Research Article

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Changing incidence patterns of hepatocellular carcinoma among age groups in Taiwan

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Background & Aims: This study examined and compared the incidence patterns of hepatocellular carcinoma among age groups in Taiwan, 30 years after a universal hepatitis B virus immunization program was launched.

Methods: Data for hepatocellular carcinoma diagnosed in 2003–2011 were collected from the population-based Taiwan Cancer Registry. Age-standardized incidence rates were calculated to analyze and compare the changes in incidence rates and trends. More specific analyses were performed on four age groups separated by sex.

Results: A total of 82,856 patients were diagnosed with hepatocellular carcinoma in 2003–2011 in Taiwan, yielding an age-standardized incidence rate of 32.97 per 100,000 person-years. Hepatocellular carcinoma was predominantly diagnosed in middle-aged adults (50.1%) and elderly people (49.1%), in contrast to the low incidences in children (0.04%) and adolescents and young adults (0.8%). Striking variations in trends were found for children (annual percent change: −16.6%, 2003–2010) and adolescents and young adults (annual percent change: −7.9%, 2003–2011). The incidence rate of hepatocellular carcinoma in children decreased to zero in 2011; only a slight decline in trends occurred for the middle-aged group (annual percent change: −2%, 2003–2011), and a slight upward trend was observed for elderly people (1.3%), specifically in women (1.7%).

Conclusions: In Taiwan, hepatitis B virus-related hepatocellular carcinoma was nearly eradicated in children in 2011. The findings on age-specific incidence patterns and trends of hepatocellular carcinoma suggest that different control strategies for treating this devastating disease in the future be made according to age.

Cancer

Keywords: Age group; Hepatitis B virus; Hepatocellular carcinoma; Incidence; Taiwan; Trends.

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to HCV; NHI, national health insurance; NATP, National Antiviral Treatment Program; ICD-O-3, International Classification of Diseases for Oncology, third edition; TCR, Taiwan Cancer Registry; MV%, the percentage of microscopically verified cases; DCO%, the percentage of death-certificate only cases; IARC, International Agency for Research on Cancer; CI, confidence intervals; SRR, standardized rate ratio; ASR, age-standardized incidence rate; AYAs, adolescents and young adults; APC, annual percent change; M/F, male-to-female; ULN, upper limit of normal; ALT, alanine transaminase; NAHSIT, Nutrition And Health Survey in Taiwan; NAFLD, non-alcoholic fatty liver disease.

Introduction

Primary liver cancer is the second leading cause of cancer-related deaths worldwide [1], including Taiwan [2,3]. The incidence rate of primary liver cancer in Taiwan is more than 10-fold that of other areas of the world such as Australia, New Zealand, and those in South America and Northern Europe [1,4]. The numbers of newly diagnosed cases and deaths reported in 2011 were approximately 11,000 and 8000, respectively [5]. The overall mortality rate accounts for nearly 70% of the incidence rate. This reflects a poor prognosis of primary liver cancer, which can become a major threat to the health of Taiwanese people.

Hepatocellular carcinoma (HCC) is the most common type of liver cancer [5]. Chronic infection from hepatitis B virus (HBV) or hepatitis C virus (HCV) has been recognized as a major etiological factor leading to HCC [4,6]. In Taiwan, a prevalence of 80–90% positivity to the hepatitis B surface antigen (HBsAg) and an approximately 25% positivity to the HCV antibody (anti-HCV) in overall cases of HCC were documented [6]. Most chronic HBV infections in Taiwan were vertically transmitted from mothers to their offspring. To prevent mother-to-infant transmission of HBV, Taiwan launched the world's first nationwide HBV universal vaccination program in 1984 [6]. The most recent rate of infants completing the 3-dose HBV vaccination was 97.66% in 2013 [7], and the prevalence of HBV infection and the incidence of HCC have been substantially reduced among children and young adults over the past two decades [8–12]. In addition, since the Taiwan Bureau of National Health Insurance (NHI) launched the

National Antiviral Treatment Program (NATP) in 2003 to reimburse the costs of antiviral drugs for chronic hepatitis B and C, the mortality of chronic liver disease and cirrhosis as well as the incidence and mortality of HCC were significantly reduced [13]. The effectiveness of all these factors has changed the incidence patterns of HCC over time in Taiwan.

The incidence of HCC in Taiwan among children and young adults has been described substantially in previous reports [9–12]. However, the incidence trends for HCC across age groups in the last 10 years have not been compared. To fill this gap, this study aimed to examine the incidence patterns and trends of HCC across age groups, to update the knowledge of the changing incidence patterns of HCC by age group in the early twenty-first century, and to evaluate the impact of the HBV immunization program after 30 years. Moreover, to identify the geographical variation of risk for HCC, the incidence rates of primary liver cancer according to cities and counties were analyzed and compared.

Materials and methods

Data collection

The numbers of cases with primary liver cancer diagnosed in 2003–2011 were obtained from the nationwide Taiwan Cancer Registry (TCR) database [5]. Primary liver cancer was classified according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3: C22, cancer of the liver and intrahepatic bile ducts) [14]. The histology codes for HCC were ICD-O-3: 81703, 81713, 81723, 81733, 81743, and 81753. Census and land data were obtained from the Department of Statistics, Ministry of the Interior, Taiwan [15,16]. The TCR began data collection in 1979. Previous reports have shown the improvement of TCR over time [17,18], with an increased microscopically verified (MV) and decreased death-certificate only (DCO) rate. The MV and DCO rates were indicators defined by the International Agency for Research on Cancer (IARC) for measuring the quality of cancer diagnosis and the completeness of cancer registration. In addition, the Taiwan NHI system, a compulsory social insurance plan that centralizes the disbursement of healthcare funds, was launched in 1995 [19]. The system promises equal access to healthcare for all citizens, and the population coverage of the NHI had reached 99% by the end of 2004. Following the enactment of the Cancer Control Act in 2003, all hospitals in Taiwan with more than 50 beds were mandated to submit cancer data to the central registry; between 2003 and 2011, the number of hospitals participating in cancer registration ranged from 203 to 212. For all cancers, the percentage of MV cases (MV%) increased from 85.6% in 2003 to 91.6% in 2011, and the percentage of DCO cases (DCO%) decreased slightly from 2.7% in 2003 to 0.82% in 2011. The variations in quality indicators were markedly lower after 2003, suggesting that the validity and quality of cancer registration data have significantly improved and stabilized since 2003. Therefore, to provide the most reliable data and to minimize potential confounding effects on trend analysis, we analyzed the TCR data from the period 2003–2011.

Analyses

The rates, standard error, 95% confidence intervals (CIs), and standardized rate ratio (SRR) were calculated according to previously published methods by the IARC [20,21]. Age-specific rates were estimated by stratifying patients into 5-year age groups (0–4, 5–9, 10–14, 15–19, etc. and 85+ years), 18 in total. An age-standardized incidence rate (ASR) is a weighted average of age-specific (crude) rates, for which the weights are the proportions of individuals in the corresponding age groups of a standard population. The potential confounding effect of age can be reduced when comparing ASRs computed using the same standard population. In this study, ASRs were calculated using the direct method on the 2000 world standard population for 5-year age groups [21], and applied to examine geographic variations. The ASRs were compared more specifically to determine the impact of HBV immunization since 1984 among four age categories: (1) children (aged 0–14 y); (2) adolescents and young adults (AYAs, aged 15–29 y); (3) middle-aged adults (aged 30–64 y); and (4) elderly people (aged $\geqslant$65 y). Trends were analyzed using the Joinpoint regression model and permutation tests (Joinpoint Regression Program, Version 4.0.4) to identify significant changes [22,23], where up to one joinpoint produced was used to express the annual percent change (APC). The APC was considered significant if the 95% CI did not include zero. The relative risk of cancer, SRRs (ratio of ASRs), and 95% CI were calculated to compare the cancer incidence data between cities and counties; the SRRs were considered significantly different if the estimated 95% CI did not contain one. To prevent the effect of comparing heavily populated cities and counties (e.g., New Taipei City with 16.3% of the total population of Taiwan) with the total population, an effect that is influenced by their contribution, the rate for each city or county was compared with the rest of Taiwan (e.g., the ASR of New Taipei City *vs.* the ASR of Taiwan minus New Taipei City).

Results

A total of 97,157 patients were diagnosed with primary liver cancer in 2003–2011, yielding an annual average of 10,795 patients. Primary liver cancer accounted for 14.9% of all cancers in 2003 and 12.2% in 2011. The median age was 64–65 years. Regarding data quality indicators for primary liver cancer, the MV% ranged from 40.1% in 2003 to 47.9% in 2011, and the DCO% ranged from 4.2% in 2003 to 1.6% in 2011.

Of the patients diagnosed with primary liver cancer, 82,856 (85.3%) were diagnosed with HCC, with a crude rate of 40.14 and an ASR of 32.97 per 100,000 person-years (Table 1). The cumulative risk of developing HCC from birth to 74 years was 3.65%. Males were more frequently diagnosed with HCC than females, with a male-to-female (M/F) SRR of 2.74 (95% CI: 2.70–2.78, p <0.05). HCC was predominantly diagnosed in middle-aged adults and elderly people, accounting for 50.1% and 49.1% of all HCC cases, respectively. By contrast, children and AYAs were rarely affected, and the proportions of both groups were less than 1%, (0.04%, and 0.8%, respectively). Furthermore, a significant male predominance was found in all four age groups. The difference was most striking in the middle-aged group (M/F SRR: 4.34, 95% CI: 4.24–4.44, p <0.05), whereas the M/F SRR for elderly people was the lowest (M/F SRR: 1.84, 95% CI: 1.80–1.88, p <0.05). Age-specific incidence rate curves showed low rates before the age of 30 for both sexes, a rapid increase after the age of 30, followed by an accelerated increase from 45–49 years of age, peaking at ages 70–74 for men and 75–79 for women, and then declining thereafter (Fig. 1).

Temporal trends

No significant difference in trend analysis was determined in the 9-year period for all HCC patients (APC: −0.5%, 95% CI: −1.2% to 0.2%). However, significant differences among age groups were noted (Table 2, Fig. 2). The variations were most striking in children (APC: −16.6%, 95% CI: −29.7% to −1.0%, 2003–2010, p <0.05) and the AYA group (APC: −7.9%, 95% CI: −10.0% to −5.7%, 2003–2011, p <0.05), with a significant decline in the incidence rates for both groups. Specifically for children, the incidence rate dropped to zero in 2011 for the first time. By contrast, the rate declined only slightly for the middle-aged group (APC: −2%, 95% CI: −2.8% to −1.1%, 2003–2011, p <0.05), and elderly people exhibited a slight but significant upward trend (APC: 1.3%, 95% CI: 0.6–1.9%, 2003–2011, p <0.05). Although the incidence rates decreased for males of all age groups except elderly people in 2003–2011, the decrease was most significant in children (APC: −22.5%, 95% CI: −34.8% to −8.0%, 2003–2010, p <0.05), followed by AYAs (APC: −7.8%, 95% CI: −11.8% to −3.8%, 2003–2011, p <0.05), and the middle-aged group (APC: −1.5%, 95% CI: −2.4% to −0.6%, 2003–2011, p <0.05). For female patients, the incidence rate only significantly declined in AYAs (APC: −8.1%,