Surveillance, Epidemiology, and End Results 2003–2011 registry evaluated birth cohort-specific disparities in the prevalence and outcomes of HCC, including multivariate logistic regression models to evaluate disparities in HCC stage at diagnosis and HCC treatment received. Birth cohort-specific survival was evaluated with Kaplan–Meier methods and multivariate Cox proportional hazard models.

Results: The proportion of HCC represented by the 1945–1965 cohort increased by 64% from 2003–2011, and accounted for 57.4% of all HCC in 2011. Compared to patients born after 1965, the 1945–1965 cohort were more likely to have HCC within Milan criteria (OR, 3.66; 95% CI, 3.13–4.28; p <0.001). However, among patients with HCC within Milan criteria, the 1945–1965 cohort had no difference in receipt of surgical treatment, but had higher overall long-term survival (HR, 0.82; 95% CI, 0.69–0.97; p <0.03).

Conclusions: The 1945–1965 birth cohort accounts for the majority of HCC in the United States. Despite earlier HCC stage at diagnosis, no difference in receipt of surgical treatment was observed, but higher overall survival was achieved.

Keywords: Liver cancer; SEER; Hepatitis C virus.

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Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; BB, baby boomers; SEER, Surveillance, Epidemiology, and End Results; TACE, transarterial chemoembolization.

Introduction

Hepatocellular carcinoma (HCC) has become the most rapidly rising cause of cancer-related deaths in the United States (U.S.) [1,2]. The rising incidence of HCC is largely attributed to complications of chronic hepatitis C virus (HCV) infection, the incidence of which increased dramatically in recent decades, disproportionately affecting Americans born between 1945 and 1965 [“baby boomers” (BB)], who represent 27% of the population, but account for nearly 75% of HCV infections in the U.S. [3,4]. The high prevalence of HCV in this birth cohort has been attributed largely to higher prevalence of high risk behaviors including injection drug use and/or transfusion of blood products before 1992 [4–6]. As this cohort ages, progressive HCV-related liver disease leading to cirrhosis and cirrhosis-related complications such as HCC will place a significant burden on the healthcare system.

HCV is the leading etiology of HCC in the U.S. [7–10]. Current clinical guidelines recommend a one-time HCV screening among individuals born between 1945 and 1965 given the significantly higher prevalence of chronic HCV in this birth cohort. It is estimated that 40–85% of HCV-infected persons are unaware of their infection [11–14]. Improved HCV screening should lead to earlier diagnosis and initiation of highly effective antiviral therapy, and likely lead to improved screening and surveillance for HCC [15,16]. However, it is unclear whether this improved emphasis on liver disease management among the 1945–1965 birth cohort has translated into improved HCC outcomes, specifically earlier tumor stage at diagnosis, more surgical treatment, and higher long-term survival. The current study used a large population-based cancer registry to evaluate birth cohort-specific disparities in stages of disease at diagnosis, receipt of treatment, and survival outcomes among adults with HCC in the U.S.

Cancer

Methods

Study design and patient population

All U.S. adults (age >20) with HCC were identified using the most recent version of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based cancer registry [17]. The SEER data includes data from 18 regions in the U.S. and represents approximately 28% of the U.S. population. Since the MELD exception policies for prioritizing HCC patients for liver transplant were implemented in 2002, we chose to focus on the 2003–2011 patient cohort to improve consistency of HCC evaluation and management.

Definitions

SEER identifies HCC by using the International Classification of Disease for Oncology, Third Edition [18]. Birth cohort-specific disparities in HCC epidemiology were evaluated by categorizing patients into BB (born 1945–1965) and non-baby boomers (non-BB) (born pre-1945 or post-1965). In addition, we utilized SEER's expanded race/ethnicity classifications to evaluate race/ethnicity-specific disparities: non-Hispanic whites, blacks, white Hispanics (Hispanics), and Asian/Pacific Islanders (Asians).

HCC staging definitions were based on SEER historic summary staging, which is unique to SEER and used primarily for describing the extent of disease and not necessarily for prognosis [18]. Localized stage describes tumors confined to one lobe of the liver. Distant stage tumors include metastatic disease, extension of cancer to nearby organs (pancreas, pleura, or stomach) or involvement of distant lymph nodes. Given that eligibility for surgical resection or liver transplantation rely on additional staging characteristics, we evaluated HCC based on whether a patient's tumor met Milan criteria (single lesion less than 5 cm or no more than 3 lesions each less than 3 cm). We additionally evaluated HCC based on patients who had solitary lesions less than 5 cm.

HCC treatment categories were based on SEER site-specific surgery definitions and included the following categories: no therapy, locoregional therapy, surgical resection, liver transplant [17]. From prior communications with SEER registrar, inclusion of data on transarterial chemoembolization (TACE) is relatively new in the SEER registry, and the data quality is hindered by inconsistency of reporting. A preliminary analysis of the 1998–2010 HCC cohort indicated that 95.8% of HCC patients were categorized as not receiving any form of TACE or unknown TACE treatment status. Due to concerns of data inconsistency, TACE was not included in the current study. We additionally focused on receipt of surgical treatment, which we defined as surgical resection or liver transplantation.

Statistical analysis

Clinical and demographic characteristics were compared across birth cohorts and presented as proportion (%) and frequency (N) for categorical variables, or mean and standard deviation for continuous variables. The X^2 test was used to compare categorical variables, and the Student's *t* test was used to compare continuous variables. Birth cohort-specific disparities in stage of HCC at presentation and treatment outcomes were evaluated using multivariate logistic regression models. Long-term survival was analyzed with Kaplan–Meier methods and multivariate Cox proportional hazards models. Forward stepwise regression methods were utilized to develop multivariate models, and variables that were clinically important (e.g. age, sex) or those that demonstrated significant associations (p <0.10) in the univariate models were included in the final analyses. Statistical significance was met with a 2-tailed p value <0.05. All statistical analyses were performed with Stata (version 10; Stata Corporation, College Station, TX). Review by the institutional review board was not required for this study because human subjects were not involved, as per U.S. Department of Health and Human Services guidelines and the SEER database is publicly available without individually identifiable private information.

Results

Overview

A total of 50,723 HCC patients were identified between 2003 and 2011, including 26,749 patients in the non-BB cohort (25,659 born pre-1945 and 1090 born post-1965) and 23,974 patients in the BB cohort.

Males and non-Hispanic whites comprised the majority of HCC patients among all birth cohorts (Table 1). Compared to the BB cohort, there was a significantly greater proportion of Asians in the pre-1945 and post-1965 birth cohorts (Table 1). As expected, HCC patients in the pre-1945 cohort were significantly older than the BB cohort at time of cancer diagnosis whereas patients in the post-1965 cohort were significantly younger. The differences in age at HCC diagnosis is a function of our study design that separated cohorts based on year of birth. Compared to non-BB, BB with HCC were significantly more likely to have tumor within Milan criteria at time of diagnosis (38.7% (BB cohort) *vs.* 24.5% (pre-1945 cohort) *vs.* 25.3% (post-1965 cohort), p <0.001), and significantly more likely to have a solitary HCC less than 5 cm in size (34.8% (BB cohort) *vs.* 20.4% (pre-1945 cohort) *vs.* 22.7% (post-1965 cohort), p <0.001) (Table 1).

Among all HCC patients, patients in the BB cohort were more likely to receive any form of therapy compared to patients in the pre-1945 cohort (25.7% *vs.* 19.8%, p <0.001), but less likely to receive therapy compared to the post-1965 cohort (25.7% *vs.* 34.2%, p <0.001) (Table 1). However BB with HCC were more likely to receive liver transplantation than both the pre-1945 and post-1965 birth cohorts (Table 1).

Temporal trends in hepatocellular carcinoma

Overall HCC prevalence increased by 57.2%, from 4387 in 2003 to 6898 in 2011 (Fig. 1). During this period, the proportion of HCC represented by the BB cohort increased by 64% (n = 1535/4387 in 2003 to n = 3961/6898 in 2011), and in 2011, BB accounted for 57.4% of all HCC in the U.S. (Fig. 1). The incidence of HCC among the BB cohort increased from 7.5 per 100,000/year in 2003 (95% confidence interval (CI), 7.2–7.9) to 15.8 per 100,000/year in 2011 (95% CI, 15.3–16.3). HCC incidence among the pre-1945 birth cohort increased from 21.8 per 100,000/year in 2003 (95% CI, 21.0–22.7) to 29.4 per 100,000/year in 2011 (95% CI, 28.3–30.4), and among the post-1965 birth cohort increased from 0.5 per 100,000/year in 2003 (95% CI 0.4–0.6) to 0.7 per 100,000/year in 2011 (95% CI, 0.6–0.8). Among the cohort of BB with HCC, the prevalence of HCC increased by 158% among non-Hispanic whites, increased by 175% among Hispanics, increased by 166% among blacks, and increased by 128% among Asians (Fig. 2).

Hepatocellular carcinoma stage at diagnosis

Compared to the post-1965 birth cohort, BB with HCC had earlier tumor stage at diagnosis (localized HCC: odds ratio (OR), 1.93; 95% CI, 1.60–2.34; p <0.001; HCC within Milan criteria: OR, 3.66; 95% CI, 3.13–4.28-1.49; p <0.001; solitary HCC less than 5 cm: OR, 3.94; 95% CI, 3.32–4.69; p <0.001) (Table 2). Compared to the post-1965 birth cohort, the pre-1945 cohort also had earlier stage at HCC diagnosis (Table 2).

Among the cohort of BB patients with HCC, males were less likely to have localized HCC, less likely to have HCC within Milan criteria, and less likely to have solitary HCC <5 cm when compared to females with HCC (Table 2). Compared to non-Hispanic whites, blacks were less likely to have HCC within Milan criteria (OR, 0.68; 95% CI, 0.63–0.74; p <0.001) and less likely to have solitary HCC less than 5 cm (OR, 0.65; 95% CI, 0.60–0.71;