Epidemiology of hepatocellular carcinoma in Canada, 1995: Analysis of death certificates

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Abstract

A descriptive analysis of hepatocellular carcinoma (HCC) deaths in Canada for 1995 was undertaken. Cases (ICD-9 155.0) were identified from the Statistics Canada annual mortality file; age-adjusted death rates by age, sex and province were calculated. Antecedent causes and conditions leading to death listed on the death certificate, including viral hepatitis infection and cirrhosis, were examined, in addition to birthplace information. The 403 cases identified resulted in an annual age-standardized mortality rate of 2.11 deaths per 100,000 persons among men and 0.64 deaths per 100,000 persons among women. Mean age at death was 65.5 years with male-to-female ratio approximately 3:1. Compared to the age-standardized rate for birthplace of Canada of 0.96 per 100,000 (95% CI: 0.84, 1.10), the age-standardized mortality rates were significantly elevated for birthplace of Europe 1.72 (95% CI: 1.37, 2.28), Asia 5.17 (95% CI: 4.11, 6.44), and non-significantly elevated for all other countries 1.54 (95% CI: 0.94, 2.39). In total, 60 patients (15 %) were reported to have had viral hepatitis; sufficient information was not provided for the remainder. Of the total population, 8.7 % were reported to have had viral hepatitis B and 5.2 % had viral hepatitis C. Information on cirrhosis was provided in 103 (26 %) of cases. Of these, the largest proportion (45 %) was of unknown type while 23 patients (22 %) had alcohol-related cirrhosis. Prevalence of antecedent causes was slightly lower than reported previously and may be considered minimum estimates since inadequate information was provided in over 50% of deaths.

Key words: *death certificates, hepatitis B, hepatitis C, hepatocellular carcinoma, liver cirrhosis*

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. It ranks as the fifth most common cancer, accounting for five to six percent of all newly diagnosed cancers in both sexes.[1] The global incidence of HCC varies substantially between geographical regions, ethnic groups, and men and women.[2] International variation is noteworthy because of the low incidence in North America, northern Europe, Latin America and India, and the high incidence in East and Southeast Asia and sub-Saharan Africa. Intermediate rates are reported in regions adjacent to the high-risk areas and in southern Europe.[1] Independent of race and geography, rates for men are at about three times those for women. Estimated Canadian incidence rates for liver cancer using a world standard population were reported in the database Globocan 2002 by the International Agency for Research on Cancer (IARC) as 4.0 per 100,000 among men and 1.4 per 100,000 among women. For men and women, corresponding rates in Eastern Asia were 36.9 and 13.4 and 27.8 and 13.4 in middle Africa, repectively.[3] For the period 1992–2001, the average annual percent change of HCC incidence rates in Canada was 3.7% among men and 1.8% among women.[4]

Chronic hepatitis B virus (HBV) infection is by far the most important risk factor for HCC in humans. It is estimated that 80% of HCC worldwide is etiologically associated with HBV.[2] In developed countries, the prevalence of hepatitis C virus (HCV) infection correlates with HCC incidence and mortality rates.[5] Dietary aflatoxin exposure, excessive alcohol intake, cigarette smoking, oral contraceptive use in women, androgen use in men and primary hemochromatosis disease also are risk factors for HCC, but they play a relatively minor role in the development of the disease.[6]

Since standard vital statistics data specify only the underlying cause of death and do not provide information on HBV infection or other antecedent causes or risk factors, such as place of birth, an epidemiologic analysis of HCC in Canada was conducted using additional death registration information. The listed antecedent causes and conditions contributing to death from the medical certificate of death were examined at Statistics Canada in order to identify known HCC antecedent causes, such as type of cirrhosis, alcoholism and viral hepatitis infection.

Methods

The year 1995 was chosen for this analysis as this was the last year of data available at the time of the data capture of the underlying and contributing causes of death reported on the death certificate. This additional information is not available on the regular Canadian annual mortality file. For deaths where ICD-9 Code 155.0 was coded

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as the underlying cause of death,[7] information from the death registration not routinely available was manually extracted at Statistics Canada and the data entered into a SAS dataset. Antecedent causes of death and other significant conditions leading to death listed on the death certificate were reviewed for mention of viral hepatitis and cirrhosis. Age-standardized mortality rates were calculated per 100,000 persons using the direct method with five-year age groups and the 1991 Canadian population as the standard.[8] Age of the deceased, sex, birth country/province and autopsy indication were collected. The birth country category was created by classifying the birth country and city information from the death registration into one of four categories: Canada, Europe, Asia and other. Populations by birth country among Canadians were obtained from the 1996 census.[9]

There was some concern that contributing causes not reported on the death certificate may not necessarily mean the person did not have the disease. For purposes of comparison with the mortality results, in-patient hospital morbidity records with HCC as the tabulating diagnosis for fiscal 1995–1996 and 2002–2003 were extracted from data provided by the Canadian Institute of Health Information and comorbidity examined (other causes listed on the discharge abstract). For morbidity when only ICD-9 coding was available, non-A non-B hepatitis was used as a surrogate for hepatitis C and the percentage compared to provinces in 2002–2003 which used ICD-10, for which a specific hepatitis C code was available. Chi-square tests for contingency tables using exact conditional inference were obtained with the EXACT statement of the SAS procedure FREQ.[10]

Results

In 1995, 403 deaths were reported in Canada with HCC coded as the underlying cause. The annual age-standardized mortality rates were 2.11 deaths per 100,000 persons among men and 0.64 deaths per 100,000 persons among women. The male-to-female death ratio is approximately 3:1. The mean age at death was 65.5 years (median age 68 years). Approximately

90% of the deaths were in persons 50 years of age and older (Table 1). The ASMR was found to be the highest in the 70–79 age group. The country of birth distribution indicated that most of the deceased cases were born in Canada (51.9%), Europe (20.8 %), and Asia (20.8%) while other and missing birthplaces accounted for 6.5% of HCC deaths (Table 1). Compared

to the age-standardized rate for Canadian birthplace of 0.96 per 100,000 (95% CI: 0.84, 1.10), the age-standardized mortality rates were significantly elevated for European birthplace (1.72; 95% CI: 1.37, 2.28), Asia (5.17; 95% CI: 4.11, 6.44), and non-significantly elevated for all other countries (1.54; 95% CI: 0.94, 2.39).

TABLE 1
Hepatocelluar carcinoma deaths in Canada and age-standardized rate* per 100,000 by sex, age group, province of residence and country of birth (1995)

Characteristics		Number of deaths	Age-standardized rate	(95% CI)
Sex	Male	294	2.11	(1.88, 2.37)
	Female	109	0.64	(0.53, 0.77)
Males				
Age group (years)	0-39	8	0.09	(0.04, 0.18)
	40-49	28	1.28	(0.87, 1.83)
	50-59	50	3.55	(2.66, 4.65)
	60-69	96	8.61	(7.01, 10.5)
	70-79	88	12.6	(10.2, 15.5)
	80+	24	8.84	(5.77, 13.0)
Females				
Age group (years)	0-39	4	0.05	(0.01, 0.11)
	40-49	5	0.22	(0.08, 0.51)
	50-59	13	0.92	(0.51, 1.54)
	60-69	30	2.50	(1.72, 3.53)
	70-79	36	3.89	(2.76, 5.33)
	80+	21	4.01	(2.54, 6.04)
Province of residence	NF & Labrador	2	0.43	
	PEI	0	0.0	
	NS	8	0.84	(0.38, 1.62)
	NB	4	0.54	(0.16, 1.38)
	QC	115	1.61	(1.33, 1.93)
	ON	175	1.58	(1.35, 1.83)
	MB	14	1.13	(0.63, 1.87)
	SK	10	0.82	(0.41, 1.49)
	AB	33	1.39	(0.97, 1.94)
	BC	42	1.07	(0.78, 1.44)
	YK	0	0.0	
	NWT & Nunavat	0	0.0	
Country of birth	Canada	209 (51.9%)	0.96	(0.84, 1.10)
	Europe	84 (20.8%)	1.72	(1.37, 2.28)
	Asia	84 (20.8%)	5.17	(4.11, 6.44)
	Other	19 (4.7%)	1.54	(0.94, 2.39)
	Missing	7 (1.7%)		–
Total		**403**		

*   Standard population used is 1991 Canadian population for men and women combined

An autopsy was reported in 9% of the HCC cases (results not shown). Based on province of residence, this ranged from zero to a maximum of 30% in Saskatchewan (three out of ten deaths). The percentage of cases in which the autopsy information was used in assigning the cause of death was not available in the Statistics Canada database for 1995 or earlier years, pending a system redesign.

For the HCC patients, Table 2 indicates whether, from the listed cause-of-death fields reported in the medical death certificate, hepatitis was identified as present. A total of 60 cases (15%) were reported to have had hepatitis. The largest percentages of deaths reported to have had hepatitis were found in the 40–69 age groups for both males and females. The null hypothesis of a uniform proportion among all age-sex-specific categories was rejected ($p = 0.002$). The highest proportion reported with viral hepatitis were hepatitis B cases (8.7% of total), followed by those reported to have had hepatitis C (5.2%). Less than two percent of total cases were reported to have had hepatitis of unknown type. Less than one percent of total cases were reported to have had both hepatitis B and C and these cases are included in the marginal totals for hepatitis B and C above.

For comparison, hospital admissions were used as a second source of information. Age-standardized admission rates for HCC

with non-A non-B hepatitis reported as comorbidity had increased from 0.19 per 100,000 to 0.43 from 1995 to 2002, a larger increase than for hepatitis B or alcoholic cirrhosis. The percentage of cases reported to have had non-A non-B hepatitis increased from 5.5 in fiscal year 1995–96 to 15.1 in 2002–03. Provinces using ICD-10 in 2002–03 reported a similar percentage: 15.0 for hepatitis C specifically. Over the same period, the percentage of admissions reported to have had hepatitis B increased only from 8.7 to 11.3.

Cirrhosis was reported in the cause of death fields for 103 (26%) of the total number of cases (Table 3). Of these, alcohol consumption was reported in 23 deaths (22% or 5.7% of total deaths), followed by hepatitis in 14 cases (14%). Twenty cases (19%) of cirrhosis were reported due to other factors, while for 46 deaths (45%) the causes of cirrhosis were not stated. The hypothesis of a type-of-cirrhosis uniform distribution among men and women with the disease was not rejected ($p = 0.11$). When using hospital morbidity data, over the period 1995 to 2002, the percentages of HCC admissions reported to have had alcoholic cirrhosis were relatively constant at 11.2 and 12.6, respectively.

Discussion

This study is unique in its extraction of listed contributing causes of death from death registrations for the purpose of gathering

additional, more complete information not reported in the Vital Statistics database. Rates of HCC mortality in Canada for 1995 were consistent with the findings of previous studies. Rates were higher for men than women and an increased risk was observed for immigrants from Europe and especially from Asia, compared to persons born in Canada. These results are consistent with higher incidence rates observed in these areas.[3]

A concern with an analysis based on death certificates is that absence of an antecedent cause may not ensure the absence of disease, resulting in an underestimation of prevalence or minimum estimates. Studies on completeness of death certificates in this regard were not available. The percentage of deaths reported to have had hepatitis among men and women were similar, although the information was not provided for 85% of deaths. Nevertheless, the figure of five percent of 1995 death certificates indicating the presence of hepatitis C was similar to the percentage of hepatitis C comorbidity available from hospitalization data. This comorbidity percentage had increased to about 15% in the fiscal year 2002–2003. An examination of temporal trends in electronic records from 172 United States Veterans Administration hospitals reported that the percentage of the overall rate associated with HCV increased from 7.5 to 18.3 between 1993–1995 and 1996–1998.[11] The increase in rates of HCC associated with HCV was greater than those associated with HBV or alcohol-induced cirrhosis. On the other hand, the frequency of HCV seropositivity in seven other studies in the United States, including 1,429 persons with HCC, was reported to be higher at 27%.[11]

An indication of cirrhosis was provided in only 26% of all HCC cases. Reporting on the type of cirrhosis was also incomplete. In our study, a large proportion (45%) of records had cirrhosis listed on the medical death certificate but without further specification, making it difficult to accurately identify the antecedent or co-existent causes as stages in the disease process. The percentage of deaths reported to have indicated alcoholic cirrhosis on the death certificates (six percent) was lower than

TABLE 2
Hepatitis status of hepatocellular carcinoma deaths in Canada*, by sex and age group (1995)

	Age group	Number and percentages of reported cases of hepatitis	Total
Male			
Age group (years)	0-39	4 (50.0%)	8
	40-69	35 (20.1%)	174
	70+	8 (7.1%)	112
Female			
Age group (years)	0-39	0 (0.0)	4
	40-69	9 (18.8%)	48
	70+	4 (7.0%)	57
Total		60 (14.9%)	403

* Obtained from medical records of death

Pearson chi-square test for uniform proportions with 5 df = 20.9, $p=0.002$ (exact test)

TABLE 3
Cirrhosis status of hepatocellular carcinoma deaths in Canada*, by sex (1995)

Sex	Type of cirrhosis (% of total)				
	Alcohol	Hepatitis	Other	Not stated	Total
Male	22 (24.2)	10 (11.0)	16 (17.6)	43 (47.3)	91
Female	1 (8.3)	4 (33.3)	4 (33.3)	3 (25.0)	12
Total	23 (22.3)	14 (13.6)	20 (19.4)	46 (44.7)	103

* Obtained from medical records of death

Pearson chi-square test for independence 3 df = 5.85 p=0.11 (exact test)

the 11% reported from the Canadian hospital comorbidity data and the 28% from the United States Veterans Administration hospitals.

An examination of medical records and hospital admission records would enhance the ability to accurately identify the type of cirrhosis as well as confirm the absence of these antecedent or co-existent causes when not present on death certificates. Alcoholic cirrhosis for example, has been found to be underestimated using cause-of-death information from medical death certificates when compared to autopsy and coroner reports.[5]

As in many other studies, the use of ICD-9 code 155.0 denoting primary liver cancer was used as a surrogate for HCC. Medical certificates of death in the current study were selected solely based on the ICD-9 code of 155.0 being reported as the underlying cause of death. A particular concern with this method may include the possibility of cases of metastatic liver cancer, or other rare types of primary liver cancer, being reported as HCC.[12,13]

The causes of death reported in the medical certificate of death may not always be accurate. The two main reasons given for inaccurate cause-of-death data are erroneous clinical diagnoses and incorrect entering of a diagnosis.[14–16] Our review of listed contributing cause-of-death data did not have access to clinical or complete autopsy information. The present study shows the need and importance for physicians to complete death certificates as fully and accurately as possible since valuable epidemiologic information may be derived from this source and future health care decisions may be made based on such studies.

The three main risk factors associated with HCC in Canada are infection with HCV, with HBV and alcoholic cirrhosis.[17,18] Many epidemiological studies have concluded that chronic infection with either HBV and HCV is a major risk factor for HCC. Our study showed that HBV infection was reported on nine percent of the HCC death certificates, while five percent of deaths were reported to have had HCV. This trend is expected to increase over the next two decades due to the chronic nature of HBV and HCV infections. It has been suggested that approximately 240,000 Canadians are infected with HCV.[19] Major risk factors, such as intravenous drug use, needle sharing, transfusion of unscreened blood and blood products and unsafe sexual practices in the 1960s and 1970s, have been associated with the transmission of HBV and HCV infections. The long latency period between HBV and HCV infection and cancer, combined with a large pool of persons to be chronically infected with hepatitis C, may account for some of the HCC cases.[20,21] Progression of cirrhosis after infection with Hepatitis C infection can take 20 years on average. Once cirrhosis is established, HCC occurs at an annual rate of one to four percent.[22]

Consumption of alcohol, especially at high levels and over prolonged periods, increases the risk of HCC. In Canada, a decline in alcohol consumption has been observed amongst persons age 14 and over.[23] Similar observations have been cited in Australia and the US.[5,12,13] Furthermore, there has been a pronounced decrease in alcoholic cirrhosis mortality in Canada in the past decade. In this study, medical certificates of death identified very few cases where cirrhosis due to alcohol consumption was specified as an underlying cause of death.

Alcohol-related cirrhosis is, nevertheless, considered a major risk factor where the incidence of chronic viral hepatitis is low.[6]

It is expected that the incidence and mortality of heptacellular carcinoma will increase in Canada and other Western countries over the next several years. The evidence suggests that persons infected with HBV and HCV will represent a greater proportion of cirrhosis, leading to HCC. Prevention strategies, such as hepatitis B vaccination, hepatitis C awareness campaigns and anti-alcoholism programs, would be expected to reduce the incidence of HCC.

While most current studies suffer from obstacles (e.g., small size, limited follow-up or selection bias) that create controversy around the opinion that treatment of both hepatitis B and C may reduce the incidence of HCC, it is likely that prevention or elimination of hepatitis C infection will prevent HCC particularly if patients are treated before the onset of cirrhosis. It is possible that treatment will delay the progression to HCC, but the extent of the delay is unknown (Personal communication via e-mail. Dr. Morris Sherman. Associate Professor of Medicine, University of Toronto. November 11, 2002). This is less certain for hepatitis B, as permanent eradication of the virus does not occur, and the permanency of viral suppression is unclear.

Acknowledgments

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