An Epidemiologic Study of Hepatocellular Carcinoma in Canada

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ABSTRACT

Background and Methods: To provide information on poorly described Canadian hepatocellular cancer epidemiology, we analyzed incident cases abstracted from the Canadian Cancer Registration Database (1969-1997) and Canadian annual death data (1969-1998). Age, sex, geographic distribution, and secular trends were described. Projection models were developed for the next decade.

Results: Results indicated much higher incidence and mortality rates in males than females, with substantial increases for both with age. Age-standardized incidence rates increased an average of 3.4% per year in males, 1.2% per year in females (1969-1997). Age-standardized mortality rates increased an average of 1.48% in males, but decreased an average of 0.46% per year in females (1969-1998). Joinpoint analysis of the linear trends in the age-standardized incidence and mortality rates suggested that a new trend started to emerge about 1991. The fitted non-linear multiplicative model predicted the occurrence of 1,565 new cases and 802 deaths in the year 2010. HCC incidence was the highest in British Colombia, followed by Quebec, and the lowest in the Atlantic region.

Conclusions: Incidence rates of hepatocellular carcinoma have increased substantially, consistent with the reported increase in the prevalence of Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) infections in recent decades.

La traduction du résumé se trouve à la fin de l'article.

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Hepatocellular carcinoma (HCC) is an important worldwide health problem, accounting for 250,000 to one million deaths per year across 33 countries.[1] The prognosis of HCC is poor, with a relative 5-year survival rate after diagnosis of approximately 16% for females and 11% for males.[2] Currently there is no available publication describing epidemiologic features of HCC in Canada. To provide health professionals, researchers, and policy-makers with updated information on this severe disease, we carried out an epidemiological analysis to examine the age, sex, geographical distribution, and secular trends of HCC incidence and mortality in Canada. We further used a projection model to predict the burden of HCC incidence from 1998, and mortality from the year 1999, to the year 2010.

METHODS

A HCC case was identified by the ninth revision of the International Classification of Disease (ICD-9) code 155.0. HCC incident cases (1969-1997) were obtained from the Canadian Cancer Registration Database and Cancer Care Ontario, and HCC mortality cases (1969-1998) were extracted from Canadian annual death files. Both national incidence and mortality databases are managed by Statistics Canada. Crude incidence and mortality rates were expressed as the number of cases per 100,000, and age-standardized incidence and mortality rates were calculated by the direct method, using the 1991 Canadian population as the standard. For trend analysis, the annual percent change was calculated using a linear regression of the log of the rates. Age, sex, geographic distribution and secular trends of HCC incidence and mortality were described first. For age, sex, and geographic distributions, most recent data (1990 to 1997 for incidence, and 1990 to 1998 for mortality) were utilized. Age-period-cohort models were fit to evaluate the improvement in model fit resulting from the period and cohort factors.[3,4]

A non-linear multiplicative model was then developed to fit the counts and rates of incidence and mortality cases for males and females separately.[5,6] This function modelled the rates as $(A + Dt)\exp(-B(s - C)^2)$ where t represents year and s represents age,

which is non-linear in the four parameters A,B,C and D. This model assumes the age-specific absolute change in incidence is proportional to the corresponding age-specific baseline rate, the adequacy of which was evaluated by the model fit. Joinpoint analysis was used to select the period on which to base the projection.[7] This multiplicative model was then extrapolated to the year 2010, taking into account the predicted change in population profile (adjusting for the aging population). Fitting was accomplished using the S-plus 2000 non-linear least squares algorithm 'nls'.[8]

RESULTS

Secular trends and age distribution of incidence and mortality

Figures 1 and 2 present the number of incident cases and deaths respectively, and the corresponding age-standardized rates for Canadian men and women. Age-standardized incidence rates of HCC, as shown in Figure 1, increased from 1.97 per 100,000 in 1969 to 4.43 per 100,000 in 1997 for males (an average of 3.4% per year increase, trend significant p<0.001) and from 0.99 per 100,000 in 1969 to 1.26 per 100,000 in 1997 for females (an average of 1.2% per year increase, trend significant p<0.001). Age-standardized mortality rates of HCC, as shown in Figure 2, increased from 1.96 per 100,000 in 1969 to 2.67 per 100,000 in 1998 for males (an average of 1.48% per year increase, significant p<0.001), but decreased from 0.99 per 100,000 in 1969 to 0.70 per 100,000 in 1998 for females (an average of 0.46% per year decrease, not significant p=0.10). Rates of incidence and mortality increased by age with the highest rates observed among men in the age group 70-79 and among women aged 80 or more (Tables I and II). Age-period-cohort models for incidence data indicated a significant role for both period and cohort factors among men, while among women either factor provided an adequate fit of the increased rates (results not shown).

Geographic distribution

The annual mean number of incident cases in 1990-1997, as shown in Table III, was 726 (523 male, 203 female) and the annual mean number of deaths in 1990-1998, as shown in Table IV, was 419 (303 male, 116 female). HCC incidence was the high-
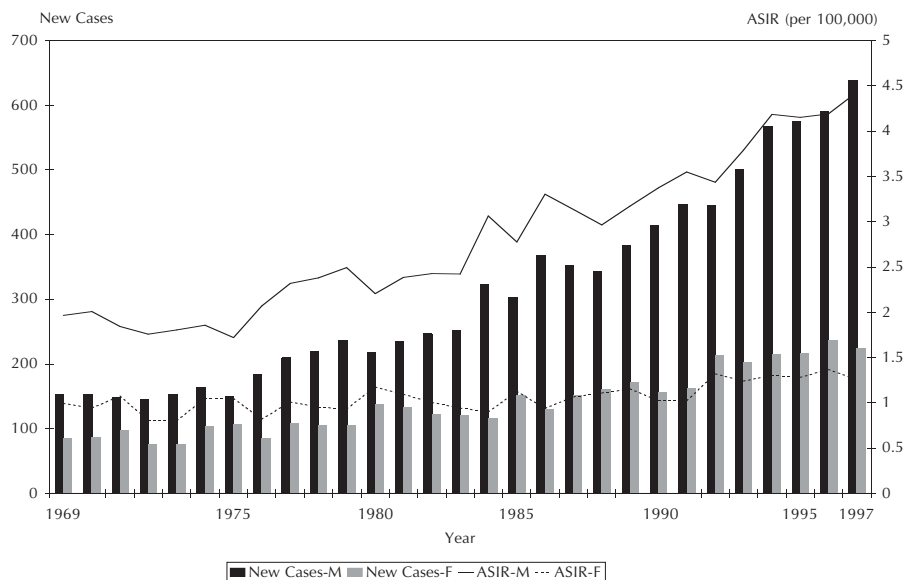

Figure 1. New Cases and Age-standardized Incidence Rates of HCC for Canada by Gender, 1969-1997
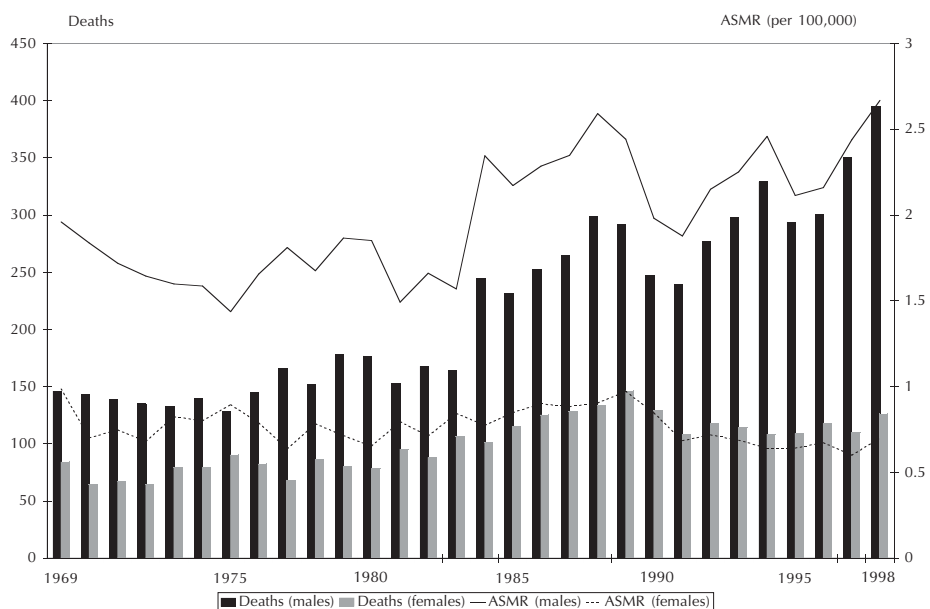

Figure 2. Deaths and Age-standardized Mortality Rates of HCC for Canada by Gender, 1969-1998

est in British Colombia, followed by Quebec, and the lowest in the Atlantic region (Table III). HCC mortality rates were highest in Quebec and British Columbia, and lowest in the Atlantic region (Table IV).

Projected HCC incidence and mortality in Canada in 2010

Joinpoint analysis of the linear trends in the age-standardized incidence and mortality rates suggested that a new trend started to emerge about 1991. Stepwise selection from the hierarchy of Poisson regression models for age-specific rates indicated that the model selected with age-specific intercepts and a common slope parameter fit the data well. The fitted non-linear multiplicative model predicted that 1,565 new cases (1,132 male, 433 female) and 802 deaths (654 male, 148 female) of HCC are expected to occur in Canada in 2010.

DISCUSSION

The rates of HCC incidence and mortality in Canada increased over the past 30 years. The number of incident cases and deaths

TABLE I

Age- and Sex-specific Incidence Rates (per 100,000) of Hepatocellular Carcinoma in Canada, 1990-1997

Age Group	Males		Females		Both Sexes	
	# of Cases	Rates	# of Cases	Rates	# of Cases	Rates
0-9	64	0.40	37	0.24	101	0.32
10-19	21	0.13	12	0.08	33	0.10
20-29	33	0.19	25	0.15	58	0.17
30-39	131	0.64	39	0.19	170	0.41
40-49	362	2.15	71	0.42	433	1.29
50-59	646	5.91	172	1.55	818	3.73
60-69	1353	15.39	408	4.23	1761	9.81
70-79	1141	21.42	504	7.04	1645	14.23
80+	433	21.28	356	9.15	789	15.21
All ages	4184	3.91	1624	1.23	5808	2.57

TABLE II

Age- and Sex-specific Mortality Rates (per 100,000) of Hepatocellular Carcinoma in Canada, 1990-1998

Age (year)	Male		Female		Both Sexes	
	# of Deaths	Rates	# of Deaths	Rates	# of Deaths	Rates
0-9	13	0.07	11	0.06	24	0.07
10-19	9	0.05	7	0.04	16	0.05
20-29	17	0.09	11	0.06	28	0.07
30-39	78	0.33	23	0.10	101	0.22
40-49	193	1.01	51	0.27	244	0.64
50-59	451	3.61	99	0.78	550	2.20
60-69	903	9.09	257	2.37	1160	5.73
70-79	810	13.34	344	4.22	1154	8.78
80+	257	11.08	237	5.31	494	8.19
All ages	2731	2.25	1040	0.69	3771	1.47

TABLE III

Incidence Rates (per 100,000) of Hepatocellular Carcinoma in Canada by Region, 1990-1997

Region Name	Number of Cases	Rate	95% CI
British Columbia	999	3.28	3.08 - 3.50
Prairies	812	2.23	2.08 - 2.39
Ontario	2152	2.52	2.42 - 2.63
Quebec	1514	2.75	2.61 - 2.89
Atlantic	314	1.69	1.51 - 1.89
Canada	5808	2.57	2.50 - 2.64

TABLE IV

Mortality Rates (per 100,000) of Hepatocellular Carcinoma in Canada by Region, 1990-1998

Region Name	Cases	Rate	CI 95%
British Columbia	555	1.61	1.48 - 1.75
Prairies	505	1.22	1.12 - 1.34
Ontario	1478	1.53	1.45 - 1.61
Quebec	1088	1.73	1.63 - 1.84
Atlantic	143	0.68	0.58 - 0.81
Canada	3771	1.47	1.42 - 1.52

will continue to rise as the Canadian population ages. However, the influence of aging alone cannot explain the rising rates of this cancer. It should be noted that the ICD-9 code 155.0 was selected to capture primary liver cancers and to exclude secondary cancers which may carry different risk factors, although this likely results in a conservative estimate of the mortality rates because of death certificates coded as not specified as primary or secondary. A number of risk factors have been associated with the development of HCC. Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) are quantitatively important causes of HCC.[9-13] Tobacco smoking was also found to be an important risk factor of HCC, independent from HBV and HCV.[13]

Alcoholic cirrhosis is also an important etiologic risk factor of HCC.[14] Periodic behaviour surveys for persons aged 14 and over have shown that alcohol consumption is declining in Canada.[15] The percentage of regular drinkers (1 or more drinks per month) decreased from 63% in 1985 to 55% in 1991 as reported in the General Social Survey (GSS)[15] with respondents aged 15 or more. The National Population Health Survey (NPHS) reported values of 55% in 1994, and 53% in 1995.[16,17] Further, the per capita sales of alcohol in Ontario have progressively decreased from 11.3 litres of ethanol in 1977 to 7.5 litres in 1997, and the percent of respondents consuming 5 or more drinks per day declined from 13.4% to 5.9%.[18] The changes in alcohol consumption should result in a decreased rate of HCC. Indeed, there has been a substantial decrease in alcoholic cirrhosis mortality in Canada. In 1979, the age-standardized mortality rate in Canada, per 100,000, was 7.5 for males and 3.0 for females, while in 1996 corresponding rates were 3.9 for males, and 1.2 for females.[19] Cirrhosis mortality in Alberta also declined significantly for the period 1975-1993.[20] Thus, HBV and HCV infection would become the main contributors of rising incidence and mortality of HCC.

Considering the chronic nature of HBV and HCV, it is likely that infections acquired in previous decades would have had a significant influence on the observed increasing trends of HCC. Practices of intravenous drug use, needle sharing and transfusion of unscreened blood and blood products were likely major risk factors associated with the transmission of HCV and HBV infections. Unsafe sexual practices in the 1960s and 1970s to early 1980s were also a major risk factor for HBV, and sexual activity – as a route of transmission of HCV infection – contributes approximately 5% to the total infection.[21] Increased immigration from areas of high endemicity for HBV and HCV is likely another important contributor to the increased rate of HCC.[22] Several Canadian studies have demonstrated the burden of HCV in Canada.[23,24] These studies showed that the increase in the prevalence of HCV infections is, in part, due to the presence of a large pool of persons infected with these viruses in whom the cancer is still in the latency stage.[23-25]

Implementation of effective prevention measures, such as hepatitis B vaccination, treatment of HBV and HCV infection, education programs aimed at the reduction of injection drug use and heavy alcohol consumption, will have an important impact on slowing down the increase in incidence and mortality of HCC. Collier and Sherman[26] discussed the practical

aspects of establishing a screening program for HCC as a secondary prevention measure that may result in a decrease in disease mortality. Moreover, from the tertiary prevention point of view, better treatment with improved survival needs to be developed as well.

We have no explanation for the recent decrease in HCC mortality in females, despite a continuous increase in incidence. This phenomenon of discrepancy in HCC incidence and mortality for females has been observed in other studies as well.[27-29] Investigation of the causes of the recent decline in HCC mortality in females may provide useful information for HCC treatment.

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RÉSUMÉ

Contexte et méthodes : Afin de combler le manque d'information sur l'épidémiologie du cancer hépatocellulaire au Canada, qui a été peu décrite jusqu'à maintenant, nous avons analysé les nouveaux cas tirés de la base de données du Registre canadien du cancer (1969-1997) et les données annuelles sur la mortalité au Canada (1969-1998). L'âge, le sexe, la répartition géographique et les tendances à long terme ont fait l'objet d'une description. Des modèles de projection ont été élaborés pour la prochaine décennie.

Résultats : Les résultats indiquent des taux d'incidence et de mortalité beaucoup plus élevés chez les hommes que chez les femmes. Pour les hommes comme pour les femmes, on observe une importante croissance des taux avec l'âge. Les taux d'incidence normalisés selon l'âge ont augmenté en moyenne de 3,4 % par année chez les hommes et de 1,2 % par année chez les femmes (1969-1997). Les taux de mortalité normalisés selon l'âge ont augmenté en moyenne de 1,48 % chez les hommes, mais ont diminué en moyenne de 0,46 % par année chez les femmes (1969-1998). L'analyse par point de retournement des tendances linéaires des taux d'incidence et de mortalité normalisés selon l'âge suggère l'émergence d'une nouvelle tendance vers 1991. Le modèle multiplicatif non linéaire ajusté prévoit la survenue de 1 565 nouveaux cas et de 802 décès en 2010. C'est en Colombie-Britannique, suivie du Québec, qu'on trouve l'incidence la plus élevée de CHC, alors que l'incidence la plus basse s'observe dans la région de l'Atlantique.

Conclusions : Les taux d'incidence du carcinome hépatocellulaire ont augmenté de façon notable, ce qui est compatible avec l'augmentation signalée de la prévalence de l'infection par le virus de l'hépatite C (VHC) et de l'infection par le virus de l'hépatite B (VHB) dans les dernières décennies.