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Trends in Hepatocellular Carcinoma Incidence and Mortality in Canada from 1976 through 2000.

by

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Abstract

This study examined trends in hepatocellular carcinoma (HCC) incidence and mortality in Canada by age and sex from 1976-2000, described these trends by birth cohort, and projected HCC incidence for the period 2001 through 2015. Using data from the Canadian Cancer Registry and from the Vital Statistics Section of Statistics Canada, annual HCC incidence and mortality rates were calculated by age and sex for persons aged 20 years and older. An age and birth cohort Poisson regression model was used to project HCC incidence rates. The age-adjusted incidence of HCC rose faster in males compared to females, 3.4% per year (from 2.8 to 5.5 cases per 100,000) versus 2.1% per year (from 1.4 to 2.0 cases per 100,000). There was an increasing trend in HCC risk for successive birth cohorts from 1896 through 1956. The projection showed that a continued increasing trend in HCC incidence is expected for males and females through 2015.

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I. Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer mortality (1). The occurrence of HCC has great geographic variation (2;3). Regions of high incidence (greater than 30 cases per 100,000 population) include sub-Saharan and west Africa, southeast Asia, China and Japan. Regions of intermediate incidence (5 to 30 cases per 100,000) include France, Spain and Italy. A low HCC incidence (less than 5 cases per 100,000) is found in the United States, Canada, Scandinavia, the United Kingdom and Australia (2;4). The two major risk factors for the development of HCC are chronic infection with the hepatitis B virus and chronic infection with the hepatitis C virus (5). Among high incidence countries, with the exception of Japan (6), HCC incidence rates correlate to the prevalence of hepatitis B viral (HBV) infections in the general population (3;4). In low to intermediate incidence countries, and Japan, HCC incidence rates correlate to the prevalence of hepatitis C viral (HCV) infections in the general population (4;6;7). HCC treatment options are poor and the disease is almost always fatal (3).

Several studies have examined HCC incidence and mortality trends in low and intermediate incidence countries. The results of these European (8-12), Australian (13), American (14-16), and Canadian (17) studies were consistent for an increase in HCC incidence and mortality during a period that fell within a range from 1970 to 1998. But the magnitude of the increase and the sex-specific trends varied between studies.

To fully examine the trends over time in HCC incidence and mortality the potential influence of effects related to the age distribution of the population at risk for HCC, the time period of HCC diagnosis, and birth cohorts (persons born within similar

time periods) should be considered (18). The risk for HCC increases strongly with age (19), and therefore changes over a given time period in the age distribution of the Canadian population will influence crude HCC incidence and mortality trends in Canada during that time period.

Factors related to the period of diagnosis include the diagnostic techniques and the treatments used in a population in a given time period (18). An improvement in HCC diagnostic techniques that is taken up broadly by the medical community could result in an increase in HCC incidence for a period of time after uptake relative to before the uptake. Such a change in diagnostic techniques could also influence HCC mortality trends if the change led to increased HCC survival (e.g. if tumors were detected at an earlier stage compared to the previous diagnostic technique and better treatment options were available for earlier compared to later stage tumors). An effect on HCC incidence and mortality that is related to a change in HCC diagnostic technique would be unlikely in Canada for a period of observation extending back 25 years through to the present because the current diagnostic tests for HCC, serum alpha-fetoprotein levels and ultrasonography, have been routinely used since the late 1970's (20) or early 1980's (9;14).

An improvement in HCC treatment options in a given period of time that leads to increased survival times could result in declining HCC mortality trends in subsequent periods of time. But unfortunately in the last 25 years there has been little improvement in HCC survival. Among persons diagnosed with HCC in the U.S, from 1974 through 1976, from 1983 through 1985, and from 1992 through 1999, five-year relative survival was estimated to be 4%, 6%, and 7%, respectively (21).

Birth cohorts effects occur when persons born in different years (e.g. different generations) experience different exposures to risk factors for a given disease (18). Different exposures to a risk factor for a disease among different generations can result in different lifetime risks for that disease in one generation relative to another generation. A classic example of such an effect occurred when young men, newly recruited to the US army during World War II, were given cigarettes as part of their rations (22). Young men during the period of World War II belonged to one generation (ie. they were born in a narrow interval of time (in years)). The age-specific risks for lung cancer were greater for this generation relative to the corresponding age-specific risks for lung cancer in the preceding generation (22).

The rationale for evaluating the influence of birth cohorts on HCC incidence trends in Canada is related to the recent trends in the prevalence of the major risk factors for HCC in Canada (HBV and HCV), and to the modes of transmission of these risk factors. From 1980 through 1995 age-adjusted incidence for HBV infections in Canada rose 465% from 1.8 to 10.2 reported cases per 100,000 population (23). Age-adjusted mortality from non-A, non-B hepatitis was stable from 1980 through 1990 but from 1990 through 1995 it rose 230% from 0.12 to 0.40 deaths per 100,000 population (the molecular cloning of HCV occurred in 1989 and non-A, non-B hepatitis mortality rates are proxy measures of HCV mortality rates(24)) (25). Surveillance for HCV infections started in Canada in 1991 and from 1995 through 1999 age-adjusted incidence for reported HCV infections rose 30% from 47 to 61 cases per 100,000 population (26).

HCV is transmitted by direct exposure, through the skin, to blood (27). In North America, persons at the greatest risk for HCV infections are intravenous drug users, and

before 1990 persons at the greatest risk for HCV infections included hemophiliacs that had had a blood transfusion (24;28;29). HBV is transmitted by direct exposure, through the skin, or through mucous membranes, to blood or semen (27). Intravenous drug users, persons with multiple sexual partners and men that have sex with men are at greatest risk for HBV (30). Sexual transmission of HCV can occur but it is a less common mode of transmission in HCV compared to HBV (27). Because of the increasing prevalence of these infections in Canada since 1980, young men and women that used drugs intravenously or that had multiple sexual partners in the more recent years of the past two decades may face a greater risk for HCC compared to the risk faced by young persons in the earlier years of the past two decades.

The implication for primary prevention of HCC of identifying the subgroups of the Canadian population (age, sex, and birth cohort) that face the greatest risk for HCC is that these groups can be targeted with resources to prevent exposure to HCC carcinogens. To date, no study has published the results of a birth cohort analysis of HCC trends in Canada. The purpose of this study is to update the trends in HCC incidence and mortality in Canada by age and sex from 1976 through 2000, to describe these trends by birth cohort, and to project hepatocellular carcinoma incidence rates in Canada for the period from 2001 through 2015.

II. Background

A. Primary liver cancer (PLC) and hepatocellular carcinoma (HCC) nomenclature

The liver is the primary site for a number of malignant tumor types: hepatoblastomas, intrahepatic bile duct (cholangio-) carcinomas, and hepatocellular carcinoma (3). Relative to HCC incidence, the incidence of all of these tumor types,

except HCC, are rare (3;5;31). The eighth (1969) and ninth (1979) revisions of the World Health Organization's International Classification of Diseases (ICD) combines cancers of the liver and intrahepatic bile ducts into one class, 155 (32;33). Subclasses distinguish PLC (HCC and hepatoblastoma), ICD-8 and ICD-9:155.0, from intrahepatic bile duct cancer (cholangiocarcinoma), ICD-8 and ICD-9: 155.1. Hepatoblastoma is a very rare childhood cancer that is usually diagnosed before age 3 years (31). The following risk factors are specific to HCC.

B. Hepatocellular carcinoma Risk Factors

Hepatitis B Virus (HBV)

Geographically, countries that have a high incidence of HCC also have a high proportion of HBV surface antigen (HBsAg) carriers (indicating a chronic HBV infection) in the general population (34;35). Almost all countries with a prevalence of HBV carriers greater than 2% have a higher mortality rate from HCC compared to countries with carrier rates below 2% (3).

In a 1998 meta-analysis Donato and colleagues identified 32 case-control studies from 1989 through 1997 that tested for HBsAg antibodies among HCC cases and control patients with chronic liver disease. They found a summary odds ratio (OR) of 13.7 (95% confidence interval (CI) = 12.2-15.4) for persons with HCC being HBV-positive.

An increased risk for HCC among HBV-infected persons was also found in several prospective cohort studies (36-39). The earliest study involved 22,707 male civil servants from Taiwan, tested at baseline for the HBsAg (36). After a nine year follow-up Beasley and colleagues found a relative risk (RR) of 98 (95% CI = 50-193) for the development of HCC among the HBsAg-positive subjects compared to the rest of the

cohort (40). This estimated relative risk for the development of HCC did not account for potentially different age distributions in the HBsAg-positive HBsAG-negative subjects (The age distributions for these two groups were not described in the 1981 and 1988 publications of the results but 82% of the cohort were between 40 years and 59 years of age (40)). A recently published prospective study followed 58,545 men from 1992 through 2000 in Haimen City, China, and found an age-adjusted relative risk for death from HCC of 22.3 (95% CI = 18.7-26.6) among males positive for HBsAg at baseline compared to males negative for HBsAg at baseline (39). Because there is no effective treatment for HCC in China and the median survival time from HCC in Haimen City was less than 6 months during the period of observation, the risk for death from HCC was a good proxy for the risk for developing HCC in Haimen City during the period of observation (39).

Chronic HBV infections are defined by the persistence of HBsAg in serum for 6 months or longer (41). Age at the time of HBV exposure is the major determinant for whether an acute HBV infection will become chronic (42). HBV transmissions that occur perinatally, or during childhood are more likely to result in chronic infections compared to transmission that occur during adulthood (43). In low prevalence areas such as Europe and North America, HBV infections occur most often in adults by exposure to contaminated blood through intravenous drug use or by sexual contact with an HBV carrier (41;44). In areas of high HBV prevalence, such as Africa and Asia, infections are most likely to occur during the perinatal period, from mother to infant, or during childhood (27;43). Of the of infants born to mothers positive for the hepatitis B e antigen (HBeAg), indicating ability to spread the virus to other people, approximately 90%

develop chronic HBV infections (45). The HBeAg is present among persons with acute or chronic HBV infections (27).

There is evidence to support both a direct and indirect mechanism of HBV carcinogenesis. The direct mechanism requires integration of HBV into the DNA of liver cells (27;43;46-49). The indirect mechanism may result in HBV integration into the host chromosome, but it is not required for carcinogenesis to occur (27;43;46-49). Indirectly, carcinogenesis can occur during the process of chronic necroinflammation of the liver, a condition that occurs in patients with cirrhosis (27;43;46-49). The accelerated cycle of hepatocyte death and regeneration that characterizes this condition is hypothesized to be carcinogenic in three ways: an increased rate of cell division increases the probability of HBV DNA integration into the host chromosome, accelerated cell deaths allow less time for DNA repair, and the inflammation process itself generates oxygen reactive molecules that may be mutagenic (46;47). Seventy percent to 90% of HBV-related HCCs occur in the presence of cirrhosis (40). In Italy, among all cases of HBV-related HCC's seen at 14 hospitals from 1996 through 1997, 93% had underlying liver cirrhosis (50). Additional evidence for an indirect mechanism comes from studies that showed that HBV DNA is not integrated into the cellular DNA of all HBV-related tumors (51;52).

Evidence for a direct mechanism, that requires integration of HBV into the host chromosome, comes mainly from observations that some tumors arise in the absence of cirrhosis, and therefore in the absence of chronic necroinflammation of the liver (53). In the woodchuck animal model, HCC develops in the absence of cirrhosis among woodchucks infected at birth with the HBV-related woodchuck hepatitis virus (54).

Hepatitis C Virus (HCV)

After the molecular cloning of HCV in 1989, cross-sectional studies of non-HBV-related HCC patients found a high prevalence of anti-HCV antibodies in these patients compared to the general population (55-58). The geographic distribution of HCV-related HCC varies. The prevalence of anti-HCV antibodies among HCC cases is 80% in Japan, 60% to 80% in Southern Europe, 30% to 60% in the U.S, and 30% in China and South Africa (59;60). A meta-analysis of 32 case-control studies found the summary odds ratio for persons with HCC being positive for anti-HCV antibodies or HCV RNA was 11.5 (95% CI = 9.9-13.3) (61). Several prospective studies also found an increased risk for HCC among HCV positive patients compared to HCV negative controls (62-66). In a 2000 population-based study in Japan, among 3,052 persons over the age of 29 years tested at baseline for anti-HCV antibodies, and followed for five years, the relative risk for developing HCC was RR = 38.8 (95% CI = 11.4-131.6) for those that were positive for anti-HCV antibodies at baseline compared to those that were negative for these antibodies at baseline (64).

HCV is transmitted through blood and blood products. The most common modes of transmission include intravenous drug use and blood transfusion prior to 1990 (67). Other modes include organ transplantation, patient-to-patient transmission in hospitals, and tattooing (67;68). Sexual and perinatal transmission are less common modes in HCV than HBV (27). Before the molecular cloning of HCV, and the subsequent mandatory screening of blood and blood products in 1990, it is estimated that 16,000 Canadians were infected with HCV through blood and blood products (69). Eighty percent to 90% of persons with acute HCV infections develop chronic HCV infections (24;70). Twenty

percent of chronic HCV infections result in cirrhosis and the risk of HCC among persons with cirrhosis is 1% to 4% per year (70). Based on studies of transfusion associated HCC's, the time interval from infection to the development of HCC is roughly 10 to 30 years (55).

Except for rare cases (71), cirrhosis always precedes HCC development in HCV patients (72). This, in addition to a lack of evidence for the integration of HCV into the host chromosome, supports an indirect mechanism for HCV carcinogenesis through the induction of chronic necroinflammation of the liver (27;46;47;49;72).

Alcohol

In a review of 22 studies from 1982 through 1990 that evaluated the association between alcohol abuse and HCC, 14 studies found a positive association and 8 studies found no association (34). The dose effect relationship between alcohol intake and HCC was examined separately for men and women for the first time in a 2002 hospital-based case-control study (73). Accounting for age, HBV, and HCV infections, the authors found, for males the risk for HCC increased linearly with increasing alcohol intakes greater than 60 grams per day: 61-80 grams per day, OR = 2.4; 81-100 grams per day, OR=4.2; 101-120 grams per day, OR= 7.7; 121-140 grams per day, OR=9.8; and for alcohol intakes greater than 140 grams per day, OR=11.0 (73). Among females, the risk for HCC also increased with increasing alcohol intake greater than 60 grams per day: 61-80 grams per day, OR=3.1, and for alcohol intake greater than 80 grams per day, OR=16.5 (73). Because of the small numbers of female HCC cases and female controls with alcohol intakes greater than 60 grams per day, alcohol intakes greater than 80 grams per day were collapsed into a single category (73).

Two models for the involvement of alcohol in the development of HCC have been proposed: one, that alcohol acts indirectly by causing cirrhosis that results in chronic necroinflammation of the liver, and the other, that alcohol is directly carcinogenic (3). Currently there is little evidence that alcohol is directly carcinogenic in HCC (3). Experimentally, there is no animal model for alcohol induced HCC in the absence of cirrhosis, yet an animal model for alcohol induced cirrhosis has been described (3;74). Support for an indirect mechanism for alcohol in HCC comes from a 2001 Swedish prospective cohort study that compared HCC incidence among 186,395 patients hospitalized with either chronic viral hepatitis, alcoholism, cirrhosis or any combination of these conditions between 1965 and 1994 to HCC incidence in the general population (75). The relative risk for HCC with a diagnosis of alcoholism alone was RR=1.6 (95% CI = 1.4-1.8), for cirrhosis alone, RR=12.1 (95%CI = 10.2-14.2), and for alcoholism and cirrhosis, RR=7.9 (95% CI = 6.2-10.0). The increased risk for alcoholism alone was suggested to be caused by the presence of preclinical cirrhosis (75).

Cirrhosis

Cirrhosis from any cause increases the risk for HCC (3). But the magnitude of risk depends on the underlying cause of the cirrhosis (4;76). Cirrhosis that results from viral hepatitis carries a greater risk for HCC than alcohol-related cirrhosis (77). Among patients with cirrhosis caused by viral hepatitis, the risk for HCC may be greater for HCV- related compared to HBV- related cirrhosis (4). An Italian study found the 10-year and the 15-year cumulative incidences for HCC in patients with HBV-related cirrhosis was, 23% and 32% versus 24% and 56%, respectively, for HCV-related cirrhosis (78). Similarly, a Japanese study found the cumulative incidence for HBV-related cirrhosis

was 27% at 10 years and 27% at 15 years compared to 53% and 75% for HCV-related cirrhosis (79). But age is a risk factor for HCC and HBV infected patients are, on average, younger than HCV infected patients (4). In both of these studies the estimated 10-year and 15-year risks for HCC in the cirrhotic patients were not adjusted for age. The Italian study did not describe the separate age distributions of the HBV-infected and HCV-infected cirrhotic patients. In the Japanese study, the mean age of the HBV infected patients with cirrhosis was 43 years (range: 19 years-79 years) versus 55 years (range: 25 years – 84 years) in the HCV infected patients with cirrhosis.

Age

Worldwide, HCC incidence increases with age. HCC is rarely seen in patients less than 40 years (3;5;35). A 1991 literature review concluded the mean age of HCC patients in high incidence countries was significantly lower than in intermediate and low incidence countries (35). The different age distributions of HCC patients reflects the geographic variations in exposure to HCC risk factors (5). HCC's caused by HCV infection and alcohol occur, in general, one to two decades later than HBV-related HCC's (4).

Sex

HCC is more common among males than females (76). The higher risk in males is seen worldwide, and the male to female HCC ratio is greater in low compared to high incidence countries (20). In the U.S. the male to female ratio is 2.7 (5). Even accounting for the increased frequency of viral hepatitis and alcoholic cirrhosis in males, an increased risk for HCC persists among males compared to females (4). A factor

hypothesized to predispose males to HCC is higher levels of androgenic steroids (5). The results of a recent nested case-control study showed that among HBV carriers, the odds ratio for HCC was 2.1 (95% CI= 1.1-15.4) for males in the highest tertile of testosterone compared to males in the lowest tertile of testosterone (80) .

Aflatoxin B1

Aflatoxin B_1 is a mycotoxin that contaminates the food supply in certain areas of the world (3;81;82). It is produced by a fungus, *Aspergillis flavus*, that grows on improperly stored foods including corn, rice, and peanuts (3). Two major prospective cohort studies have examined the relationship between aflatoxin exposure and HCC incidence (83;84). Both studies found an increased risk for HCC in persons with detectable levels of the aflatoxin B_1 biomarker, aflatoxin B_1-N^7-guanine, in the urine compared to those without detectable levels of this aflatoxin biomarker in the urine. A nested case-control study in the Shanghai cohort suggested that HBV modifies the aflatoxin HCC relationship: after a 4 to 6 year follow-up period, among the subjects that were positive for the urinary aflatoxin biomarkers at baseline, the respective relative risks for developing HCC were RR=3.4 (95% CI=1.1-10.0) and RR=59.4 (95%CI=16.6-212.0) for persons negative for HBsAg at baseline and persons positive for HBsAg at baseline (83).

Hereditary Hemochromatosis

Hereditary hemochromatosis is a genetic disorder that causes the body to absorb and store abnormally high levels of iron (85). If untreated the excess iron will build up in organs such as the liver, pancreas, and heart (86;87). An accumulation of iron in these

organs will lead to organ damage (85-87). The prevalence of hereditary hemochromatosis is roughly 2 to 5 per 1000 population among persons of northern European origin (86). Hereditary hemochromatosis increases the risk for HCC mainly because it increases the risk for the development of cirrhosis (88). Almost all HCCs that occur in persons with hereditary hemochromatosis develop in the presence of cirrhosis (88). But rare cases of HCC developing in the absence of cirrhosis, among persons with hereditary hemochromatosis, have been reported (89). But these cases had evidence of some fibrosis in the liver (89).

Accounting for age and sex, survival among persons with hereditary hemochromatosis but without cirrhosis was found to be the same as survival in the general population (90;91). But among persons with hereditary hemochromatosis and cirrhosis, the relative risks for the development of HCC compared to the risk for the development of HCC in the general population was RR = 240 (95%CI = 138-390), accounting for age and sex (92). And the risk for death from HCC compared to the risk for death from HCC in the general population, among persons with hereditary hemochromatosis and cirrhosis, was RR = 219 (95% CI not shown for this estimate), accounting for age and sex (93).

Fortunately hereditary hemochromatosis is easily treated by phlebotomy, that is, the removal of blood (87). Maintenance of normal iron levels may require a person with hereditary hemochromatosis to give 500 milliliters of blood every three to four months, for the rest of their lives (87). If the treatment is started before organ damage occurs it will prevent future organ damage (caused by excess iron levels) from occurring (87).

Temporal trends in U.S. hereditary hemochromatosis hospitalization rates were described for the period from 1979 through 1997 using data from the National Hospitalization Discharge Survey (NHDS) (94). The NHDS is a population-based survey that estimates inpatient use of short-stay, non-federal hospitals in the U.S. (94). From 1979 through 1997 overall hereditary hemochromatosis-associated hospitalization rates increased slightly from 2.2 per 100,000 population in 1979-1982 to 3.0 per 100,000 in 1993-1997 (94). The increase may be due to an increased awareness of and increased testing for this disorder after 1995; the gene that carries the mutation for hereditary hemochromatosis was identified in 1996 (87;94). Rates of hereditary hemochromatosis-associated hospitalization are low relative to the prevalence of hereditary hemochromatosis in the population. The suggested causes for the low hospitalization rates include an infrequent need for hospitalization among persons with hereditary hemochromatosis and under-reporting or under-diagnosis of hereditary hemochromatosis by physicians (94).

C. Changing trends in HCC incidence and mortality

Several recent studies have found an increasing trend in HCC incidence in developed countries (generally regions of low and intermediate incidence) and a decreasing trend in HCC incidence in developing countries (generally regions of high incidence). An increasing trend occurred from the mid-1970's through the mid-1990's in European countries including, the U.K. (8), France (9;10), Portugal (11), and in Australia (13), Canada (17), and the U.S. (14-16). In contrast, in China, among both men and women HCC incidence decreased 22% and 21% respectively between 1972-73 and 1993-94 (95). Sixty percent to 90% of HCC diagnoses in China and are associated

with HBV infections (96). A decrease in HCC incidence between 1978 and 1992 occurred in other regions of Asia including, Singapore (-30%) and Bombay (-20%) (20). In Taiwan, the incidence of HCC among children decreased dramatically during the period from 1981-1986 through 1990-1994 (97). (HCC occurs in children in high incidence countries when HBV infections are acquired perinatally (97).) This decrease in HCC incidence that occurred in Taiwan was attributed to a nationwide HBV vaccination program for infants that started in 1984 (97). The HBV vaccine was licensed for use in 1982 and it is included in the national immunization programs of most Southeast Asian countries (98).

Among developed countries Japan is an exception because it is a region of high HCC incidence (6). Although the increasing trend in HCC incidence among developed countries (other than Japan) was first described in 1997 (8-14), such a trend was observed in Japan 10 years earlier (99). A 1987 report was the first evidence for a dramatic increase in the occurrence of HCC in Japan for the period from 1963 through 1983 (99). HCC incidence has continued to increase in Japan and today is almost 40 per 100,000 population per year (7). Approximately 80% of HCCs in Japan are etiologically associated with HCV (7). HCV transmission increased after World War II among those aged 15 to 25 years (6;7). Social conditions during this period were poor; intravenous methamphetamine use and remuneration of blood donors were major factors in its transmission among the young age groups (6;7). HCV spread to the general population by blood transfusions and tattooing (6;7).

In Canada, among current HCV cases with known risk factor information, 60% of those aged 15 to 44 years reported intravenous drug use between 1982 and 1985 and

90% of those older than 44 years reported a blood transfusion during this period (100). It is estimated that currently 192,000 persons have a chronic HCV infection in Canada (100). Up to 1990, an estimated 16,000 blood transfusion recipients were infected with HCV through blood or blood products (69). On average, the currently surviving Canadian cases of post-transfusion hepatitis C were infected 20 years ago (100).

III. Specific Aims

1. To describe the overall HCC incidence and mortality trends in Canada from 1976 through 2000, by sex.

2. To describe the age-specific HCC incidence and mortality trends in Canada, from 1976 through 2000, by sex and birth cohort.

3. To project HCC incidence rates in Canada from 2001 through 2015, by sex.

IV. Research Design and Methods

A. General Study Design

This project is a descriptive study of the overall trends in HCC incidence and mortality in Canada from 1976 through 2000, by sex, and of the age-specific trends in HCC incidence and mortality in Canada, from 1976 through 2000, by sex and birth cohort. All analyses are based on HCC incidence data from the Canadian Cancer Registry (101) and HCC mortality data from the Causes of Death publications from 1976 through 2000 (102) from the Vital Statistics and Disease Registries Section of the Health Division of Statistics Canada.

B. Methods

HCC cases and HCC deaths from 1976 through 2000.

HCC incidence data from 1976 through 2000 are from the Canadian Cancer Registry (CCR) (101). Since 1975 each province and territory in Canada has operated a cancer registry that attempts to identify all cases of cancer that occur among persons with a permanent residence in a given province or territory (101). Provincial and territorial cancer registries report to the CCR, on an annual basis, all incident cancer cases, by primary site of cancer occurrence (categorized by International Classification of Diseases, ninth revision (ICD-9) (33) for 1976 through 2000), diagnosis date, province or territory of residence, sex, birth date, and death date (101). The data sources for the provincial and territorial registries include: pathology reports, radiology reports, cytology reports, death certificates, autopsy reports, hospital discharge records, out-patient records, and cancer center treatment files (101). The percentage of all cancer cases in the CCR that were registered by death certificate only remained stable at 2% to 3% between 1974 and 1988 (101).

To comply with the confidentiality requirements of Statistics Canada's Statistics Act, the number of HCC cases for a given sex, age-group, and period of diagnosis were suppressed by the CCR if the number of cases was less than 4 cases. Therefore, from 1976 through 2000, if the number of HCC cases for a given sex, age-group, and year of diagnosis was suppressed the number of cases was assumed to be the average of 0, 1, 2, and 3 cases (ie. $(0 + 1 + 2 + 3) / 4 = 1.5$), that is 1.5 cases.

HCC mortality data from 1976 through 2000 are from the annual Cause of Death publications from the Vital Statistics and Disease Registries Section of the Health

Statistics Division of Statistics Canada (102). These publications are based on death registration data provided to Statistics Canada from Vital Statistics Registries in each province and territory (102). For each death in all provinces and territories the data recorded on the death certificate include: age at death, sex, marital status, place of residence and birth place, date of death, underlying cause of death (ICD-8 (32) from 1976-1978, ICD-9 from 1979-1999, and ICD-10 for 2000) and the province or territory of the occurrence of death (102).

HCC cases were identified by the ICD-9 code specific to primary liver cancer not including intrahepatic bile duct cancer (ICD-9 155.0). Deaths were identified by ICD-8 155.0, ICD-9 155.0, and ICD-10 C22.0. ICD-8 and ICD-9 155.0 include the rare childhood cancer, hepatoblastoma. Between 1973 and 1992, 124 children younger than 5 years of age were diagnosed with this cancer in the U.S. (103). Of these children, 75% were diagnosed at one year or younger (103). In contrast, HCC rarely occurs in children except in HBV endemic countries (3;5;35;97). It is unlikely that cases of hepatoblastoma were included in this study because data were only obtained for incident HCC cases and HCC deaths among persons 20 years of age or older. The ICD-10 code C22.0 is specific for HCC and does not include hepatoblastomas (104).

ICD-8 and ICD-9 155.0 also include a rare histologic type of HCC, fibrolamellar carcinoma, that may actually be a distinct liver cancer from HCC (105). Fibrolamellar carcinoma is equally likely to occur in men and women, and a higher proportion of fibrolamellar carcinomas occur in young persons compared to the proportion of HCCs that occur in young persons (105). But fibrolamellar carcinoma is very rare; in the U.S. its age-adjusted incidence was stable at 2 cases per 10,000,000 population from 1991-

1995 through 1996-2000 (105). The age-adjusted incidence of HCC (excluding fibrolamellar carcinoma) in the U.S. during the same period ranged from 220 cases to 300 cases per 10,000,000 population (15). Assuming the same proportion of HCCs in Canada and the U.S. are fibrolamellar carcinomas, (i.e. that less than 1% of the HCCs that occur each year are fibrolamellar carcinoma) and assuming that this proportion remained low and stable from 1976 through 2000 (in the U.S. this proportion ranged from 0.6% in 1984-86 to 0.9% in 1990-1992 (15;105)), the Canadian HCC trends that include and exclude fibrolamellar carcinoma are likely to be very similar.

HCC incidence and mortality rates

Annual age-specific HCC incidence and mortality rates are presented per 100,000 person-years for 11 age groups: a single group for persons aged 20-39, 9 consecutive 5-year age groups and a single group for persons aged 85 years or older (Appendices A-D). The denominators for the annual age-specific rates were the age-specific population estimates from 1976 through 2000 obtained from Statistics Canada's Data Liberation Project at the University of Calgary (106).

The period from 1976 through 2000 was divided into five five-year intervals: 1976-1980, 1981-1985, 1986-1990, 1991-1995, and 1996-2000. The census counts over the study period occurred in 1976, 1981, 1986, and 1996. Based on the results of post-censal coverage studies, Statistics Canada adjusts the census counts for estimated under coverage or duplicate coverage (107). The adjusted census counts are used to produce annual population estimates for non-census years (107). Annual estimates for non-census years contain the same types of errors as those for census years plus other errors that are related to the length of time since the reference census (106).

The number of person-years of observation for each five-year interval was estimated by the method described by Esteve and colleagues (108). For example, for the first five-year time interval, from January 1, 1976 to December 31, 1980, for the age group 50 to 54 years, the number of person-years of observation was estimated by summing the number of individuals aged 50 to 54 years in 1977, 1978, 1979, 1980 and the arithmetic average of the number of individuals in 1976 and 1981 (i.e. the number of individuals at the beginning of 1976 and the end of 1980) (108) . The estimated person-years contributed for each five-year interval by this method is more accurate than simply using five times the midpoint population estimate (108).

The age-adjusted rates were calculated by the method of direct standardization (108). The 1991 Canadian population was used for age-adjustment. The ninety-five percent confidence intervals for the age-adjusted rates were calculated using the t-distribution and the following formula (109):

Lower 95% CI = $e^{[\ln(Yi)-2.0*\sqrt{Vi})]}$

Upper 95% CI = $e^{[\ln(Yi)+(2.0*\sqrt{Vi})]}$

Where,

Y_i = the age-adjusted rate for a given time interval, i.

V_i = the estimated variance of the natural logarithm of an age-adjusted rates for a given time interval, i (in calendar years).

$V_i = [\sum_{(j=1 \text{ to } A)} c_j^2 \, z_{ij} / n^2_{ij}] / (\sum_{(j=1 \text{ to } A)} c_j \, z_{ij} / n_{ij})^2$

Where,

j = age-group (grouped from 1 to A, units = years)

c_j = age-specific age standard (1991 Canadian population)

z_i = cancer cases or cancer deaths for a given time interval (years) and age-group (years)

$n_{i\,j}$= population (person-years) for a given age-group and time interval (years).

Estimated annual percent change in the age-adjusted HCC incidence and mortality rates.

The annual percent changes in the age-adjusted incidence and mortality rates during the period of observation (1976 through 2000) were estimated. This was done by fitting a regression line to the natural logarithm of the annual age-adjusted rates for the period 1976 through 2000 (110). The calendar year of HCC diagnosis was the independent variable in this linear regression analysis (110). The linear regression equation for estimating the annual percent change in the age-adjusted HCC incidence rates from 1976 through 2000 was (110),

$$Y = \beta_0 + \beta_1 X + \varepsilon$$

Where, Y = ln (annual age-adjusted HCC incidence rates)

X = calendar year of HCC diagnosis

β_0 = a constant

ε = the variance in the ln (population age-adjusted HCC incidence rate) for a given calendar year of HCC diagnosis, X.; i.e. the error term.

Then, $(e^{\beta 1}-1)* 100$ was the annual percent change in the age-adjusted incidence rates (110).

A separate model was used to estimate the annual percent change in HCC mortality rates; the natural logarithm of the annual age-adjusted mortality rates from 1976 through 2000 were regressed against the calendar year of HCC death. And for both the

age-adjusted incidence rates and the age-adjusted mortality rates, the annual percent changes from 1976 through 2000 were estimated using separate models for males and females. Separate models were also used to estimate the annual percent changes in the age adjusted incidence and mortality rates for males and females aged 20-49, 50-64, 65-74, and 75 years and older. The linear regression coefficients were estimated by weighted least squares where the weights were proportional to the inverse of the variance of the natural logarithm of the age-adjusted rates (where the variance was equal to V_i (see preceding section for the formula for V_i)) (111).

The 95% confidence intervals for the estimated annual percent changes used the t-distribution and the following formula (111),

Lower 95% CI = $100\{\exp[\beta_1-(\text{standard error of } \beta_1)* \ t_{n-1}^{-1}, _{0.975}] -1\}$

Upper 95% CI = $100\{\exp[\beta_1+(\text{standard error of } \beta_1)* \ t_{n-1}^{-1}, _{0.975}] -1\}$

Where,

n = the total number of annual age-adjusted rates.

Joinpoint analysis of age-adjusted HCC incidence and mortality rates.

Estimating a single average annual percent change in age-adjusted HCC incidence (or mortality) rates for the period from 1976 through 2000 assumes that a constant rate of change in age-adjusted HCC incidence (or mortality) occurred during this period. Joinpoint regression analysis was used to evaluate this assumption (109). A joinpoint is defined as the estimated year of HCC diagnosis (or death), when there was a change in the rate of increase or decrease in the age-adjusted HCC incidence (or mortality) rates. Joinpoint regression analysis was used to test for a maximum of three joinpoints and a

minimum of zero joinpoints. The algorithm of hypothesis tests for the joinpoint regression analysis is described in Appendix E. Three hypotheses were tested to evaluate whether there were changes in the rate of change of HCC incidence (and mortality) rates for the period from 1976 through 2000. To account for the greater probability of detecting a joinpoint statistically (or detecting an additional joinpoint), when a true joinpoint (or a true additional joinpoint) did not exist (i.e. the probability of a type I error), the alpha levels for each of the three hypothesis tests was adjusted by the Bonferroni method (111). The alpha level for each hypothesis test was equal to 5% divided by three (i.e. 1.67%) and the overall probability of a type I error remained 5%.

At the 1.67% level of statistical significance there was little evidence against the null hypotheses of no joinpoint over the period of observation (1976 through 2000), (versus 3 joinpoints, versus 2 joinpoints , and versus 1 joinpoint, Appendix E) and therefore a constant rate of change from 1976 through 2000 was assumed for: overall female HCC incidence and mortality rates, overall male HCC incidence and mortality rates, age-adjusted HCC incidence rates for males 20-49 years, 50-64 years, 65-74 years and 75 years and older, and age-adjusted HCC incidence rates for females 20-49 year, 50-64 years, and 65-74 years. There was evidence, at the 1.67% level of statistical significance, against the null hypothesis of zero joinpoints versus one joinpoint for the HCC mortality rates among females aged 75 years and older (joinpoint at year of HCC death = 1987 (95% CI = 1984-1991). The annual percent changes were estimated separately for the period of death from 1976 through 1987 and for the period of death from 1987 through 2000 (Table 3).

In the previous study of trends in HCC incidence and mortality in Canada, ElSaadany stated that the joinpoint regression analysis of the trends in incidence and mortality rates from 1969 through 1997 suggested a change in the trends occurred in 1991 (17). But the ElSaadany study showed no evidence to support this statement (e.g. the rates of change for the 1969 through 1991 and 1991 through 1997 [or 1998 for mortality rates] were not shown) and instead a single average annual rate of change is shown for entire period of observation, for both the HCC incidence and the HCC mortality rates.

Birth-cohort analysis of HCC incidence and mortality trends.

Thirteen birth cohorts were constructed based on nine five-year age groups at diagnosis (or death) from 40-44 years through 80-84 years, and five five-year periods of diagnosis (or death) from 1976-1980 through 1996-2000. The birth cohorts were constructed using the formula:

Year of diagnosis (or death) – Age at diagnosis (or death) = Year of birth

The earliest year (or lower limit) of a given birth cohort was obtained by subtracting the oldest age at diagnosis (or death) in a given five-year age group from the and earliest year of diagnosis (or death) in a given five-year period of diagnosis (or death). The most recent year (or upper limit) of a given birth cohort was obtained by subtracting the youngest age at diagnosis (or death) in a given five-year age group from the most recent year of diagnosis (or death) in a given five-year period of diagnosis (or death) (112). Thirteen, overlapping, nine-year birth cohorts were constructed (Appendix

H). The overlap between adjacent birth-cohorts occurs because the data obtained from the Canadian Cancer registry was aggregated for age (into five-year groups) and for the period of diagnosis (or death) (into five-year groups). Consider the period of diagnosis 1976 through 1980 and the age-group 65-69. Persons aged 65-69 years when diagnosed in 1976 were born sometime from 1907 through 1911. Persons aged 65-69 years when diagnosed in 1980 were born sometime from 1911 through 1915. Therefore persons aged 65-69 years that were diagnosed in the period from 1976 through 1980 were born during the period from 1907 through 1915. Similarly, persons aged 70-74 years when diagnosed in 1980 were born sometime from 1906 through 1910 and persons aged 60-64 years when diagnosed in 1976 were born sometime from 1912 through 1916. As a result except for persons born in the middle year of the birth-cohort (e.g. 1911) persons in a given birth-cohort also contribute to the population at risk for HCC in an adjacent birth-cohort (22;112).

One method proposed to reduce the overlap in the population at risk for disease in adjacent birth-cohorts is to use smaller age-groups and shorter periods of diagnosis (or death) (e.g. two-year age-groups and two-year periods of diagnosis (or death))(113). But using smaller age groups and shorter intervals of HCC diagnosis would have resulted in greater suppression of data from the Canadian Cancer Registry (cells with less than 4 cases were suppressed).

Age-specific rates were compared graphically for successive birth cohorts to evaluate whether the lifetime risk for HCC changed between successive birth cohorts.

The magnitude of the risk for HCC associated with each birth cohort was evaluated using an age-cohort model (114). The age-cohort model assumes that there are

no period effects during the time period of observation (1976-1980), it assumes the underlying distribution of the incident HCC cases and HCC deaths are Poisson, and that the difference between the observed HCC rates and the HCC rates fitted by the age-cohort model (i.e. the residuals) are independent and identically distributed when plotted against the fitted HCC rates (114).

The age-cohort model was $\mu_{ij} = a_i * c_j$

Where, μ_{ij} = the incidence rate for the ith age category and the jth birth cohort.

a_i = the age-specific incidence (or mortality) rate for the ith age category

c_j = the cohort effect for the jth birth cohort.

The reference group for the cohort effects was the 1916 birth cohort. The 1916 birth cohort was the first birth cohort to have the maximum number of age-specific incidence rates for a given birth cohort among persons aged 40-44 through 80-84 at diagnosis (or death) from 1976-1980 through 1996-2000 (Appendix H). Given this reference group, the a_i estimates are the estimated age-specific incidence rates for the 1916 birth cohort (114).

Standardized residuals (chi-residuals) were calculated to assess the goodness-of-fit of the age-cohort models. The formula for the standardized chi-residuals (114) was,

$$S_{ij} = (C_{ij} - \hat{C}_{ij}) / \sqrt{\hat{C}_{ij}}$$

Where, S_{ij} = the chi-residual for the ith age-group and the jth birth-cohort

C_{ij} = the observed number of cases for the ith age-group the jth birth-cohort

$\hat{C}_{ij}$ = the expected number of cases for the ith age-group and the jth birth-cohort (this value was obtained by multiplying the expected rate for the ith age-group and the jth birth-cohort by the person-years of observation for the corresponding age-group and birth-cohort)

Projected HCC incidence rate for 2001-2005 through 2011-2015

To project beyond the 1952-1960 birth-cohort, the risk for HCC for the subsequent 3 birth-cohorts, 1957-1965, 1962-1970, and 1967-1975 was assumed to be the same as the 1952-1960 birth-cohort for males and the average of the risks for the 1947-1955 and 1952-1960 birth-cohorts for females. The projected incidence rates for a given age-group and a given birth-cohort were calculated based on the age-cohort model.

The projected counts for a given age group and birth cohort were obtained by multiplying the projected rate for the ith age-group and the jth birth cohort by the person-years of observation for the corresponding age-group and birth cohort. The person-years of observation for a given age-group and birth cohort for the period 2001-2015 were obtained from Statistics Canada's age-specific population estimates for the years 2001, 2002, 2003, 2004, 2005, 2006, 2011, and 2016 (115). The population estimates for the medium population growth scenario were used. The medium growth scenario assumes continuation of the current trends in population growth and life expectancy for 2001 through 2015 (115).

The age-specific population estimates for the years 2007 and 2008 were assumed to be the same as the year 2006, the estimates for years 2009, 2010, 2012, and 2013 were

assumed to be the same as the year 2011, and the estimates for the year 2014, and 2015 were assumed to be the same as the year 2016.

The projected cases were summed across birth cohorts for the three five-year periods 2001-2005, 2006-2010, and 2011-2015 to obtain the numerator for the projected age-specific rates for these time periods. The projected rates for these three time periods were age-adjusted to the 1991 Canadian population using the method of direct standardization (108).

Graphical presentation of the incidence and mortality trends.

To facilitate the comparison of HCC trends over time, the y-axis of the graphs are plotted on a logarithmic scale, and for all graphs, a 10-fold difference on the y-axis is the same length as a 40-year difference on the x-axis (116). Visually one can get a rough estimate of the rate of change of HCC incidence and mortality with these graphs because a slope of 10 degrees reflects a rate of change equal to one percent per year (116).

Statistical software

All statistical analyses, except the joinpoint regression were done using Stata Intercooled version 8. The joinpoint regression was done using the Joinpoint Regression Program available from the U.S. Surveillance Epidemiology and End Results Program website (111). All graphs were generated using Stata Intercooled version 8.

V. Results

A. Hepatocellular Carcinoma Incidence and Mortality Trends

During the period from January 1, 1976 through December 31, 2000 there were 13,993 reported cases of HCC and 8933 reported deaths from HCC among persons in Canada aged 20 years or older. Among females, there were 244.5 million person-years of observation and 4,077 incident cases and 2,686 deaths from HCC. Among males there were 234.7 million person-years of observation and 9,916 incident cases and 6,247 deaths from HCC.

There was an increasing trend in the incidence of HCC among males and females during this period (Figure 1) and for each year from 1976 though 2000 the age-adjusted incidence rate was higher among males compared to females. The highest age-adjusted incidence rate occurred in 2000 among males (5.8 per 100,000 person-years) (Appendix A) and in 1998 and 2000 among females (2.3 per 100,000 person-years) (Appendix B). For the period from 1976 through 1980 compared to the period from 1996 through 2000 the age-adjusted incidence rate rose 96% from 2.4 to 5.5 per 100,000 person-years among males and 43% from 1.4 to 2.0 per 100, 000 person-years among females (Table 1). Although the age adjusted incidence rates were higher among both males and females in 2000 relative to 1976, the average rate of increase in the age adjusted incidence rates from 1976 though 2000 was greater for males, 3.4% per year (95% CI = 3.1% to 3.8% per year) compared to females, 2.1% per year (95% CI = 1.5% to 2.8% per year)) (Table 1).

Similarly to the HCC incidence trends, the average annual rate of increase in HCC mortality from 1976 through 2000 was greater for males compared to females (Table 1).

In terms of a comparison of incidence versus mortality rates within the sexes, for females, despite an increasing trend in the age-adjusted incidence rates from 1976 through 2000, the age-adjusted mortality rates were roughly stable (Figure 1 and Table 1). The average rate of increase in HCC incidence among females was 2.1% per year (95% CI = 1.5% to 2.8% per year) compared to a rate of decrease in female HCC mortality of 0.36% per year (95% CI = 0.54% to 1.2% per year) (at the 5% level of statistical significance the 0.36% per year rate of change was not different from a rate of change equal to 0 (P=0.413)). As a result, there was a diverging trend for female incidence and mortality during the period of observation, from a 40% to a 100% lower age-adjusted mortality versus incidence rate for the period from 1976 through 1980 relative to the period from 1996 through 2000.

For males, the average annual rate of increase in age-adjusted incidence was approximately 2.5 times the average annual rate of increase of age-adjusted mortality, 3.4% per year (95% CI= 3.1% to 3.8% per year) compared to 1.4% per year (95% CI=0.68% to 2.2% per year) for the period 1976 through 2000 (Figure 1 and Table 1). As a result, male age-adjusted incidence and mortality also diverged from a 27% to an 83% lower mortality versus incidence rate for the period from 1976 through 1980 relative to the period 1996 through 2000.

Because the rate of increase in HCC incidence and mortality was greater for males compared to females during the period of observation (1976 through 2000), the trends for males and females were analyzed separately, and for the remainder of this paper they will be presented separately.

B. Incidence and mortality trends by age

Figure 2 shows the age-specific incidence of HCC among males and females for each five-year time period from 1976-1980 through 1996-2000. The five-year age-specific incidence rates among males show a roughly uniform proportional percentage increase in the incidence of HCC from the earliest (1976 through1980) compared to the most recent (1996 through 2000) period of diagnosis for all age groups. A similar trend occurred among females but the proportional percentage increases in age-specific incidence was smaller for females compared to males. Among females, one of the greatest increases in incidence between successive time periods occurred from the period 1991 through 1995 compared to the period from 1996 through 2000 among those aged 65-69 years and 70-74 years at diagnosis.

Age-specific HCC incidence rates for broader than five-year age groups are presented in Table 2. The broad age-specific rates were age-adjusted to account for changes over time in the age distribution of the Canadian population within these age categories. The greatest increase in HCC incidence occurred in both males and females aged 65-74 years. HCC incidence increased 51% from 4.3 (95% CI = 3.3-5.5) to 6.5 (95% CI = 5.5-7.6) per 100,000 person-years among females aged 65-74 years and 115% from 10.2 (95% CI = 8.6-12.2) to 21.9 (95% CI = 19.9-24.1) per 100,000 person-years among males in the same age-group from the period 1976 through 1980 compared to the period 1996 through 2000.

The average annual rate of increase from 1976 through 2000 was similar for males aged 20-49 years, 50-64 years and 65-74 years (range 3.3% per year (95% CI = 2.3% to 4.3% per year) to 3.7% per year (95%CI = 3.2% to 4.3% per year) (Table 2 and

Appendix F). The rate of increase for females aged 65-74 years was 2.8% per year (95% CI = 1.9% to 3.8% per year).

Age-specific mortality trends were also examined among males and females (Table 3 and Appendix G). Because of the small number of female deaths from HCC per year within each age group, the standard error for each estimated annual mortality rate was relatively large compared to the rates themselves, and as a result, the slope of each age-specific regression line (i.e. the estimated annual rate of change of the mortality rates for each age-group for the period from 1976 through 2000) was influenced by a large number of outliers relative to the total number of annual mortality rates within each age group. As a result, the estimated rates of change for the female age-specific mortality rates in Table 3 may not be valid approximations of the true rates of change for these age groups. But Figure 3 shows little change in the age-specific mortality rates from HCC among females for all five-year age groups from age 40-84 years during the period of observation (1976 through 2000).

Among males, for corresponding age groups, the proportional percent increase in HCC mortality was two-fold to three-fold lower than the proportional percent increase in HCC incidence during the period from 1976 through 1980 compared to the period from1996 through 2000 (Table 2 and Table 3). A slight increase in the rate of HCC mortality occurred from 1976 through 2000 among all male age groups: the rate of increase ranged from 1.0% per year (95% CI = 0.2% to 1.9% per year) among those 75 years or older to 1.6% per year (0.5% to 2.7% per year) among those 20-49 years. Figure 3 shows the age-specific mortality rates from HCC did not increase among males aged 55-70 years from 1986-1990 through 1996-2000.

C. Incidence and mortality trends by birth cohort

The age-specific incidence and mortality trends by year of birth are presented for males and females in Figure 4. The rates vertically above a given year of birth are the age-specific risks for HCC for persons born in that year. Corresponding age-specific rates can be compared for successive birth cohorts to evaluate whether the age-specific risks for HCC changed from one birth cohort to the next. If the age-specific risks for HCC did not differ between successive birth cohorts, on a semi-logorithmic graph (ie. Figure 4) the corresponding age-specific risks between the birth cohorts would be linked by horizontal lines, resulting in a graph with a series of age-specific parallel lines representing age-specific rates.

Among males, the age-specific incidence rates increased from the 1896 birth-cohort through the 1956 birth-cohort. There was a striking acceleration in the age-specific incidence of HCC among males born from 1941 through 1956 compared to the rate of increase of the age-specific rates among males born from 1896 through 1941. Among females, there was an increasing trend in age-specific incidence rates from the 1896 through the 1931 birth cohorts. The female age-specific rates were roughly stable from the 1931 birth cohort through the 1951 birth cohort. The age-specific trend among females diagnosed at age 40-44 years was influenced by relatively large standard errors for each birth-cohort-specific rate. Therefore, the rapid increase in the incidence rate from the 1951 birth cohort through the 1956 birth cohort only suggests that an acceleration in HCC incidence rates occurred between these two birth cohorts.

In terms of HCC mortality trends by birth cohort, among males, age-specific mortality rates increased from the 1896 through the 1931 birth cohorts. And despite an

increasing trend in age-specific incidence from the 1896 through the 1956 birth cohorts, male age-specific mortality rates were stable from the 1931 birth cohort through the 1946 birth cohort. Age-specific mortality rates increased among those born in the more recent birth cohorts (1951 and 1956) compared to those born from 1931 through 1946.

Among females, age-specific mortality rates were roughly stable from the 1896 birth-cohort through to around the 1936 birth cohort. There was a sharp decline in age-specific HCC mortality rates among females born from 1936 through 1946. The mortality rates in the more recent female birth cohorts suggest that an acceleration in age-specific mortality occurred among those born from 1946 through 1951.

D. Age-cohort model

The HCC cases and HCC deaths from 1976 through 2000 were fit (separately for males and females) with Poisson regression models that considered the effects of age and cohort of birth. The age-cohort models compared the risk for HCC for birth-cohorts from 1892-1900 through 1952-1960 relative to the 1912-1920 birth-cohort, accounting for age (5-year group) (114). Appendix I shows the results of the age-cohort model of the incident HCC cases from 1976-1980 through 1996-2000 for males and females. The results of the age-cohort model show the estimated birth-cohort relative incidence rates for HCC (relative to the 1912-1920 birth-cohort) and the estimated age-specific incidence rates for the 1912-1920 birth-cohort, by sex.

If the age-cohort models were true (ie. if the age and cohort effects explained the variance in the incidence and mortality rates from 1976 through 2000, by sex) then the standardized residuals (chi-residuals) from the age-cohort models would be approximately normally distributed with a mean equal to zero and a standard deviation

equal 0.90 (ie. standard deviation = √[(A-1) (C-1)/(AC), where A is the degrees of freedom for the age-groups (8) and C is the degrees of freedom (4) for the birth-cohorts (114)). The degrees of freedom for the birth cohort are not the number of birth-cohorts minus 1 because there are not values for all age-groups and all birth-cohort from 1976-2000. There are age-specific and birth-cohort specific rates for each of the 5 time period from 1976-1980 through 1996-2000. There are 45 standardized residuals per model, one for each possible age-group and birth-cohort combination for the period from 1976 through 2000. A residual value was considered to be an extreme residual if it was greater than or less than two standard deviations from the mean.

The means of the standardized residuals for the incidence and mortality models, for males and females were approximately zero. Assuming the standard deviation of the standardized residuals was equal to 0.90, an extreme residual was greater than 1.8 (i.e. 2*0.90) or less than -1.8. For the incidence data, among males and females, the standardized residuals are approximately evenly distributed at all levels of the fitted number of cases (Appendix J.A.), they are approximately normally distributed, but may have slightly heavier than normal tails (Appendix K.A.), and none fell outside of the expected extreme values (i.e. -1.8 to 1.8).

For the mortality data among males, there were 3 standardized residuals greater than 1.8 and 3 standardized residuals less than 1.8 (Appendix J.B.). The standardized residuals for the male deaths show a systematic pattern with less variance at lower values of the fitted number of HCC deaths and greater variance at higher values of the fitted number of HCC deaths. For the mortality data among females, there were 3 standardized residuals greater than 1.8 and 4 standardized residuals less than 1.8. The standardized

residuals for the female deaths do not showed a systematic pattern in the variance at different levels of the fitted numbers of HCC deaths. The distribution of the male and female standardized residuals for the mortality data shows more deviance from normality than the incidence data, but the distributions can be considered to be approximately normal (Appendix K.B.).

Table 4 and Table 5 show the observed and fitted incidence rates and incident HCC cases for males and females. Appendix L.A. shows a plot of the observed versus the fitted number of incident HCC cases for a given 5-year age-group and 5-year period of diagnosis among males and females aged 40-84 in Canada from 1976-1980 through 1996-2000. Not surprisingly, given the characteristics of the standardized residuals for the incidence data, the magnitude of the difference between the observed and expected HCC cases is small. Therefore, the variance in the incidence rates among males and females from 1976-1980 through 1996-2000 is explained well by age and birth-cohort effects.

Figure 5 compares the magnitude of the birth-cohort effects for males and females diagnosed from 1976-1980 through 1996-2000, accounting for age. There was an increasing trend in the risk for HCC with successive birth-cohorts from 1896 through 1931 among both males and females relative to the 1916 birth-cohort. The increasing trend in HCC risk continued for males through 1941 and then the risk for HCC accelerated: there was sharp increase in HCC risk with each successive birth-cohort from 1941 through 1956. In contrast, among females the risk for HCC was stable from 1931 through 1951, and then from the 1951 through the 1956 birth-cohort there is a suggestion of a sharp increase in the risk for HCC.

The characteristics of the standardized residuals for the mortality data provide evidence that the age-cohort model is as good a fit for the mortality data, among males and females, compared to the fit for the incidence data. Appendix M and Appendix N show the observed and fitted mortality rates and the number of HCC deaths for males and females. Appendix L.B. shows a plot of the observed versus the fitted number of HCC deaths for a given 5-year age-group and 5-year period of diagnosis among males and females aged 40-84 in Canada from 1976-1980 through 1996-2000. These tables show that there is a greater magnitude of difference between the observed and fitted HCC deaths compared to the incidence data. Therefore, the variance in the mortality data among males and females from 1976-1980 through 1996-2000 is only partly explained by the age and birth-cohort effects during this time period.

E. Projected incidence rates and projected number of HCC cases from 2001-2005 through 2011-2015.

Appendix O and Appendix P show the projected age-specific HCC incidence rates among males (Appendix O) and females (Appendix P) for the 1961, 1966, and 1971 birth-cohorts based on the age-cohort models of male and female incident HCC cases from 1976-1980 through 1996-2000. Among males the risk for HCC for the 1961, 1966, and 1971 birth cohorts was assumed to be the same as the risk for HCC in the 1956 birth cohort (RR = 5.29), and among females the risk for these birth-cohorts was assumed to be the average of the 1951 (RR = 2.00) and 1956 birth-cohorts (RR = 2.66), that is RR = 2.33.

The projected age-adjusted incidence rates for males and females aged 40-84 years in Canada from 2001-2005 through 2011-2015 are shown in Table 6 and Figure 6.

Among males, assuming the risk for HCC in the three birth-cohorts after the 1956 birth-cohort is the same as the risk for HCC in the 1956 birth-cohort, age-adjusted HCC incidence rates will increase 74% from 10.1 (95% CI = 8.1-12.6) to 17.6 (95% CI = 14.1-22.0) per 100,000 person-years from 1996-2000 through 2011-2015. Overall, among males, this projection shows a 245% increased in age-adjusted HCC incidence rates from 1976-1980 through 2011-2015. Given the assumptions for this projection, the number of HCC cases is projected to increase by approximately 2000 cases from 5641 HCC cases in the five-year period from 2006-2010 to 7672 HCC cases in the subsequent five-year period from 2011-2015. This striking increase in the projected number of HCC cases during the period from 2006-2010 relative to the period from 2011-2015 reflects, in part, the combined influences of an aging Canadian population and a strong positive relation between age and the risk for HCC.

Among females, assuming the risk for HCC in the three birth-cohorts after the 1956 birth-cohort is the same as the average of the risks for HCC in the 1951 and 1956 birth-cohorts, age-adjusted HCC incidence rates will increase 29% from 3.4 (95% CI = 2.7-4.2) to 4.4 (95% CI = 3.5-5.5) per 100,000 person-years from 1996-2000 through 2011-2015. Overall, among females, this projection shows a 100% increase in age-adjusted HCC incidence rates from 1976-1980 through 2011-2015.

VI. Discussion

From 1976 through 2000 there was an increasing trend in overall HCC incidence among males and females in Canada. But the increase in HCC incidence was 1.6 times faster in males compared to females during this period (1976 through 2000). There was an increasing trend in overall mortality from HCC among males but the trend was stable

among females from 1976 through 2000. Within each sex a roughly uniform increase in the age-specific risk for HCC occurred from 1976 through 2000, but a slightly greater increase occurred in the 65-74 year age group relative to the other age groups. Assuming the trend in the age-adjusted risk for HCC is stable from the 1956 through the 1971 birth-cohorts, age-adjusted HCC incidence in Canada is projected to continue increasing from 2001-2005 through 2011-2015.

ElSaadany and colleagues also evaluated HCC incidence in Canada from 1967 through 1997 and HCC mortality in Canada from 1967 through 1998 (17). And similarly to the results from the study by ElSaadany and colleagues (17), the results from this study show an increasing trend in age-adjusted HCC incidence in Canada from 1976 through 1997. Both studies also show that age-adjusted HCC mortality increased among males during this period but remained stable among females. The data from 1998, 1999, and 2000 (that were not included in the HCC incidence estimates in the study by ElSaadany (17)) show a continued increasing trend in age-adjusted HCC incidence among males and females. And the data from 1999 and 2000 (that were not included in the HCC mortality estimates in the study by ElSaadany (17)) show a continued increasing trend in age-adjusted HCC mortality among males and a continued stable trend in age-adjusted HCC mortality among females.

The annual numbers of HCC cases in Canada from 1976 through 1997 that were observed in the present study are similar in the annual numbers of HCC cases in Canada that were observed by ElSaadany for the same period (1976 through 1997) (the annual number of HCC cases that were observed in the study by ElSaadany (17) are presented using a bar chart with a range from zero to 700 cases and therefore the exact number of

HCC cases are difficult to determine but they can be easily approximated from this chart). As well, the annual numbers of deaths from HCC in Canada from 1976 through 1998 are similar in the current study compared to the study by ElSaadany (17). Both studies obtained the annual number of HCC cases from the Canadian Cancer Registry and both studies obtained the annual number of HCC deaths from the Vital Statistics and Disease Registries Section of the Health Division of Statistics Canada. Both studies also identified HCC cases and HCC deaths using the ICD-9 code 155.0 (or ICD code equivalent to ICD-9 155.0) (17). Despite similar numbers of annual HCC cases and annual HCC deaths in these two studies, both studies used different, but overlapping, populations at risk for HCC. The current study only considered persons 20 years of age and older to be at risk for the development of HCC and the ElSaadany study considered persons aged zero years and older to be at risk for the development of HCC (17). As a result the annual age-adjusted HCC incidence rates and mortality rates are different in the current study compared to the ElSaadany study (both studies used the 1991 Canadian population and the method of direct standardization to calculate the age-adjusted rates). The age-adjusted rates in the study by ElSaadany are lower compared to the current study (e.g. age-adjusted male HCC incidence in Canada for 1997 was 4.5 per 100,000 males in the ElSaadany study compared to 5.6 per 100,000 males in the current study (Appendix A)). This occurred because the numbers of HCC cases and HCC deaths among persons less than 20 years of age are so low, (as shown by similar numbers of HCC cases and HCC deaths among persons zero years and older compared to persons 20 years and older), so the only difference in the calculation of the annual age-adjusted rates between the two studies was the size of the overall denominator (i.e. the population at risk for

HCC). The current study had a smaller overall denominator compared to the study by ElSaadany. It is probable that the current study provides better estimates of the true (age-adjusted) annual risks for the development of HCC and for death from HCC because persons under 20 years of age in Canada are likely not at risk for the development of HCC. In Canada in 2000, among persons 0-14 years of age, the incidence of HBV and HCV was less than 1 case per 100,000 population (117) and the time period from HBV or HCV infection to the development of HCC is often more than one decade (34).

Another problem with considering persons less than 20 years of age to be at risk for the development of HCC is that the rare childhood cancer, hepatoblastoma, is also coded by the ICD-9 code 155.0. Theoretically, the risk estimates presented in the ElSaadany study are a mixture of the risk for hepatoblastoma and for HCC. While the impact of including hepatoblastoma cases is probably minimal, the risk estimates in the current study are less likely to include hepatoblastoma cases because children were excluded from the analysis.

Among males, the greatest increase in HCC incidence from 1976 through 2000 occurred among those aged 20-49 years, 50-64 years and 65-74 years and the smallest increase occurred among those aged 75 years or older. Among females the greatest increase in HCC incidence occurred among those aged 50-64 years and the smallest increase occurred among those aged 20-49 years and 75 years or older. Temporal trends in age-specific HCC incidence and mortality in Canada were not described in the ElSaadany study (17) and have not been described in any previously published paper. The trends in the age-specific risks for HCC in Canada from 1976 through 2000 are roughly similar to those observed in the U.S. during a similar time period. In the U.S.,

from 1981-1985 through 1991-1995 among both males and females aged 20 years and older, the greatest increased in HCC incidence occurred in those aged 40-79 years (14). Comparing similar time periods in France, among males aged 30 years and older, the greatest increase in HCC incidence occurred in those aged 55-74 years and there was no increase in HCC incidence among females (10).

There is a consistent finding among published studies (including the previous Canadian study by ElSaadany (17)) that examined recent trends in HCC incidence: in a given population the rate of increase in HCC incidence is greater for males compared to females (8;10;13-15;17). In this study the annual rate of increase in HCC incidence from 1976 through 2000 was 62% greater among males in Canada compared to females in Canada, 3.4% per year (95% CI = 3.1%-3.8% per year) versus 2.1% per year (95% CI = 1.5%-2.8% per year), respectively.

The study by ElSaadany found the annual rate of increase in HCC incidence from 1969 through 1997 was 183% greater among males compared to females, 3.4% per year versus 1.2% per year (17). But these rates of can not be compared to the rates of change reported in the current study because in each study the average annual rates of change were estimated for different time periods:1969 through 1997 in the ElSaadany study (17) and 1976 through 2000 in the current study. The method currently used to detect HCC, serum alpha-fetoprotein and ultrasonography, started to be routinely used for the detection of HCC in the late 1970s (20) or early 1980s (9;14). The current study provides an estimate of the rate of change during a period when a uniform method for HCC detection was used and the ElSaadany study provides an estimate of the rate of change during a period when the detection method for HCC changed. But a comparison of the

rate of change between males and females in the ElSaadany study is valid and this comparison shows that HCC incidence increased more rapidly among males compared to females during the period from 1969 through 1997.

It remains unclear why HCC incidence has increased more rapidly among males compared to females in recent decades in Canada and other developed countries. But data from Canada show the risk for HBV infections increased more rapidly in males compared to females from 1980 through 1990 (118) and the risk of death from non-A non-B hepatitis (considered a proxy for the risk of death from HCV (119)) also increased more rapidly in males compared to females during this period (119).

The disparity between HCC incidence and mortality increased more rapidly during the period of observation (from 1976 through 2000) among females in Canada compared to males in Canada. The proportional percent difference between HCC incidence and mortality among females increased from a 40% difference in 1976-1980 to a 100% difference in 1996-2000, compared to an increase among males from a 27% difference in 1976-1980 to a 45% difference in 1996-2000. In other words, survival from HCC likely increased in both males and females in Canada from 1976 through 2000 and the increase was likely greater for females compared to males. Data from the U.S. Surveillance and Epidemiology and End Results program (SEER) show an increase in short-term relative survival from HCC from 1976 through 2000 in the U.S., and little change in relative survival beyond five years (120). From 1975-1979 compared to 1992-1996 one-year relative survival from HCC increased from 14% to 23%, three-year relative survival increased from 5% to 9% and five-year relative survival increased only slightly from 4% to 7% (120). Survival from HCC was only slightly greater among

females compared to males in the U.S., for example, among those diagnosed from 1992-1996, the relative probabilities of surviving beyond one-year, three-years and five-years for females compared to males were, 26% versus 22%, 10% versus 9% and 7% versus 6%, respectively (120).

Better survival from HCC among females compared to males was observed in countries other than the U.S. including China, Japan and Thailand (121). A study in Thailand of 260 male and 39 female HCC patients showed the median survival time among the male and female patients was 4 months and 14 months respectively. The female patients were more likely to have a less advanced stage and were less likely to have hepatic or portal venous invasion at the time of the initial diagnosis compared to the male patients (121).

To date, two other studies have considered the influence of birth cohorts on HCC incidence trends and presented these results in published papers. Based on U.S. data from 1973 through 1995, age-specific incidence rates for HCC were compared graphically for birth cohorts from 1888 through 1958 for persons aged 40-44 years through 80-84 years. (The age-specific rates among persons less then 40 years of age were also plotted by birth cohort, but the rates were low (less than 0.2 per 100,000 population) and were considered unstable.) From the 1888 through the 1958 birth cohorts the age-specific risk for HCC increased in successive birth cohorts. This analysis was not stratified by sex.

Based on data from France from 1976-1979 through 1992-1995, and accounting simultaneously for the influence of age, period of diagnosis, and birth-cohort, the lifetime risk for HCC was 0.82% in the 1906 birth-cohort, 1.1% in the 1916 birth-cohort, 1.4% in

the 1926 birth-cohort and 2.1% in the 1936 birth-cohort (10). This analysis was not stratified by sex.

Because of the relation between birth-cohort, age at diagnosis, and period of diagnosis (i.e. any two of these variables perfectly predict the third variable), a single model that simultaneously accounts for these three factors can not estimate the effects for all three of these variables. To avoid this problem a constraint may be applied to an age-period-cohort model, but the model under this constraint does not provide a unique set of estimates for the effect of age, period, and cohort of birth, that is, an infinite number of estimates for these parameters are possible under this constraint (122). The incidence of HCC in Canada from 1976 through 2000 was fit well by an age-cohort model and thus, in this study, the problem of using regression analysis to model the effect of three factors (age, period of diagnosis, and birth-cohort) that are linearly dependent (i.e. any two of these factors perfectly predict the third) (114;123) was avoided.

This study is the first to show the influence of birth-cohort on HCC incidence trends in Canada. Among males aged 40-84 years from 1976-1980 through 1996-2000, the risk for HCC increased in successive birth-cohorts from 1886 through 1956 relative to the risk for HCC in the 1916 birth-cohort. There was a striking increase in the relative risk for HCC among males born from 1941 through 1956 compared to the increase in the relative risk for HCC among males born from 1896 through 1941. In contrast, among females, the relative risk for HCC from the 1931 through the 1951 birth-cohort was stable compared to the increase in the relative risk for HCC that occurred from the 1896 through the 1931 birth-cohort. Among males and females aged 40-84 years in Canada from 1976 through 2000, the greatest risk for HCC (relative to the risk for HCC in the 1916 birth-

cohort) occurred among those born in the most recent birth-cohort (1956). Accounting for age, the relative risk for HCC (the 1916 birth-cohort was the reference group) in the 1956 birth-cohort was RR = 5.3 (95% CI = 4.7-6.0) among males, and RR = 2.7 (95% CI = 2.1-3.3) among females.

The variance in the HCC mortality rates from 1976 through 2000 was not explained as well as the variance in the HCC incidence rates by age and birth-cohort factors. But Appendices M and N show that nonetheless HCC deaths for a given age-group and birth-cohort are predicted reasonably well by the age-cohort model. Because it is plausible that an increase in short-term HCC survival occurred during the period of observation (1976 through 2000), the variance in the mortality rates may have been influence by period effects (for example, a period effect may occur if there is an improvement in HCC treatment that decreases the risk for death from HCC among all age-groups in a given time period) in addition to age and birth-cohort effects. On the other hand if the improvement in HCC treatment had a different effect on different age-groups, the trends in the risk of death from HCC may still be explained well by an age-cohort model.

Interpretations of the trends in HCC mortality in Canada from 1976 through 2000, based on the results from this study, require some caution because of the source of the mortality data. The HCC mortality data is from the underlying cause of death reported on death certificates. Liver cancer is particular susceptible to misclassification on death certificates because it is a secondary site for several cancers including those of the colon, rectum, pancreas, lung, and breast (124). Among all HCC deaths in the U.S. SEER registry from 1973 through 1985, compared to the original diagnosis in the patient's

medical records or to the pathology reports, liver cancer was incorrectly reported as the underlying cause of death on the death certificates of 507 of the 2,977 (17%) deaths (124). All 507 deaths that were misclassified as deaths from HCC (reported as the underlying causes of death on the death certificates) had a primary site for cancer (based on the hospital records) that was not the liver (124). But death from HCC may also be underestimated based on the underlying cause of death on death certificates. Among all 3,220 deaths from liver cancer in the U.S. SEER registry, from 1973 through 1985, that were not specified as primary HCC or secondary HCC (ICD-8: 197.8 or ICD-9: 155.2), 1,185 (37%) had an HCC diagnosis based on the patient's medical records or the hospital pathology reports (124). Thus misclassification of cause of death may have obscured the underlying trends in HCC mortality.

The incidence of HCC in Canada is projected from 2001-2005 through 2011-2015. The projection assumes that relative to the 1916 birth-cohort, the risk for HCC that occurred in the most recent birth-cohort (1956) among males aged 40-84 years at diagnosis from 1976-1980 through 1996-2000 is the peak relative risk for HCC for all birth-cohorts for males aged 40-84 years at diagnosis for the period from 1976-1980 through 2011-2015. Among females, the projection assumes that relative to the 1916 birth-cohort, the average of the risks for the two most recent birth-cohorts (1951 and 1956), among those aged 40-84 years at diagnosis from 1976-1980 through 1996-2000, is the peak relative risk for HCC for all birth-cohorts for females aged 40-84 years at diagnosis for the period from 1976-1980 through 2011-2015.

The projections show a nearly 4-fold increase in the age-adjusted risk for HCC among males aged 40-84 years from 1976-1980 through 2011-2015, 5.1 (95% CI = 4.1-

6.4) compared to 17.6 (95% CI = 14.1-22.0) cases per 100,000 person-years, and a nearly doubling of the risk from1996-2000 through 2011-2015. Among females the projections show a doubling of the age-adjusted risk for HCC from 1976-1980 through 2011-2015, from 2.2 (95% CI = 1.8-2.8) to 4.4 (95% CI = 3.5-5.5) cases per 100,000 person-years, and a 1.3 fold increased risk from 1996-2000 through 2011-2015.

The age-adjusted incidence of HBV in Canada increased five-fold from 1980 through 1995 (125). This increasing trend changed after 1995. From 1995 through 2000 the age-adjusted risk for HBV infection decreased 2.5-fold from 10 to 4 cases per 100,000 population (126). Starting in the early 1990's provinces and territories in Canada began to include the HBV vaccine as part of the publicly funded childhood immunization programs (127). And in 2004, all provinces and territories included HBV as part of their publicly funded childhood immunization programs (128).

There was little change in the age-adjusted mortality rates from non-A, non-B hepatitis in Canada from 1980 through 1990, the rates ranged from 0.09 in 1990 to 0.17 in 1987 (129). But from 1990 through 1998 age-adjusted mortality rates from non-A, non-B hepatitis increased nearly four fold from 0.12 to 0.55 cases per 100,000 population (130). In the early 1990's there was a rapid increase in age-adjusted HCV incidence rates in Canada (131). This increase in HCV incidence was influenced by widespread use of a new method for detecting HCV in the population. But only considering the period from 1995 through 1999 the age-adjusted incidence of HCV infection increased from 47 to 61 cases per 100,000 population (132). There is currently no vaccine for HCV (24).

If HBV vaccinations in Canada cause a decreasing trend in HBV incidence for the period from 2001 through 2015, and if the increasing risk for HCC in more recent

compared to earlier birth-cohorts was driven by HBV trends over the last two decades, the HCC incidence projections for 2001-2005 through 2011-2015 may overestimate HCC incidence because the projection was based the risk for HCC in the most recent birth-cohorts.

On the other hand, if the risk for HCC observed in the most recent birth-cohorts were driven by HCV trends over the last two decades, the projections may be conservative because the risks for HCC in the 1961, 1966, and 1971 birth cohorts (the projection birth-cohorts) may be greater than the risk in the1956 birth-cohort (the most recent birth-cohort observed in the current study). There was an increase in HCV incidence in Canada among persons less than 40 years of age from the mid-1990s to the late 1990s compared to the early 1990s to mid 1990s (133). Persons aged less than 40 years in the period from 1996 through 2000 were not included in the calculation of the HCC risk estimates for the most recent birth-cohort but these persons are part of the projection birth cohorts.

It is also possible that the increasing risk for HCC in earlier birth-cohorts was driven by an increasing risk for HBV in these earlier birth-cohorts and that the increasing risk for HCC in more recent birth-cohorts (and maybe future) birth-cohorts was (or will be) driven by an increased risk for HCV in these birth-cohorts.

Health care providers and allocators of health care resources need to be aware of the projected increasing burden of HCC in Canada because HCC patients may be eligible for treatment with anti-cancer therapies, they may develop complications (such as ascites [excessive fluid in the peritoneal cavity] and encephalopathy) that require hospitalization

(134), and assuming current treatment options they will likely require palliative care at the end stages of the disease.

VII. Future Research

The cause of the increasing trend in HCC incidence in developed countries is not known. A plausible explanation is that the increase was caused by an increase in the incidence of HBV and HCV infections that occurred over the last three decades in many developed countries. A U.S. study showed that the proportion of HCC patients referred to the University of Texas M.D. Anderson Cancer Center that were positive for anti-HCV antibodies increased from 18% to 31% from 1993 through 1995 compared to from 1996 through 1998 (135). The proportion of patients with HBsAg-associated HCC decreased from 26% to 17% from 1993 through 1995 compared to from 1996 through 1998, and the proportion of patients with neither viral marker remained stable during this period. Population-based studies of HCC trends stratified by the presence of the underlying risk factor(s) are needed to evaluate the cause of the increasing HCC trends. It is likely that this type of study has not been done to date because of the difficulty in obtaining individual level risk factor information for persons diagnosed in the past with HCC because most HCC patients have died.

Another possible reason for the increasing trend in HCC incidence in developed countries is the concurrent increase in immigration from Southeast Asian countries that occurred in many developed countries. In Canada, the annual proportion of immigrants from Asia increased from 20% in 1970 to 60% in 2000 (136). Examining temporal HCC incidence trends by country of birth is an important topic for future research because the results of such an analysis are needed for the evaluation of whether or not HCC

prevention efforts should be targeted toward immigrants. A recent study from a single hospital in the U.S. found the percentage of patients diagnosed with HCC that were immigrants decreased from 46% (19/41) in 1992 through 1996 to 24% (17/70) from 1997 through 2001 (137). To date, no study of a temporal trend in the proportion of HCC cases in Canada that are immigrants is published.

VIII. Summary

Using data from the Canadian Cancer Registry and from the Vital Statistics and Disease Registries Section of the Health Statistics Division of Statistics Canada HCC incidence and mortality rates were calculated by age and sex for the period from 1976 through 2000. Among males the age-adjusted incidence of HCC increased 3.4% per year from 2.8 to 5.5 cases per 100,000 person-years and age-adjusted mortality increased 1.4% per year from 2.2 to 3.0 deaths per 100,000 person-years from 1976 through 1980 relative to 1996 through 2000. Among females the age-adjusted incidence of HCC increased 2.1% per year from 1.4 to 2.0 cases per 100,000 person-years and age-adjusted mortality was stable at 1.0 death per 100,000 person-years from 1976 through 1980 relative to 1996 through 2000. The increase in HCC incidence was similar for all age groups within each sex. The risk for HCC increased in successive birth-cohorts from 1896 through 1956 relative to the 1916 birth-cohort. Among males born in the 1956 birth-cohort the risk for HCC was 5.3 (95% CI = 4.7-6.0) times the risk for HCC among males born in the 1916 birth-cohort. Among females born in the 1956 birth-cohort the risk for HCC was 2.7 (95% CI = 2.1-3.3) times the risk for HCC among females born in the 1916 birth-cohort. Based on an age-cohort model, and assuming no further increase in the risk for HCC in the three birth cohorts after the 1956 birth cohort, the age-adjusted incidence of HCC

among males aged 40-84 years is projected to increase 74% from 10.1 to 17.6 cases per 100,000 persons-years from 1996 through 2000 relative to 2011 through 2015. And among females aged 40-84 years, the age-adjusted incidence of HCC is projected to increase 29% from 3.4 to 4.4 cases per 100,000 person-years from 1996 through 2000 relative to 2011 through 2015. Future descriptive studies of temporal HCC trends in Canada should examine whether the proportion of HCC cases that are immigrants has changed over the period of observation.

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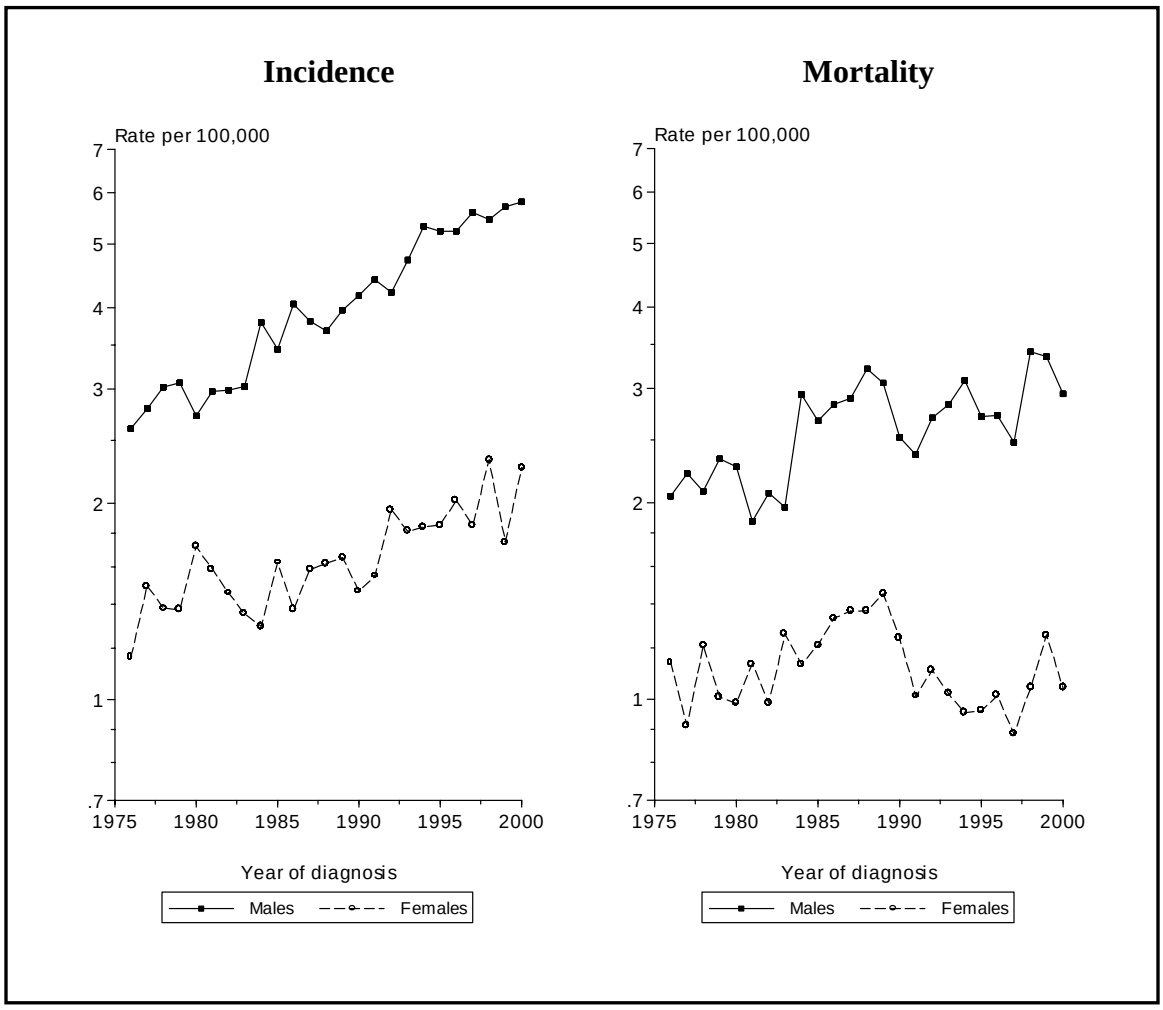


Figure 1. Age-adjusted (to the 1991 Canadian Population) hepatocellular carcinoma incidence and mortality among persons aged 20 years or older in Canada, by sex, from 1976 through 2000.

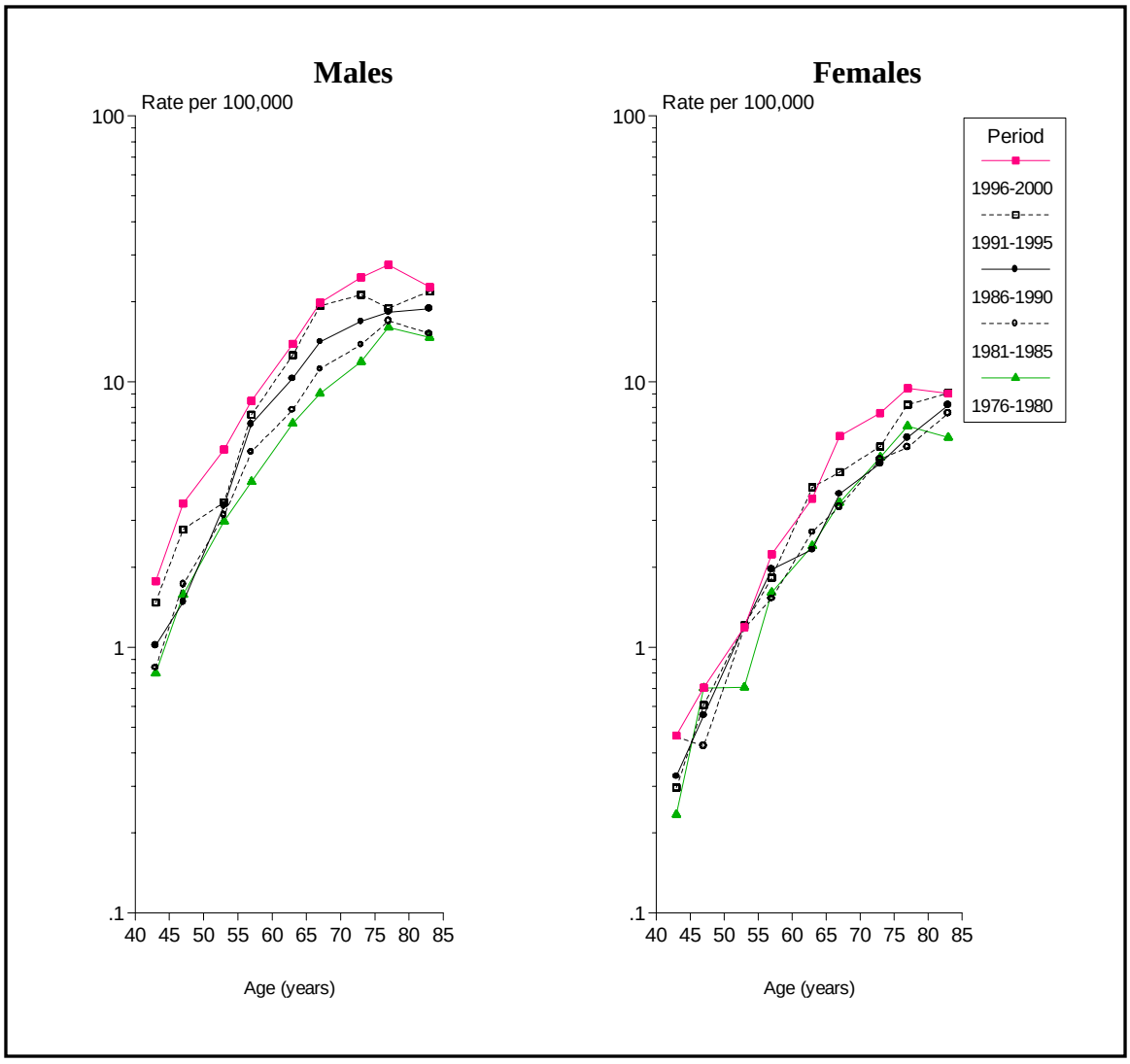


Figure 2. Age-specific hepatocellular carcinoma incidence among persons aged 40-84 years in Canada (plotted on the middle year of the 5-year age group on the x-axis), by sex and calendar year of diagnosis, from 1976-1980 through 1996-2000.

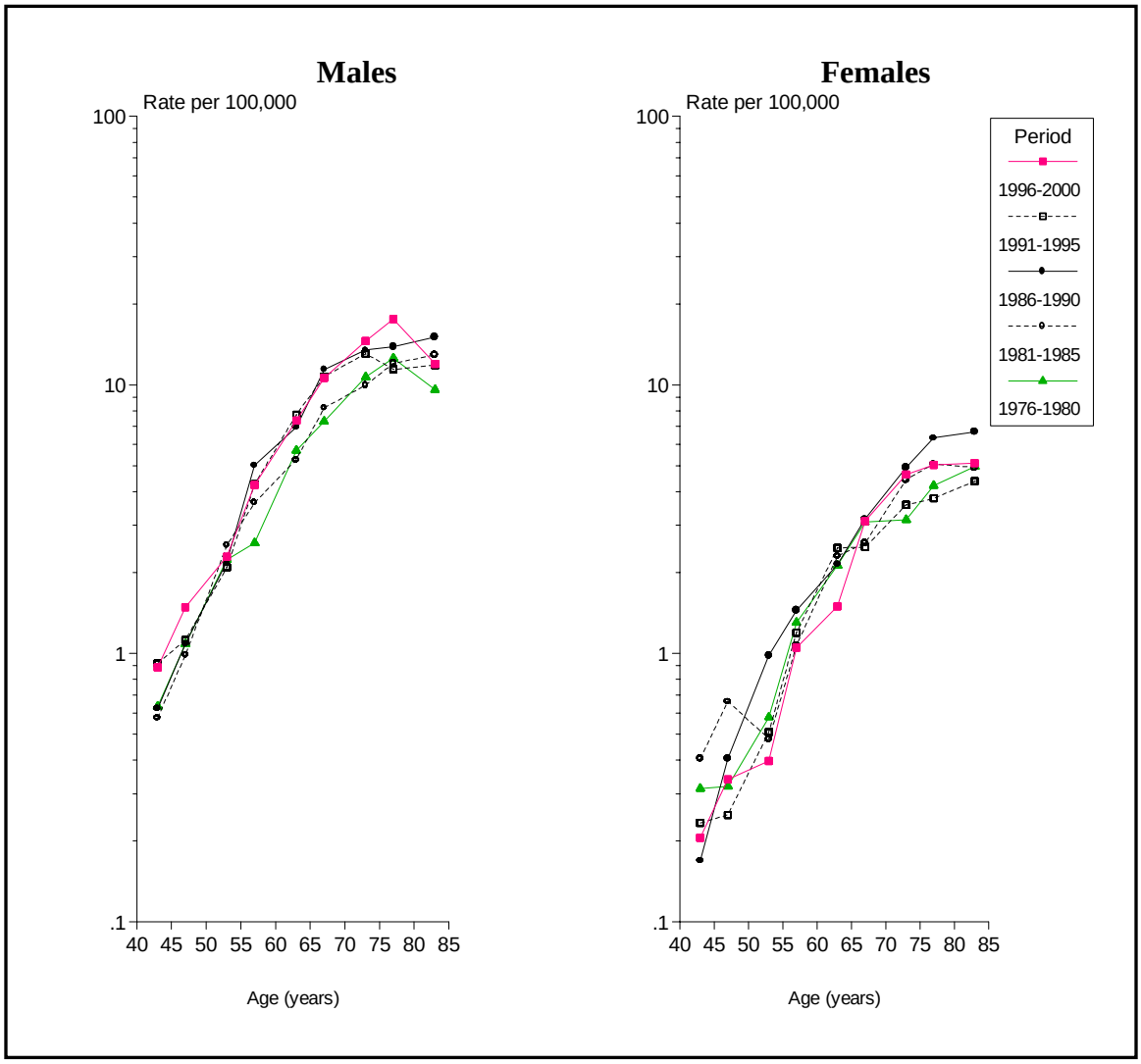


Figure 3. Age-specific hepatocellular carcinoma mortality among persons aged 40-84 years in Canada (plotted on the middle year of the 5-year age group on the x-axis), by sex and calendar year of diagnosis, from 1976-1980 through 1996-2000.

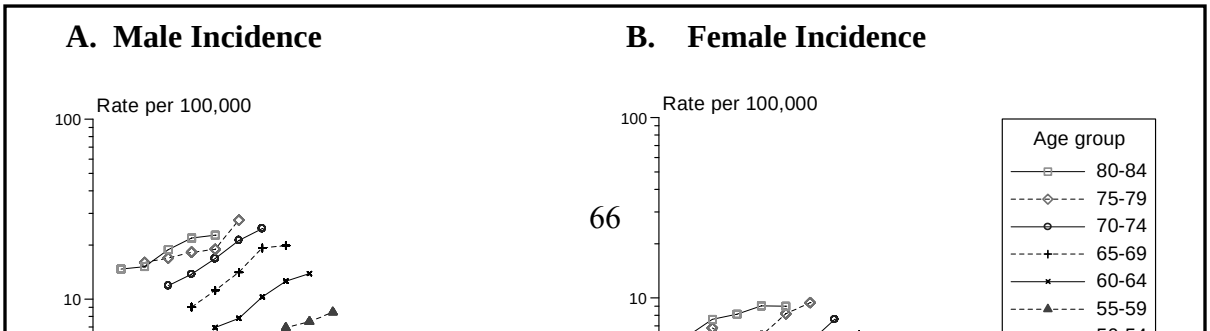


Figure 4. Age-specific hepatocellular carcinoma incidence (A and B) and mortality (C and D) among persons aged 40-84 years in Canada stratified by sex and birth cohort year (plotted on the middle year of the 5-year birth cohort on the x-axis) in Canada from 1976-1980 through 1996-2000.

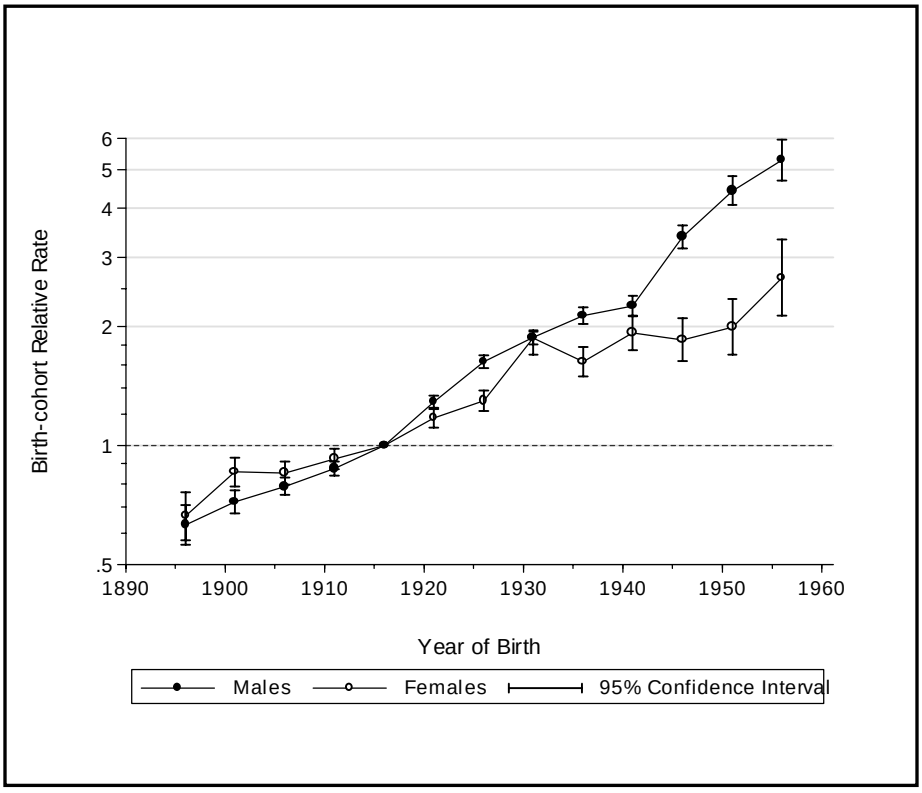


Figure 5. Birth-cohort relative rate for hepatocellular carcinoma incidence (1916 birth cohort is the referent group) among persons in Canada aged 40-84 years from 1976-1980 through 1996-2000, stratified by sex (plotted on the mid-year of the birth-cohort on the x-axis) and adjusted for 5-year age-group at diagnosis.

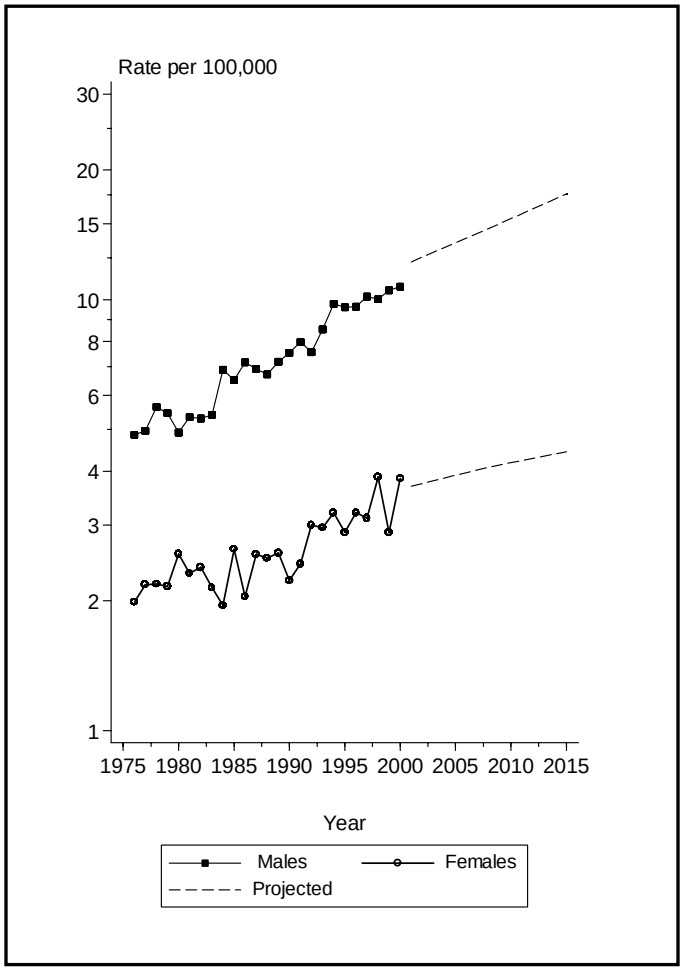


Figure 6. Hepatocellular carcinoma age-adjusted (to the 1991 Canadian population) incidence from 1976 through 2000 and the projected incidence from 2001-2005 through 2011-2015, among persons aged 40-84 years in Canada, stratified by sex. Projection assumptions:
1) The risk for HCC among males born after the1956 birth cohort is the same as the risk among males born in the 1956 birth-cohort.
2) The risk for HCC among females born after the1956 birth-cohort is the same as the average of the risks of the 1951 and the 1956 birth cohorts.

Table 1. The age-adjusted (to the 1991 Canadian population) hepatocelluar carcinoma incidence and mortality trends, by sex, among persons in Canada aged 20 years or older, from 1976-1980 through 1996-2000.

Sex/ Period of diagnosis (5-year)	Rates per 100,000 person-years (95% CI)					Change		
	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	Absolute[a]	Proportional Percent (%)[b]	Annual Percent (%) (95% CI)[c]
Incidence								
Male	2.8 (2.7-2.9)	3.2 (3.1-3.3)	3.9 (3.8-4.0)	4.7 (4.6-4.9)	5.5 (5.4-5.6)	2.7	96	3.4 (3.1-3.8)
Female	1.4 (1.3-1.5)	1.4 (1.4-1.5)	1.5 (1.4-1.6)	1.8 (1.7-1.9)	2.0 (1.9-2.1)	0.6	43	2.1 (1.5-2.8)
Mortality								
Male	2.2 (2.1-2.3)	2.3 (2.2-2.4)	2.9 (2.8-3.0)	2.7 (2.6-2.8)	3.0 (2.9-3.1)	0.8	36	1.4 (0.68-2.2)
Female	1.0 (0.97-1.1)	1.1 (1.1-1.2)	1.3 (1.3-1.4)	1.0 (0.94-1.1)	1.0 (0.98-1.1)	0.0	0	-0.36 (-1.2--0.54)

[a] Absolute change refers to the 1996-2000 rate per 100,000 person-years minus the 1976-1980 rate per 100,000 person-years.

[b] Proportional Percent (%) change refers to [(absolute change)/ (1976-1980 rate per 100,000 person-years)]*100.

[c] Annual Percent (%) change refers to the estimated annual percent change from 1976 through 2000 based on the Joinpoint regression analysis.

Table 2. Hepatocellular carcinoma incidence trends by age and sex, among persons in Canada aged 20 years or older, from 1976-1980 through 1996-2000.

Age-group (years)/ Period of diagnosis (5-year)	Age-adjusted Incidence Rates (95% CI)		Change		
	1976-1980	1996-2000	Absolute[a]	Proportional Percent (%)[b]	Annual Percent (%) (95% CI)[c]
			Males		
20-49	0.38 (0.34-0.42)	0.72 (0.68-0.76)	0.34	89	3.3 (2.3-4.3)
50-64	4.6 (3.9-5.4)	9.1 (8.3-10.0)	4.5	98	3.3 (2.5-4.0)
65-74	10.2 (8.6-12.2)	21.9 (19.9-24.1)	11.7	115	3.7 (3.2-4.3)
75+	14.6 (12.3-17.3)	24.8 (22.6-27.3)	10.2	70	2.6 (2.1-3.1)
			Females		
20-49	0.25 (0.22-0.29)	0.30 (0.27-0.34)	0.050	20	1.1 (0.00028-2.3)
50-64	1.6 (1.2-2.0)	2.3 (2.0-2.7)	0.70	44	2.2 (1.3-3.0)
65-74	4.3 (3.3-5.5)	6.5 (5.5-7.6)	2.2	51	2.8 (1.9-3.8)
75+	6.9 (5.6-8.4)	9.1 (8.1-10.3)	2.2	32	1.4 (0.6-2.3)

[a] Absolute change refers to the 1996-2000 rate per 100,000 person-years minus the 1976-1980 rate per 100,000 person-years.
[b] Proportional Percent (%) change refers to [(absolute change)/ (1976-1980 rate per 100,000 person-years)]*100.
[c] Annual Percent (%) change refers to the estimated annual percent change from 1976 through 2000 based on the Joinpoint regression analysis.

Table 3. Hepatocellular carcinoma mortality trends by age and sex, among persons in Canada aged 20 years or older, from 1976-1980 through 1996-2000.

Age-group/ Period of diagnosis (5-year)	Age-adjusted Mortality Rates (95% CI)		Change		
	1976-1980	1996-2000	Absolute[a]	Proportional Percent (%)[b]	Annual Percent (%) (95% CI)[c]
			Males		
20-49	0.23 (0.20-0.26)	0.32 (0.29-0.35)	0.090	39	1.6 (0.5-2.7)
50-64	3.4 (3.2-3.7)	4.6 (4.3-4.8)	1.2	35	1.2 (0.3-2.1)
65-74	8.7 (8.0-9.5)	12.3 (11.6-13.0)	3.6	41	1.5 (0.56-2.4)
75+	11.2 (10.3-12.2)	14.9 (14.0-15.7)	3.7	33	1.0 (0.16-1.9)
			Females		
20-49	0.16 (0.14-0.20)	0.14 (0.12-0.16)	-0.020	-13	-2.9 (-4.8--1.0)
50-64	1.3 (1.2-1.5)	1.4 (1.2-1.5)	0.10	8	-0.35 (-1.7-1.0)
65-74	3.1 (2.7-3.6)	3.8 (3.6-4.4)	0.70	23	0.50 (-0.7-1.7)
75+	4.8 (4.3-5.3)	5.0 (4.6-5.4)	0.20	4	-1.3[d] (-2.8-0.22)

[a] Absolute change refers to the 1996-2000 rate per 100,000 person-years minus the 1976-1980 rate per 100,000 person-years.
[b] Proportional Percent (%) change refers to [(absolute change)/ (1976-1980 rate per 100,000 person-years)]*100.
[c] Annual Percent (%) change refers to the estimated annual percent change from 1976 through 2000 based on the joinpoint regression analysis.
[d] The annual percent change in Table 3 assumes a constant rate of change over the period of observation (1976 through 2000). But based on the joinpoint regression analysis a change in the trend in HCC mortality rates occurred among females aged 75 years and older in the year 1987 (95% CI = 1984-1991). The annual percent change was 2.8% (95% CI=-1.4%-7.1% per year) from 1976 through 1987 and it was -3.6% per year (95% CI=-5.8--1.3 per year) from 1987 through 2000.

Table 4. Observed and fitted[a] HCC incidence rate per 100,000 person-years and number of incident HCC cases (n) by age at diagnosis and birth-cohort (mid-year of birth cohort), among males aged 40-84 years in Canada from 1976-1980 through 1996-2000.

Birth cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)
	0.63	0.72	0.79	0.87	1.00	1.29	1.63	1.88	2.13	2.26	3.38	4.42	5.29
40-44									0.80 (27)[d]	0.84 (32)	1.0 (49)	1.5 (82)	1.8 (112)
0.34									0.72 (24)[e]	0.77 (29)	1.2 (58)	1.5 (83)	1.8 (114)
45-49								1.6 (51)	1.7 (56)	1.5 (56)	2.8 (134)	3.5 (194)	
0.79								1.5 (48)	1.7 (55)	1.8 (67)	2.6 (124)	3.5 (195)	
50-54							3.0 (91)	3.1 (99)	3.4 (109)	3.5 (131)	5.6 (264)		
1.64							2.7 (82)	3.1 (97)	3.5 (112)	3.7 (138)	5.6 (266)		
55-59						4.2 (114)	5.4 (160)	6.9 (213)	7.5 (236)	8.5 (307)			
3.56						4.6 (125)	5.8 (170)	6.7 (206)	7.6 (238)	8.0 (292)			
60-64					7.0 (155)	7.8 (199)	10.3 (287)	12.6 (372)	13.9 (419)				
6.49					6.5 (145)	8.4 (213)	10.6 (295)	12.9 (382)	13.8 (418)				
65-69				9.0 (167)	11.2 (224)	14.1 (328)	19.3 (496)	19.9 (542)					
11.03				9.6 (178)	11.0 (221)	14.2 (331)	18.0 (462)	20.7 (566)					
70-74			11.9 (156)	13.8 (211)	16.8 (286)	21.2 (426)	24.7 (548)						
15.82			12.5 (163)	13.8 (212)	15.8 (268)	20.4 (410)	25.8 (573)						
75-79		16.1 (134)	16.9 (166)	18.2 (214)	18.9 (250)	27.5 (434)							
20.80		15.0 (125)	16.4 (161)	18.2 (213)	20.8 (275)	26.8 (423)							
80-84	14.7 (66)	15.2 (81)	18.8 (121)	21.9 (172)	22.7 (203)								
23.31	14.7 (66)	16.8 (90)	18.4 (118)	20.4 (160)	23.3 (209)								

[a] Fitted incidence rates and number of HCC cases are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (incidence per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed incidence rate (per 100,000 person-years) and the observed number of incident HCC cases.
[e] The second row for each age group is the fitted incidence rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of incident HCC cases and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].

Table 5. Observed and fitted[a] HCC incidence rate per 100,000 person-years and number of incident HCC cases (n) by age at diagnosis and birth-cohort (mid-year of birth-cohort), among females aged 40-84 years in Canada from 1976-1980 through 1996-2000.

Birth-cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896) 0.66	1897-1905 (1901) 0.86	1902-1910 (1906) 0.85	1907-1915 (1911) 0.93	1912-1920 (1916) 1.00	1917-1925 (1921) 1.17	1922-1930 (1926) 1.30	1927-1935 (1931) 1.82	1932-1940 (1936) 1.63	1937-1945 (1941) 1.93	1942-1950 (1946) 1.85	1947-1955 (1951) 2.00	1952-1960 (1956) 2.66
40-44 0.18									0.23 (8)[d] 0.29 (9)[e]	0.46 (17) 0.35 (13)	0.33 (16) 0.32 (15)	0.30 (17) 0.35 (19)	0.47 (30) 0.47 (30)
45-49 0.33								0.70 (22) 0.59 (18)	0.43 (14) 0.53 (17)	0.55 (21) 0.64 (24)	0.61 (29) 0.61 (29)	0.71 (40) 0.65 (36)	
50-54 0.64							0.71 (22) 0.84 (26)	1.2 (37) 1.2 (37)	1.2 (38) 1.1 (33)	1.2 (45) 1.2 (46)	1.2 (57) 1.2 (57)		
55-59 1.16						1.6 (47) 1.4 (40)	1.5 (47) 1.5 (47)	2.0 (61) 2.1 (66)	1.8 (58) 1.9 (60)	2.2 (83) 2.2 (83)			
60-64 2.17					2.4 (59) 2.2 (53)	2.7 (78) 2.6 (73)	2.3 (71) 2.8 (86)	4.0 123) 3.9 (121)	3.6 (114) 3.5 (111)				
65-69 3.44				3.5 (74) 3.2 (67)	3.4 (80) 3.4 (81)	3.8 (105) 4.0 (112)	4.6 (134) 4.5 (131)	6.2 (185) 6.3 (185)					
70-74 5.41			5.2 (84) 4.6 (75)	5.1 (99) 5.0 (97)	4.9 (108) 5.4 (119)	5.7 (147) 6.4 (164)	7.6 (207) 7.0 (191)						
75-79 7.60		6.8 (79) 6.5 (76)	5.6 (79) 6.5 (91)	6.2 (104) 7.0 (119)	8.2 (156) 7.6 (145)	9.4 (212) 8.9 (200)							
80-84 9.31	6.2 (46) 6.2 (46)	7.6 (68) 8.0 (71)	8.1 (89) 7.9 (87)	9.1 (120) 8.6 (114)	9.0 (136) 9.3 (141)								

[a] Fitted incidence rates and number of HCC cases are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (incidence per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed incidence rate (per 100,000 person-years) and the observed number of incident HCC cases.
[e] The second row for each age group is the fitted incidence rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of incident HCC cases and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].

Table 6. Observed (from 1976-1980 through 1996-2000) and projected (from 2001-2005 through 2011-2015) age-adjusted (to the 1991 Canadian population) hepatocellular carcinoma incidence rates (per 100,000 person-years) and the number of incident HCC cases among persons aged 40-84 years in Canada.

	Males		Females	
Period of diagnosis (5-year)	Incidence Rate (95% CI)	Number of Incident cases (n)	Incidence Rate (95% CI)	Number of Incident cases (n)
1976-1980	5.1 (4.1-6.4)	961	2.2 (1.8-2.8)	441
1981-1985	5.8 (4.7-7.3)	1415	2.3 (1.8-2.9)	519
1986-1990	7.0 (5.6-8.8)	1663	2.4 (1.9-3.0)	613
1991-1995	8.6 (6.9-10.8)	2299	2.9 (2.3-3.6)	829
1996-2000	10.1 (8.1-12.6)	3023	3.4 (2.9-4.2)	1064
2001-2005	12.2 (9.8-15.3)	4164	3.7 (3.0-4.6)	1287
2006-2010	14.6 (11.7-18.3)	5641	4.1 (3.2-5.1)	1555
2011-2015	17.6 (14.1-22.0)	7672	4.4 (3.5-5.5)	1877

Appendix A. Hepatocellular carcinoma age-specific and age-adjusted incidence rates (per 100,000 person-years) and number of incident cases (n) among males aged 20 years and older in Canada from 1976 through 2000.

Year	Age-group (5-year)																				All ages 20-85+[a]	
	20-39		40-44		45-49		50-54		55-59		60-64		65-69		70-74		75-79		80-84		85+			
1976	0.13 (5)		1.4 (9)		1.4 (9)		2.8 (17)		3.8 (19)		7.3 (32)		9.0 (31)		10.6 (26)		11.8 (18)		13.9 (12)		8.2 (5)		2.6 (183)	
1977	0.29 (11)		0.23 (1.5)		1.4 (9)		3.0 (18)		4.8 (25)		7.2 (32)		7.9 (28)		10.4 (26)		14.6 (23)		22.9 (20)		13.1 (8)		2.8 (201.5)	
1978	0.18 (7)	0.25 (51)[b]	1.1 (7)	0.80 (26.5)	1.5 (10)	1.6 (51)	3.0 (18)	3.0 (91)	4.1 (22)	4.2 (114)	7.5 (33)	6.9 (155)	9.9 (36)	9.0 (167)	12.8 (33)	11.9 (156)	21.3 (35)	16.0 (134)	14.8 (13)	14.7 (66)	8.1 (5)	10.3 (32)	3.0 (219)	2.8 (1043.5)
1979	0.35 (14)		0.91 (6)		0.92 (6)		3.6 (22)		4.7 (26)		7.5 (33)		9.6 (36)		13.2 (35)		18.1 (31)		13.3 (12)		14.4 (9)		3.1 (230)	
1980	0.34 (14)		0.44 (3)		2.6 (17)		2.6 (16)		3.9 (22)		5.5 (25)		9.3 (36)		13.1 (36)		15.3 (27)		9.7 (9)		7.9 (5)		2.7 (210)	
1981	0.30 (13)		0.86 (6)		1.9 (12)		2.6 (16)		4.5 (26)		7.9 (37)		9.2 (36)		11.3 (32)		14.3 (26)		20.9 (20)		12.5 (8)		3.0 (232)	
1982	0.30 (13)		0.56 (4)		0.93 (6)		2.5 (16)		6.1 (35)		6.6 (32)		10.8 (43)		12.7 (37)		18.2 (34)		10.0 (10)		17.0 (11)		3.0 (241)	
1983	0.29 (13)	0.26 (58)	1.2 (9)	0.84 (32)	1.9 (12)	1.7 (56)	2.7 (17)	3.1 (99)	5.8 (34)	5.4 (160)	6.3 (32)	7.8 (199)	9.9 (39)	11.2 (224)	13.3 (40)	13.8 (211)	16.1 (31)	16.9 (166)	10.5 (11)	15.2 (81)	15.3 (10)	14.4 (48)	3.0 (248)	3.2 (1334)
1984	0.24 (11)		0.64 (5)		1.5 (10)		4.3 (27)		6.6 (39)		9.8 (51)		12.9 (51)		17.3 (54)		17.6 (35)		20.1 (22)		21.0 (14)		3.8 (319)	
1985	0.17 (8)		0.99 (8)		2.4 (16)		3.7 (23)		4.3 (26)		8.9 (47)		13.6 (55)		14.9 (48)		19.4 (40)		15.9 (18)		7.3 (5)		3.5 (294)	
1986	0.41 (19)		1.1 (9)		1.3 (9)		4.0 (25)		8.1 (49)		11.2 (60)		13.1 (55)		16.2 (53)		19.8 (42)		15.4 (18)		24.2 (17)		4.0 (356)	
1987	0.21 (10)		1.1 (10)		0.86 (6)		2.2 (14)		4.6 (28)		13.8 (75)		14.1 (62)		17.1 (57)		17.7 (39)		19.8 (24)		23.0 (17)		3.8 (342)	
1988	0.23 (11)	0.33 (79)	1.1 (10)	1.0 (49)	1.6 (12)	1.5 (56)	3.4 (21)	3.4 (109)	6.5 (40)	6.9 (213)	7.9 (44)	10.3 (287)	14.2 (65)	14.1 (328)	17.6 (59)	16.8 (286).	15.2 (35)	18.2 (214)	21.5 (27)	18.8 (121)	18.2 (14)	18.5 (73)	3.7 (338)	3.9 (1815)
1989	0.38 (18)		1.1 (11)		1.7 (13)		3.9 (25)		9.1 (56)		8.7 (49)		14.2 (68)		16.6 (56)		19.6 (47)		15.3 (20)		14.9 (12)		4.0 (375)	
1990	0.44 (21)		0.87 (9)		2.0 (16)		3.7 (24)		6.5 (40)		10.3 (59)		16.0 (78)		17.5 (61)		20.5 (51)		23.5 (32)		15.4 (13)		4.2 (404)	
1991	0.35 (17)		1.2 (13)		2.4 (20)		3.4 (23)		7.0 (43)		10.5 (61)		19.7 (98)		19.2 (70)		16.8 (43)		22.5 (32)		21.7 (19)		4.4 (439)	
1992	0.54 (26)		1.7 (18)		2.3 (21)		3.3 (23)		5.4 (33)		9.5 (56)		16.7 (84)		18.0 (69)		21.2 (55)		20.9 (31)		13.3 (12)		4.2 (428)	
1993	0.46 (22)	0.44 (105)	1.4 (15)	1.5 (82)	2.4 (23)	2.8 (134)	3.4 (25)	3.5 (131)	7.9 (49)	7.5 (236)	11.6 (69)	12.6 (372)	21.0 (107)	19.3 (496)	20.9 (83)	21.2 (426)	17.6 (46)	18.9 (250)	21.4 (33)	21.9 (172)	19.2 (18)	17.6 (84)	4.7 (490)	4.7 (2488)
1994	0.42 (20)		1.6 (18)		3.1 (31)		4.1 (31)		8.9 (56)		17.0 (101)		21.0 (108)		21.3 (88)		19.4 (51)		26.2 (42)		18.6 (18)		5.3 (564)	
1995	0.42 (20)		1.6 (18)		3.8 (39)		3.7 (29)		8.6 (55)		14.3 (85)		18.9 (99)		27.6 (116)		20.3 (55)		20.4 (34)		17.0 (17)		5.2 (567)	
1996	0.36 (17)		1.7 (20)		3.3 (35)		4.8 (40)		9.9 (65)		14.0 (83)		15.8 (84)		22.8 (97)		28.7 (81)		21.7 (37)		19.4 (20)		5.2 (579)	
1997	0.44 (21)		2.0 (25)		3.9 (42)		5.3 (47)		10.0 (68)		12.8 (76)		19.9 (108)		24.1 (104)		23.9 (71)		27.1 (47)		25.2 (27)		5.6 (636)	
1998	0.45 (21)	0.40 (93)	2.1 (27)	1.8 (112)	2.8 (31)	3.5 (194)	6.3 (59)	5.6 (264)	7.3 (52)	8.4 (307)	12.8 (76)	13.9 (419)	21.4 (117)	19.9 (542)	24.3 (107)	24.7 (548)	28.9 (90)	27.5 (434)	20.0 (35)	22.7 (203)	16.9 (19)	20.5 (119)	5.5 (634)	5.5 (3235)
1999	0.32 (15)		1.5 (19)		4.1 (46)		5.7 (56)		7.6 (56)		15.9 (96)		22.2 (122)		24.6 (110)		27.4 (89)		22.5 (40)		24.5 (29)		5.7 (678)	
2000	0.41 (19)		1.6 (21)		3.5 (40)		6.1 (62)		8.6 (66)		14.3 (88)		20.2 (111)		28.5 (130)		30.9 (103)		23.7 (44)		19.1 (24)		5.8 (708)	

[a] Age-adjusted to the 1991 Canadian population

[b] Average annual age-specific incidence rate for the 5-year period of diagnosis and the total number of cases (n) for the 5-year period of diagnosis.

Appendix B. Hepatocellular carcinoma age-specific and age-adjusted incidence rates (per 100,000 person-years) and number of incident cases (n) among females aged 20 years and older in Canada from 1976 through 2000.

Year	Age-group (5-year)																				All ages 20-85+[a]	
	20-39		40-44		45-49		50-54		55-59		60-64		65-69		70-74		75-79		80-84		85+			
1976	0.11 (4)		0.24 (1.5)		0.96 (6)		0.24 (1.5)		1.1 (6)		3.0 (14)		2.6 (10)		6.1 (18)		4.7 (10)		5.9 (8)		1.4 (1.5)		1.2 (80.5)	
1977	0.21 (8)		0.24 (1.5)		0.64 (4)		0.24 (1.5)		2.0 (11)		2.7 (13)		5.0 (20)		4.2 (13)		4.6 (10)		7.8 (11)		10.9 (12)		1.5 (105)	
1978	0.16 (6)	0.17 (34)[b]	0.24 (1.5)	0.23 (7.5)	0.64 (4)	0.70 (22)	0.80 (5)	0.71 (22)	1.6 (9)	1.6 (47)	2.3 (11)	2.4 (59)	3.9 (16)	3.5 (74)	5.3 (17)	5.2 (84)	7.0 (16)	6.8 (79)	4.8 (7)	6.2 (46)	7.0 (8)	7.7 (45.5)	1.4 (100.5)	1.4 (520)
1979	0.15 (6)		0.24 (1.5)		0.64 (4)		0.97 (6)		1.5 (9)		1.6 (8)		3.0 (13)		3.6 (12)		9.3 (22)		7.3 (11)		7.5 (9)		1.4 (101.5)	
1980	0.24 (10)		0.23 (1.5)		0.64 (4)		1.3 (8)		2.0 (12)		2.6 (13)		3.4 (15)		7.0 (24)		8.6 (21)		5.7 (9)		12.0 (15)		1.7 (132.5)	
1981	0.17 (7)		0.22 (1.5)		0.24 (1.5)		1.1 (7)		1.5 (9)		2.5 (13)		3.9 (18)		5.9 (21)		7.1 (18)		7.4 (12)		12.9 (17)		1.6 (125)	
1982	0.19 (8)		0.86 (6)		0.64 (4)		1.4 (9)		1.5 (9)		2.7 (15)		2.8 (13)		4.6 (17)		4.5 (12)		10.7 (18)		5.8 (8)		1.5 (119)	
1983	0.14 (6)	0.18 (39)	0.21 (1.5)	0.46 (17)	0.24 (1.5)	0.43 (13.5)	1.3 (8)	1.2 (37)	1.5 (9)	1.5 (47)	2.3(13)	2.7 (78)	5.1 (24)	3.4 (80)	3.9 (15)	5.1 (99)	4.0 (11)	5.6 (79)	9.2 (16)	7.6 (68)	6.3 (9)	7.9 (58)	1.4 (114)	1.4 (615.5)
1984	0.22 (10)		0.53 (4)		0.79 (5)		0.96 (6)		1.0 (6)		2.5 (15)		1.7 (8)		5.1 (20)		5.6 (16)		4.9 (9)		8.7 (13)		1.3 (112)	
1985	0.18 (8)		0.51 (4)		0.23 (1.5)		1.1 (7)		2.3 (14)		3.7 (22)		3.5 (17)		6.3 (26)		7.5 (22)		6.8 (13)		7.1 (11)		1.6 (145.5)	
1986	0.20 (9)		0.18 (1.5)		0.91 (6)		1.1 (7)		2.1 (13)		2.2 (13)		1.6 (8)		4.5 (19)		5.6 (17)		8.1 (16)		9.9 (16)		1.4 (125.5)	
1987	0.15 (7)		0.17 (1.5)		0.73 (5)		1.9 (12)		1.4 (9)		1.7 (10)		4.0 (21)		5.6 (24)		7.2 (23)		10.7 (22)		7.7 (13)		1.6 (147.5)	
1988	0.17 (8)	0.17 (39)	0.65 (6)	0.33 (15.5)	0.55 (4)	0.55 (20.5)	1.1 (7)	1.2 (38)	1.8 (11)	2.0 (61)	2.3 (14)	2.3 (71)	3.8 (21)	3.8 (105)	5.8 (25)	4.9 (108)	7.9 (26)	6.2 (104)	6.1 (13)	8.1 (89)	11.4 (20)	9.9 (89)	1.6 (155)	1.5 (740)
1989	0.19 (9)		0.51 (5)		0.20 (1.5)		0.63 (4)		2.9 (18)		3.0 (18)		4.7 (27)		5.0 (22)		5.8 (20)		9.4 (21)		9.8 (18)		1.7 (163.5)	
1990	0.13 (6)		0.15 (1.5)		0.51 (4)		1.2 (8)		1.6 (10)		2.6 (16)		4.8 (28)		4.0 (18)		5.0 (18)		7.4 (17)		11.5 (22)		1.5 (148.5)	
1991	0.10 (4)		0.14 (1.5)		0.48 (4)		1.2 (8)		1.8 (11)		3.9 (24)		3.6 (21)		6.2 (29)		5.4 (20)		6.7 (16)		11.0 (22)		1.5 (160.5)	
1992	0.19 (9)		0.37 (4)		0.56 (5)		1.7 (12)		2.1 (13)		4.1 (25)		4.3 (25)		5.3 (26)		9.1 (34)		9.2 (23)		15.3 (32)		2.0 (208)	
1993	0.21 (10)	0.17 (41)	0.73 (8)	0.30 (16.5)	0.64 (6)	0.61 (29)	0.96 (7)	1.2 (45)	1.6 (10)	1.8 (58)	3.4 (21)	4.0 (123)	4.8 (28)	4.6 (134)	5.3 (27)	5.7 (147)	9.3 (35)	8.2 (156)	10.0 (26)	9.1 (120)	8.3 (18)	9.7 (107)	1.8 (196)	1.8 (976.5)
1994	0.11 (5)		0.13 (1.5)		0.61 (6)		1.3 (10)		2.0 (13)		4.4 (27)		5.1 (30)		7.2 (38)		8.7 (33)		10.7 (29)		4.9 (11)		1.8 (203.5)	
1995	0.27 (13)		0.13 (1.5)		0.78 (8)		1.0 (8)		1.7 (11)		4.2 (26)		5.1 (30)		5.0 (27)		8.7 (34)		9.2 (26)		10.3 (24)		1.9 (208.5)	
1996	0.22 (10)		0.13 (1.5)		0.14 (1.5)		1.3 (11)		2.4 (16)		4.1 (25)		6.6 (39)		7.8 (42)		9.1 (37)		7.3 (21)		11.2 (27)		2.0 (231)	
1997	0.17 (8)		0.49 (6)		0.65 (7)		1.3 (12)		1.7 (12)		2.8 (17)		4.5 (27)		7.0 (38)		11.2 (48)		8.9 (26)		7.2 (18)		1.9 (219)	
1998	0.26 (12)	0.20 (45)	0.79 (10)	0.47 (29.5)	0.73 (8)	0.71 (39.5)	0.64 (6)	1.2 (57)	2.5 (18)	2.2 (83)	4.4 (27)	3.6 (114)	7.6 (45)	6.2 (185)	8.1 (44)	7.6 (207)	11.7 (52)	9.4 (212)	10.5 (31)	9.0 (136)	9.2 (24)	8.7 (117)	2.3 (277)	2.0 (1225)
1999	0.15 (7)		0.55 (7)		0.80 (9)		1.1 (11)		1.5 (11)		3.5 (22)		4.7 (28)		7.5 (41)		6.3 (29)		8.6 (26)		8.4 (23)		1.7 (214)	
2000	0.18 (8)		0.38 (5)		1.2 (14)		1.7 (17)		3.3 (26)		3.6 (23)		7.8 (46)		7.7 (42)		9.8 (46)		10.2 (32)		8.7 (25)		2.3 (284)	

[a] Age-adjusted to the 1991 Canadian population

[b] Average annual age-specific incidence rate for the 5-year period of diagnosis and the total number of incident cases (n) for the 5-year period of diagnosis.

Appendix C. Hepatocellular carcinoma age-specific and age-adjusted mortality rates (per 100,000 person-years) and number of deaths (n) among males aged 20 years and older in Canada from 1976 through 2000.

Year	Age-group (5-year)																				All ages 20-85+[a]	
	20-39		40-44		45-49		50-54		55-59		60-64		65-69		70-74		75-79		80-84		85+			
1976	0.16 (6)		1.1 (7)		1.3 (8)		1.7 (10)		2.0 (10)		5.0 (22)		7.0 (24)		9.4 (23)		10.5 (16)		13.9 (12)		6.6 (4)		2.1 (142)	
1977	0.08 (3)		0.15 (1)		0.62 (4)		3.0 (18)		3.5 (18)		6.1 (27)		7.0 (25)		12.0 (30)		10.8 (17)		14.9 (13)		6.5 (4)		2.2 (160)	
1978	0.15 (6)	0.13 (26)[b]	0.92 (6)	0.63 (21)	0.92 (6)	1.1 (35)	1.7 (10)	2.2 (68)	2.6 (14)	2.6 (70)	4.5 (20)	5.7 (127)	8.0 (29)	7.3 (135)	9.3 (24)	10.7 (140)	12.8 (21)	12.5 (105)	7.9 (7)	9.6 (43)	12.9 (8)	10.0 (31)	2.1 (151)	2.2 (823)
1979	0.15 (6)		0.30 (2)		0.92 (6)		3.1 (19)		2.9 (16)		8.2 (36)		6.4 (24)		10.9 (29)		15.2 (26)		5.5 (5)		11.2 (7)		2.3 (176)	
1980	0.12 (5)		0.74 (5)		1.7 (11)		1.8 (11)		2.1 (12)		4.9 (22)		8.6 (33)		12.4 (34)		14.2 (25)		6.5 (6)		12.7 (8)		2.3 (172)	
1981	0.28 (12)		0.57 (4)		1.3 (8)		2.2 (14)		3.1 (18)		4.9 (23)		7.4 (29)		5.7 (16)		6.1 (11)		11.5 (11)		4.7 (3)		1.9 (149)	
1982	0.23 (10)		0.28 (2)		0.78 (5)		1.7 (11)		4.2 (24)		4.1 (20)		7.1 (28)		8.9 (26)		14.4 (27)		8.0 (8)		9.3 (6)		2.1 (167)	
1983	0.11 (5)	0.18 (41)	0.40 (3)	0.57 (22)	0.62 (4)	0.99 (32)	2.5 (16)	2.5 (80)	3.4 (20)	3.6 (107)	4.6 (23)	5.3 (134)	7.6 (30)	8.2 (164)	7.6 (23)	10.0 (153)	11.9 (23)	12.0 (118)	11.5 (12)	12.9 (69)	4.6 (3)	9.3 (31)	2.0 (162)	2.3 (951)
1984	0.20 (9)		0.90 (7)		0.92 (6)		2.7 (17)		4.1 (24)		6.7 (35)		10.1 (40)		15.4 (48)		16.1 (32)		17.3 (19)		12.0 (8)		2.9 (245)	
1985	0.11 (5)		0.74 (6)		1.4 (9)		3.5 (22)		3.5 (21)		6.2 (33)		9.1 (37)		12.4 (40)		12.1 (25)		16.7 (19)		16.1 (11)		2.7 (228)	
1986	0.17 (8)		0.83 (7)		1.2 (8)		2.4 (15)		4.1 (25)		8.0 (43)		8.8 (37)		15.0 (49)		15.1 (32)		14.5 (17)		10.0 (7)		2.8 (248)	
1987	0.36 (17)		0.78 (7)		0.71 (5)		1.9 (12)		3.8 (23)		7.5 (41)		10.0 (44)		15.0 (50)		14.5 (32)		14.8 (18)		14.9 (11)		2.9 (260)	
1988	0.06 (3)	0.22 (52)	0.63 (6)	0.62 (30)	1.1 (8)	1.1 (41)	2.6 (16)	2.2 (70)	4.9 (30)	5.0 (154)	8.7 (48)	7.0 (194)	14.0 (64)	11.4 (265)	16.2 (54)	13.5 (229)	13.5 (31)	13.9 (163)	18.3 (23)	15.1 (97)	15.6 (12)	10.6 (42)	3.2 (295)	2.9 (1337)
1989	0.21 (10)		0.61 (6)		1.2 (9)		2.7 (17)		6.5 (40)		6.2 (35)		12.8 (61)		11.6 (39)		16.3 (39)		19.1 (14)		9.9 (8)		3.1 (289)	
1990	0.29 (14)		0.39 (4)		1.4 (11)		1.5 (10)		5.8 (36)		4.7 (27)		12.1 (59)		10.6 (37)		11.6 (29)		10.3 (14)		4.7 (4)		2.5 (245)	
1991	0.25 (12)		0.37 (4)		0.83 (7)		1.8 (12)		3.6 (22)		7.2 (42)		11.2 (56)		10.7 (39)		10.2 (26)		7.7 (11)		5.7 (5)		2.4 (236)	
1992	0.17 (8)		0.74 (8)		1.2 (11)		2.3 (16)		3.8 (23)		6.8 (40)		10.5 (53)		14.4 (55)		12.7 (33)		12.8 (19)		9.9 (9)		2.7 (275)	
1993	0.17 (8)	0.20 (49)	1.2 (13)	0.92 (51)	1.2 (11)	1.1 (54)	2.3 (17)	2.1 (78)	4.9 (30)	4.3 (134)	8.4 (50)	7.7 (229)	10.4 (53)	10.7 (276)	13.6 (54)	13.0 (262)	12.3 (32)	11.4 (151)	9.1 (14)	11.8 (93)	12.8 (12)	10.1 (48)	2.8 (294)	2.7 (1425)
1994	0.31 (15)		1.1 (12)		1.1 (11)		1.6 (12)		4.8 (30)		9.4 (56)		11.4 (59)		13.1 (54)		12.2 (32)		19.9 (32)		13.4 (13)		3.1 (326)	
1995	0.13 (6)		1.2 (14)		1.4 (14)		2.7 (21)		4.5 (29)		6.9 (41)		10.5 (55)		14.3 (60)		10.4 (28)		10.2 (17)		9.0 (9)		2.7 (294)	
1996	0.21 (10)		1.1 (12)		1.3 (12)		1.9 (16)		5.3 (35)		6.9 (41)		8.3 (44)		11.5 (49)		17.7 (50)		11.2 (19)		11.6 (12)		2.7 (300)	
1997	0.08 (4)		0.33 (4)		0.74 (8)		1.2 (11)		2.8 (19)		7.3 (43)		8.7 (47)		13.4 (58)		17.5 (52)		13.2 (23)		10.3 (11)		2.5 (280)	
1998	0.32 (15)	0.19 (44)	1.2 (15)	0.89 (56)	1.4 (15)	1.5 (83)	3.5 (33)	2.3 (109)	6.1 (43)	4.2 (154)	7.9 (47)	7.3 (222)	13.1 (72)	10.6 (290)	15.9 (70)	14.5 (323)	16.1 (50)	17.6 (277)	10.8 (19)	11.9 (107)	14.2 (16)	11.7 (68)	3.4 (395)	3.0 (3020)
1999	0.15 (7)		0.94 (12)		1.9 (21)		2.8 (27)		3.8 (28)		8.8 (53)		12.7 (70)		16.8 (75)		22.8 (74)		12.4 (22)		7.6 (9)		3.4 (398)	
2000	0.17 (8)		1.0 (13)		2.3 (27)		2.2 (22)		3.8 (29)		6.2 (38)		10.4 (57)		15.6 (71)		15.3 (51)		13.0 (24)		15.9 (20)		2.9 (360)	

[a] Age-adjusted to the 1991 Canadian population

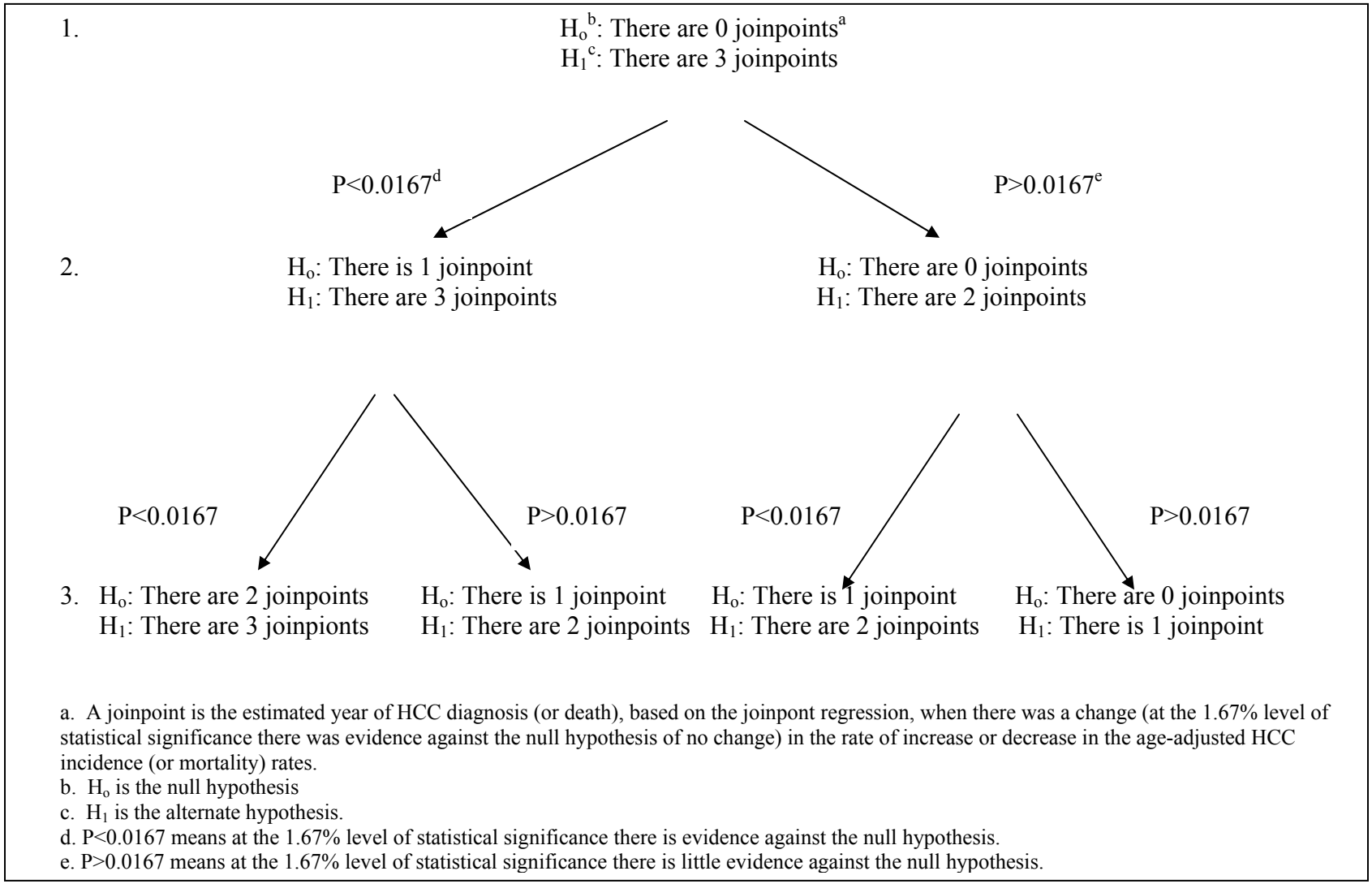
[b] Average annual age-specific mortality rate for the 5-year period and the total number of deaths (n) for the 5-year period.

Appendix D. Hepatocellular carcinoma age-specific and age-adjusted mortality rates (per 100,000 person-years) and number of deaths (n) among females aged 20 years and older in Canada from 1976 through 2000.

Year	Age-group (5-year)																						All ages 20-85+[a]	
	20-39		40-44		45-49		50-54		55-59		60-64		65-69		70-74		75-79		80-84		85+			
1976	0.03 (1)		0.32 (2)		0.48 (3)		0.32 (2)		1.70 (9)		2.54 (12)		4.41 (17)		4.75 (14)		5.15 (11)		4.40 (6)		1.89 (2)		1.1 (79)	
1977	0.16 (6)		0.16 (1)		0.48 (3)		0.48 (3)		0.72 (4)		2.71 (13)		3.25 (13)		2.61 (8)		2.28 (5)		4.24 (6)		3.63 (4)		0.91 (66)	
1978	0.10 (4)	0.10 (20)[b]	0.32 (2)	0.31 (10)	0.00 (0)	0.32 (10)	0.32 (2)	0.58 (18)	1.21 (7)	1.30 (38)	2.48 (12)	2.1 (52)	2.18 (9)	3.1 (65)	3.15 (10)	3.1 (51)	7.05 (16)	4.2 (49)	8.92 (13)	5.0 (37)	8.71 (10)	5.6 (33)	1.2 (85)	1.0 (383)
1979	0.13 (5)		0.63 (4)		0.48 (3)		0.65 (4)		1.50 (9)		1.43 (7)		3.26 (14)		2.73 (9)		3.39 (8)		3.96 (6)		5.84 (7)		1.0 (76)	
1980	0.10 (4)		0.15 (1)		0.16 (1)		1.1 (7)		1.48 (9)		1.60 (8)		2.69 (12)		2.93 (10)		3.68 (9)		3.82 (6)		7.99 (10)		0.99 (77)	
1981	0.12 (5)		0.89 (6)		0.96 (6)		0.32 (2)		1.30 (8)		2.11 (11)		2.19 (10)		3.95 (14)		3.93 (10)		5.52 (9)		6.08 (8)		1.1 (89)	
1982	0.05 (5)		0.14 (1)		0.64 (4)		0.80 (5)		0.16 (1)		2.56 (14)		2.80 (13)		3.54 (13)		5.28 (14)		4.17 (7)		4.35 (6)		0.99 (80)	
1983	0.11 (5)	0.10 (22)	0.55 (4)	0.40 (15)	0.64 (4)	0.66 (21)	0.32 (2)	0.48 (15)	1.30 (8)	1.1 (33)	1.93 (11)	2.3 (66)	3.85 (18)	2.6 (61)	6.05 (23)	4.4 (86)	4.36 (12)	5.1 (71)	5.74 (10)	4.9 (44)	5.60 (8)	6.2 (45)	1.3 (105)	1.1 (479)
1984	0.13 (6)		0.26 (2)		0.63 (4)		0.00 (0)		1.13 (7)		2.20 (13)		2.76 (13)		4.30 (17)		4.92 (14)		4.39 (8)		8.73 (13)		1.1 (97)	
1985	0.09 (4)		0.25 (2)		0.46 (3)		1.00 (6)		1.45 (9)		2.84 (17)		1.44 (7)		4.63 (19)		7.13 (21)		5.27 (10)		6.44 (10)		1.2 (108)	
1986	0.22 (10)		0.37 (3)		0.15 (1)		0.64 (4)		1.70 (11)		2.32 (14)		2.97 (15)		5.24 (22)		4.91 (15)		7.60 (15)		7.43 (12)		1.3 (122)	
1987	0.09 (4)		0.00 (0)		0.29 (2)		0.48 (3)		1.45 (9)		2.15 (13)		2.83 (15)		4.66 (20)		7.56 (24)		9.21 (19)		10.69 (18)		1.4 (127)	
1988	0.04 (2)	0.12 (29)	0.32 (3)	0.17 (8)	0.28 (2)	0.40 (15)	1.45 (9)	0.98 (31)	0.96 (6)	1.4 (45)	1.64 (10)	2.1 (65)	3.09 (17)	3.2 (88)	5.78 (25(	4.9 (108)	7.28 (24)	6.3 (107)	5.60 (12)	6.7 (73)	11.41 (20)	8.8 (79)	1.4 (130)	1.3 (648)
1989	0.11 (5)		0.10 (1)		0.40 (3)		1.42 (9)		2.09 (13)		2.13 (13)		3.67 (21)		5.49 (24)		5.80 (20)		7.63 (17)		9.26 (17)		1.5 (143)	
1990	0.17 (8)		0.10 (1)		0.88 (7)		0.93 (6)		0.97 (6)		2.46 (15)		3.44 (20)		3.77 (17)		6.70 (24)		4.33 (10)		6.25 (12)		1.2 (126)	
1991	0.06 (3)		0.28 (3)		0.12 (1)		0.75 (5)		1.94 (12)		3.10 (19)		1.87 (11)		2.12 (10)		2.99 (11)		4.57 (11)		9.48 (19)		1.0 (105)	
1992	0.06 (3)		0.37 (4)		0.22 (2)		0.87 (6)		1.29 (8)		1.46 (9)		3.07 (18)		4.47 (22)		3.75 (14)		3.60 (9)		11.03 (23)		1.1 (118)	
1993	0.09 (4)	0.06 (15)	0.37 (4)	0.23 (13)	0.43 (4)	0.25 (12)	0.41 (3)	0.51 (19)	0.48 (3)	1.2 (38)	2.43 (15)	2.5 (76)	2.72 (16)	2.5 (73)	4.10 (21)	3.6 (92)	2.92 (11)	3.8 (72)	6.16 (16)	4.4 (58)	6.46 (14)	7.2 (79)	1.0 (111)	1.0 (547)
1994	0.04 (2)		0.00 (0)		0.20 (2)		0.00 (0)		1.10 (7)		2.60 (16)		2.56 (15)		3.78 (20)		5.01 (19)		5.54 (15)		4.01 (9)		0.95 (105)	
1995	0.06 (3)		0.17 (2)		0.29 (3)		0.63 (5)		1.23 (8)		2.76 (17)		2.21 (13)		3.54 (19)		4.35 (17)		2.49 (7)		6.01 (14)		0.96 (108)	
1996	0.13 (6)		0.09 (1)		0.37 (4)		0.96 (8)		0.60 (4)		1.30 (8)		3.05 (18)		5.36 (29)		4.18 (17)		3.48 (10)		4.98 (12)		1.0 (117)	
1997	0.11 (5)		0.16 (2)		0.37 (4)		0.34 (3)		0.57 (4)		0.81 (5)		1.35 (8)		3.32 (18)		5.62 (24)		8.19 (24)		3.59 (9)		0.89 (106)	
1998	0.00 (0)	0.09 (20)	0.24 (3)	0.21 (13)	0.36 (4)	0.34 (19)	0.11 (1)	0.40 (19)	1.38 (10)	1.1 (39)	1.78 (11)	1.5 (47)	3.70 (22)	3.1(92)	4.23 (23)	4.6 (126)	6.28 (28)	5.0 (113)	4.73 (14)	5.1 (77)	3.06 (8)	4.8 (64)	1.0 (124)	1.0 (629)
1999	0.11 (5)		0.39 (5)		0.27 (3)		0.51 (5)		0.66 (5)		1.90 (12)		4.38 (26)		6.07 (33)		5.19 (24)		6.32 (19)		5.48 (15)		1.3 (152)	
2000	0.09 (4)		0.15 (2)		0.34 (4)		0.19 (2)		2.04 (16)		1.71 (11)		3.04 (18)		4.21 (23)		4.24 (20)		3.20 (10)		6.95 (20)		1.0 (130)	

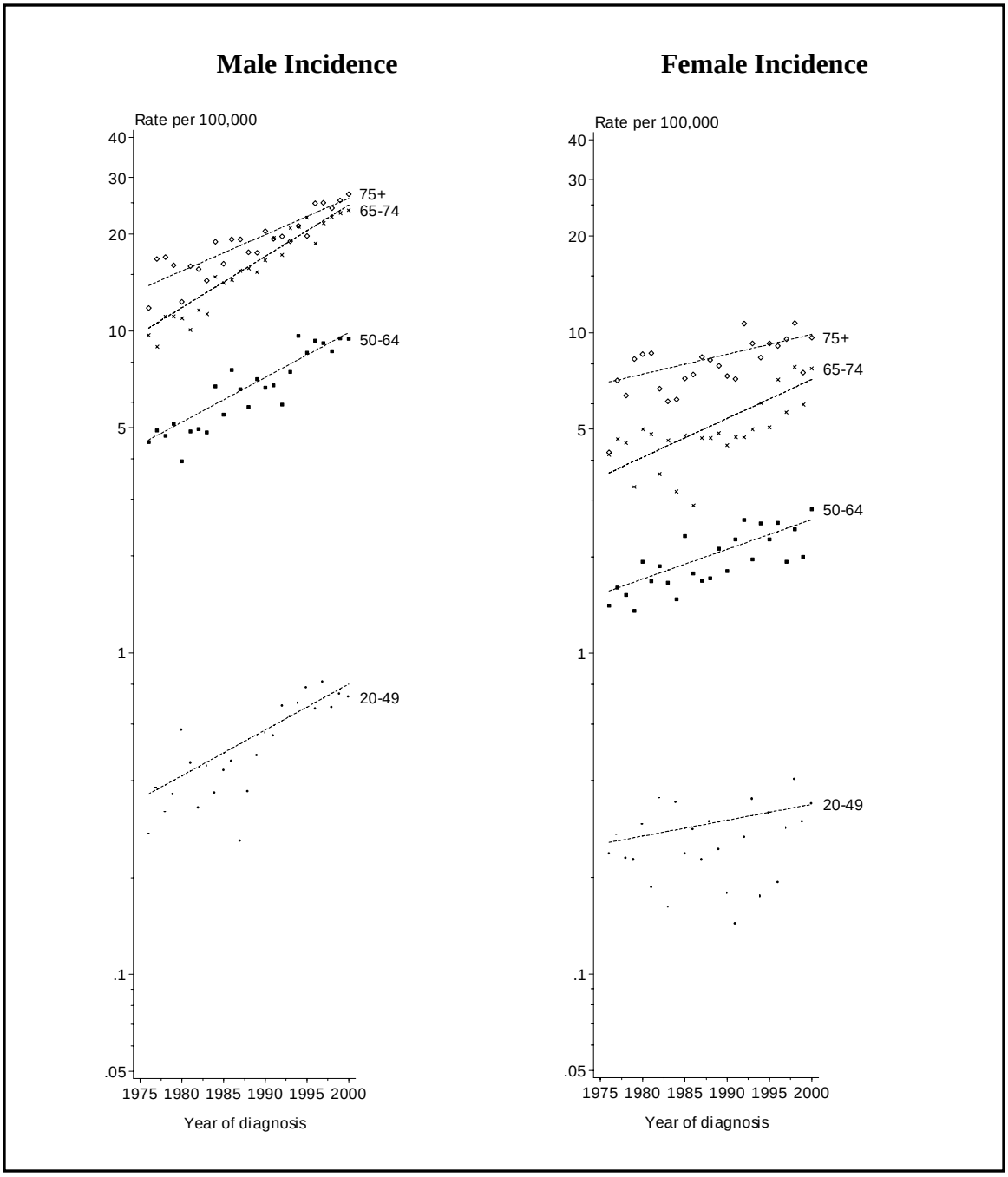
[a] Age-adjusted to the 1991 Canadian population

[b] Average annual age-specific mortality rate for the 5-year period and the total number of deaths (n) for the 5-year period.

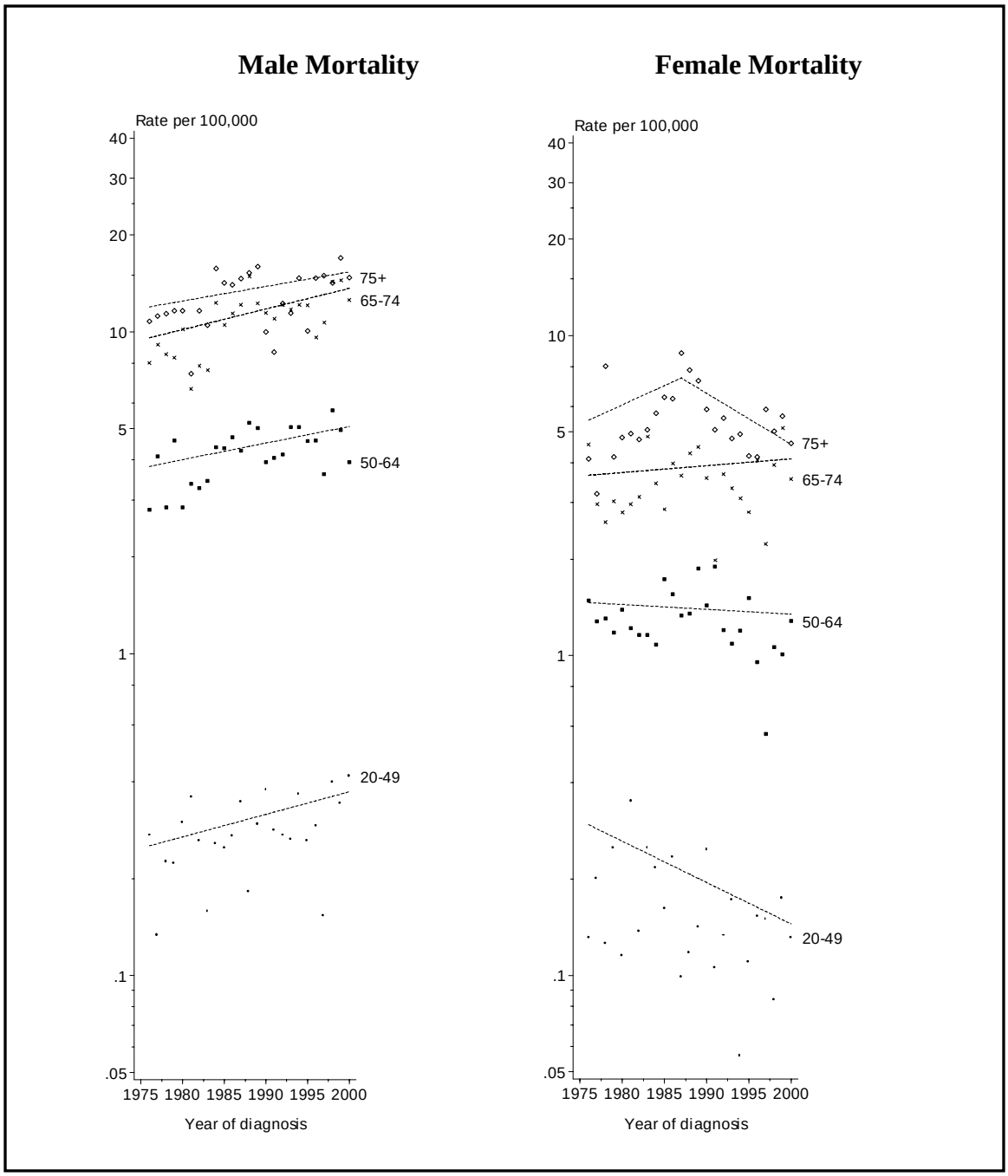


a. A joinpoint is the estimated year of HCC diagnosis (or death), based on the joinpont regression, when there was a change (at the 1.67% level of statistical significance there was evidence against the null hypothesis of no change) in the rate of increase or decrease in the age-adjusted HCC incidence (or mortality) rates.
b. H_o is the null hypothesis
c. H_1 is the alternate hypothesis.
d. P<0.0167 means at the 1.67% level of statistical significance there is evidence against the null hypothesis.
e. P>0.0167 means at the 1.67% level of statistical significance there is little evidence against the null hypothesis.

Appendix E. Algorithm of hypotheses tested in the joinpoint regression analysis (105) of the trends in the rate of change in the age-adjusted HCC incidence (or mortality) rates for a given sex (and a given age group) from 1976 through 2000 in Canada.



Appendix F. Age-adjusted (to the 1991 Canadian population) hepatocellular carcinoma incidence among persons aged 20 years or older in Canada, stratified by sex and age-group, from 1976 through 2000. The points are the observed incidence rates and the line segment joins the fitted incidence rates from the Joinpoint regression analysis. The slope of the regression line, multiplied by 100, is equal to the estimated annual percent change in the incidence rates during the period of observation (1976 through 2000).



Appendix G. Age-adjusted (to the 1991 Canadian population) hepatocellular carcinoma mortality among persons aged 20 years or older in Canada, stratified by sex and age-group, from 1976 through 2000. The points are the observed mortality rates and the line segment joins the fitted mortality rates from the Joinpoint regression analysis. The slope of the regression line, multiplied by 100, is equal to the estimated annual percent change in the incidence rates during the period of observation.

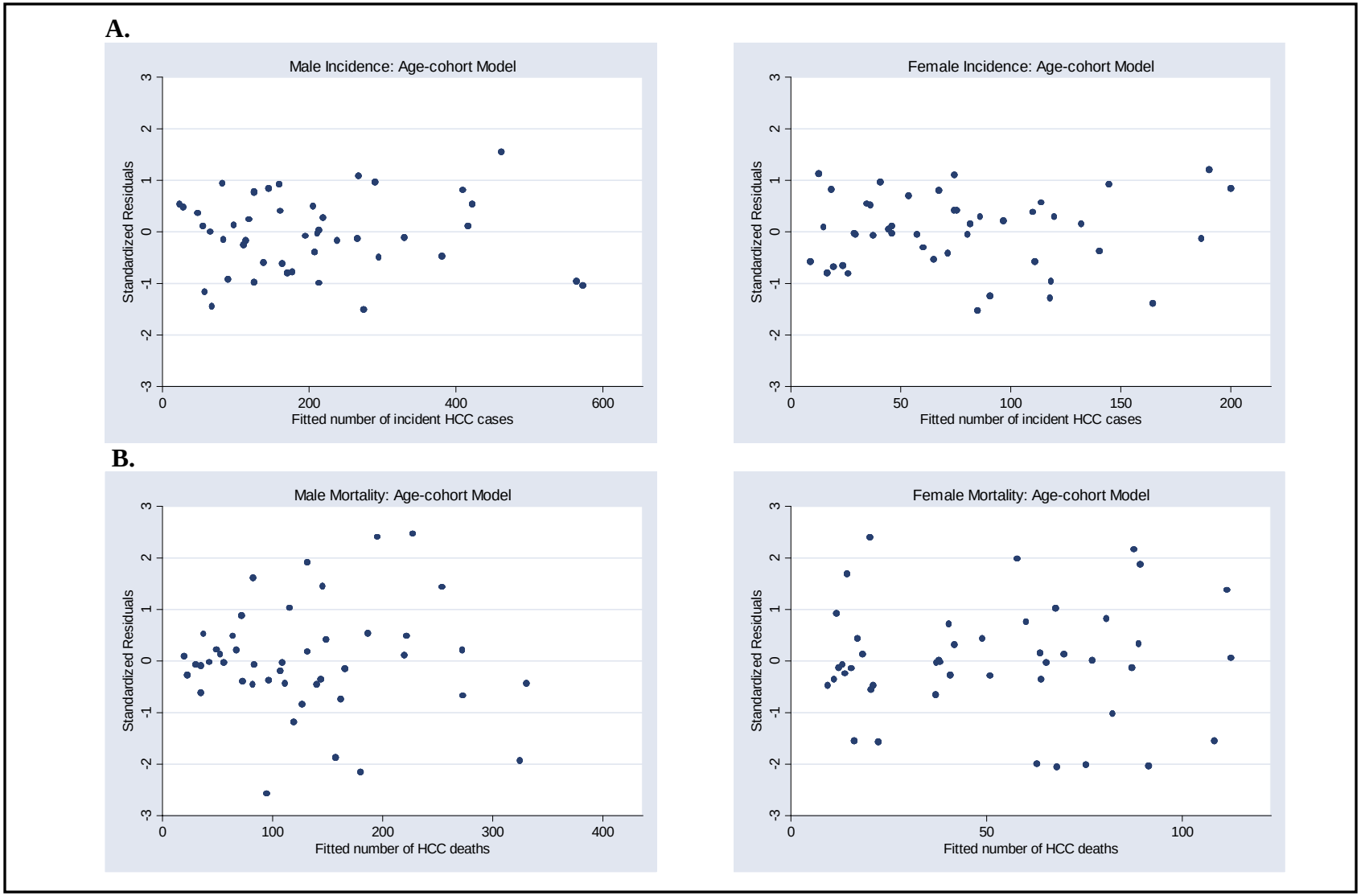
Appendix H. Period of observation (5-year) by birth-cohort and age-group (5-year) from 1976-1980 through 2011-2015.

Age-group (5-year)	Birth-cohort (mid-year)															
	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)	1957-1965 (1961)	1962-1970 (1966)	1967-1975 (1971)
40-44									1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015
45-49								1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015	
50-54							1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015		
55-59						1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015			
60-64					1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015				
65-69				1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015					
70-74			1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015						
75-79		1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015							
80-84	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015								

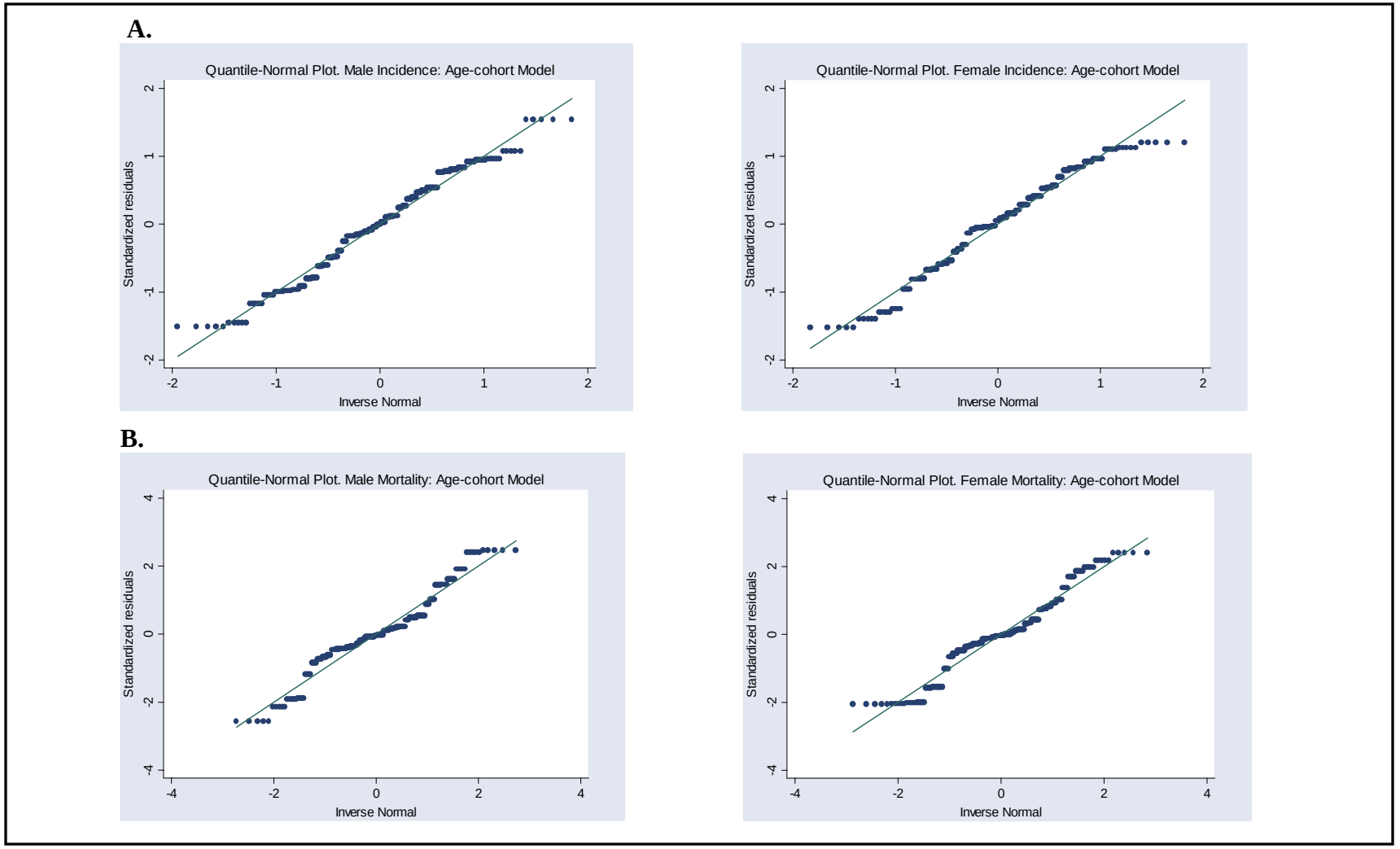
Appendix I. Relative risk for HCC associated with cohort year of birth and age-specific HCC risk (95% confidence interval (CI)) based on an age-cohort model of the observed HCC cases among persons aged 40-84 years in Canada, from 1976-1980 through 1996-2000.

	Male	Female
Mid-year of Birth-cohort	Incidence Rate Ratio (95% CI)	
1896	0.63 (0.56-0.71)	0.66 (0.58-0.76)
1901	0.72 (0.67-0.77)	0.86 (0.79-0.93)
1906	0.79 (0.75-0.83)	0.85 (0.80-0.91)
1911	0.87 (0.84-0.91)	0.93 (0.87-0.98
1916	1.0 (reference)	1.0 (reference)
1921	1.3 (1.2-1.3)	1.2 (1.1-1.2)
1926	1.6 (1.6-1.7)	1.3 (1.2-1.4)
1931	1.9 (1.8-2.0)	1.8 (1.7-1.9)
1936	2.1 (2.0-2.2)	1.6 (1.5-1.8)
1941	2.3 (2.1-2.2)	1.9 (1.8-2.1)
1946	3.4 (3.2-3.1)	1.9 (1.6-2.1)
1951	4.4 (4.1-4.8)	2.0 (1.7-2.4)
1956	5.3 (4.7-6.0)	2.7 (2.1-3.3)

Age-group (5-year)	Age-specfic Incidence rate per 100,000 person-years (95% CI)	
40-44	0.34 (0.31-0.37)	0.18 (0.15-0.20)
45-49	0.79 (0.73-0.84)	0.33 (0.29-0.37)
50-54	1.6 (1.6-1.7)	0.64 (0.59-0.71)
55-59	3.6 (3.4-3.7)	1.2 (1.1-1.3)
60-64	6.5 (6.3-6.8)	2.2 (2.0-2.3)
65-69	11.0 (10.7-11.4)	3.4 (3.3-3.6)
70-74	15.8 (15.3-16.4)	5.4 (5.1-5.7)
75-79	20.8 (20.1-21.5)	7.6 (7.2-8.0)
80-84	23.3 (22.3-24.3)	9.3 (8.8-9.8)

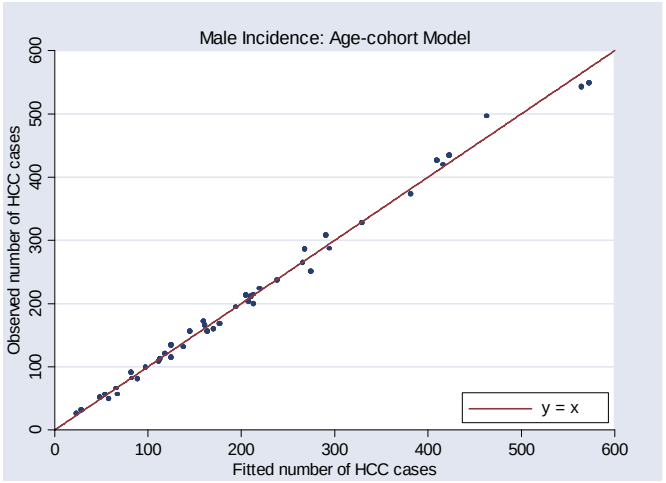


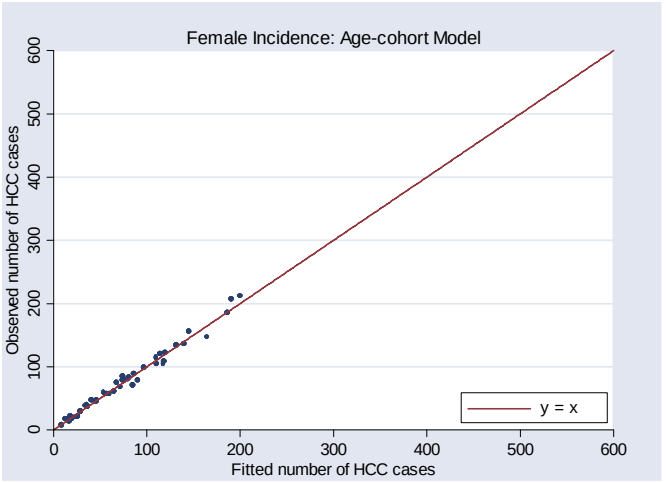
Appendix J. A. Standardized residuals (chi-residuals) from the age-cohort model of incident HCC cases among persons in Canada aged 40-84 years from 1976 through 2000 versus the fitted number of HCC cases, stratified sex. **B.** Standardized residuals (chi-residuals) from the age-cohort model of deaths from HCC among persons in Canada aged 40-84 years from 1976 through 2000 versus the fitted number of HCC deaths, stratified by sex. (Each point represents the value of the standardized residuals for given age-group (5-year) and a given birth-cohort.)



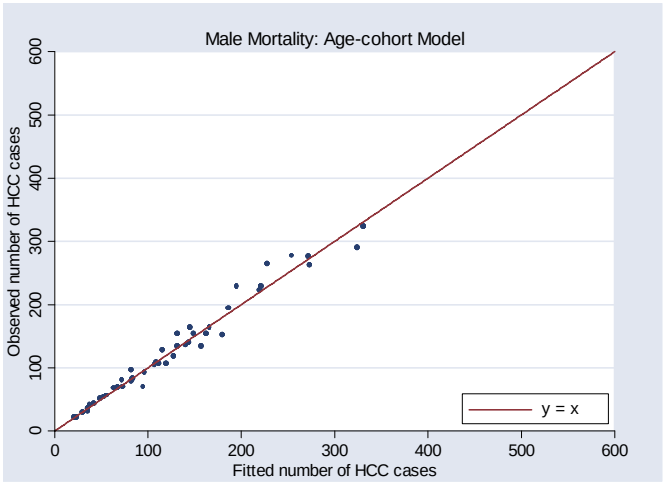
Appendix K. A. Quantile-Normal plot of the standardized residuals (chi-residuals) from the age-cohort model of incident HCC cases among persons in Canada aged 40-84 years from 1976 through 2000, stratified by sex. **B.** Quantile-Normal plot of the standardized residuals (chi-residuals) from the age-cohort model of deaths from HCC among persons in Canada aged 40-84 years from 1976 through 2000, stratified by sex.
(Each point represents the value of the standardized residuals for a given age-group (5-year) and a given birth-cohort.)

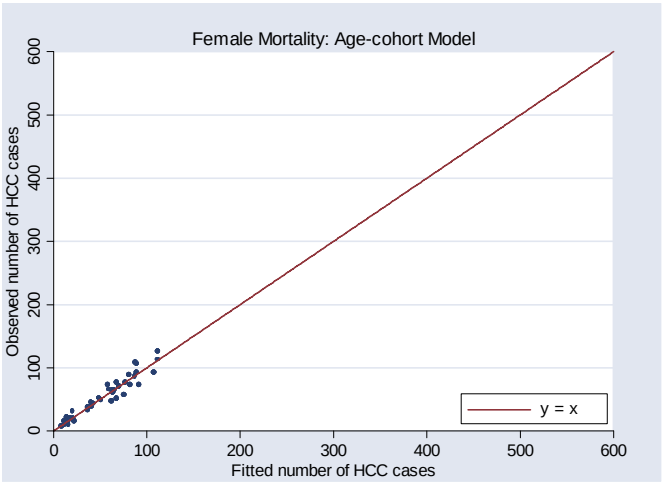
A.





B.





Appendix L. A. Observed number of HCC cases versus the fitted number of HCC cases from the age-cohort model of incident HCC cases among persons in Canada aged 40-84 years from 1976 through 2000, stratified by sex. **B.** Observed number of HCC deaths versus the fitted number of HCC deaths from the age-cohort model of HCC deaths among persons in Canada aged 40-84 years from 1976 through 2000, stratified by sex. (Each point represents the number of cases or deaths for a given age-group (5-year) and a given birth-cohort.)

Appendix M. Observed and fitted[a] HCC mortality rate per 100,000 person-years and number of HCC deaths (n) by age at death and birth- cohort (mid-year of birth-cohort), among males aged 40-84 years in Canada from 1976-1980 through 1996-2000.

Birth-cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)
	0.71	0.94	0.96	0.91	1.00	1.18	1.29	1.44	1.40	1.38	1.43	2.01	2.00
40-44 0.44									0.63 (21)[d] 0.62 (21)[e]	0.57 (22) 0.61 (23)	0.62 (30) 0.63 (30)	0.92 (51) 0.89 (49)	0.89 (56) 0.89 (56)
45-49 0.76								1.1 (35) 1.1(35)	0.99 (32) 1.1 (34)	1.1 (41) 1.0 (39)	1.1 (54) 1.1 (53)	1.5 (83) 1.5 (84)	
50-54 1.64							2.2 (68) 2.1 (64)	2.5 (80) 2.3 (74)	2.2 (70) 2.3 (73)	2.1 (78) 2.2 (82)	2.3 (109) 2.3 (110)		
55-59 2.98						2.6 (70) 3.5 (96)	3.6 (107) 3.8 (113)	5.0 (154) 4.3 (132)	4.3 (134) 4.2 (131)	4.2 (154) 4.1 (149)			
60-64 5.24					5.7 (127) 5.2 (117)	5.3 (134) 6.2 (158)	7.0 (194) 6.7 (188)	7.7 (229) 7.5 (223)	7.4 (222) 7.3 (221)				
65-69 8.26				7.3 (135) 7.6 (140)	8.2 (164) 8.3 (165)	11.4 (265) 9.8 (228)	10.7 (276) 10.6 (273)	10.6 (290) 11.9 (324)					
70-74 11.54			10.7 (140) 11.0 (145)	10.0 (153) 10.6 (162)	13.5 (229) 11.5 (196)	13.1 (262) 13.6 (274)	14.5 (323) 14.9 (330)						
75-79 13.60		12.6 (105) 12.8 (107)	12.0 (118) 13.0 (128)	13.9 (163) 12.4 (146)	11.4 (151) 13.6 (180)	17.6 (277) 16.1 (253)							
80-84 13.40	9.6 (43) 9.6 (43)	12.9 (69) 12.6 (67)	15.1 (97) 12.8 (83)	11.8 (93) 12.3 (96)	12.0 (107) 13.4 (120)								

[a] Fitted mortality rates and number of HCC deaths are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (mortality per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed mortality rate (per 100,000 person-years) and the observed number of HCC deaths.
[e] The second row for each age group is the fitted mortality rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of HCC deaths and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].

Appendix N. Observed and fitted[a] HCC mortality rate per 100,000 person-years and number of HCC deaths (n) by age at death and birth- cohort (mid-year of birth-cohort), among females aged 40-84 years in Canada from 1976-1980 through 1996-2000.

Birth-cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)
	0.98	0.92	1.04	1.12	1.00	1.05	1.02	1.10	0.99	0.89	0.55	0.69	0.58
40-44									0.31 (10)[d]	0.40 (15)	0.17 (8)	0.23 (13)	0.21 (13)
0.36									0.35 (11)[e]	0.32 (12)	0.20 (9)	0.25 (14)	0.21 (13)
45-49								0.32 (10)	0.66 (21)	0.40 (15)	0.25 (12)	0.34 (19)	
0.47								0.52 (16)	0.46 (15)	0.42 (16)	0.26 (12)	0.33 (18)	
50-54							0.58 (18)	0.48 (15)	0.98 (31)	0.51 (19)	0.40 (19)		
0.65							0.66 (21)	0.72 (22)	0.64 (20)	0.57 (21)	0.36 (17)		
55-59						1.3 (38)	1.1 (33)	1.5 (45)	1.2 (38)	1.1 (39)			
1.20						1.3 (38)	1.2 (38)	1.3 (40)	1.2 (38)	1.1 (39)			
60-64					2.1 (52)	2.3 (66)	2.1 (65)	2.5 (76)	1.5 (47)				
2.03					2.0 (49)	2.1 (61)	2.1 (63)	2.2 (69)	2.0 (63)				
65-69				3.1 (65)	2.6 (61)	3.2 (88)	2.5 (73)	3.1 (92)					
2.73				3.1 (64)	2.7 (65)	2.9 (80)	2.8 (82)	3.0 (89)					
70-74			3.2 (51)	4.4 (86)	4.9 (108)	3.6 (92)	4.6 (126)						
4.02			4.2 (68)	4.5 (87)	4.0 (88)	4.2 (108)	4.1 (112)						
75-79		4.2 (49)	5.1 (71)	6.3 (107)	3.8 (72)	5.0 (113)							
4.75		4.4 (51)	5.0 (69)	5.3 (89)	4.8 (91)	5.0 (112)							
80-84	5.0 (37)	4.9 (44)	6.7 (73)	4.4 (58)	5.1 (77)								
5.08	5.0 (37)	4.7 (42)	5.3 (58)	5.7 (75)	5.1 (77)								

[a] Fitted mortality rates and number of HCC deaths are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (mortality per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed mortality rate (per 100,000 person-years) and the observed number of HCC deaths.
[e] The second row for each age group is the fitted mortality rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of HCC deaths and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].

Appendix O. Observed and fitted[a] HCC incidence rate per 100,000 person-years and number of HCC cases (n) by age at diagnosis and birth-cohort (mid-year of birth-cohort), among males aged 40-84 years in Canada from 1976-1980 through 2011-2015.

Birth-cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)	1957-1965 (1961)	1962-1970 (1966)	1967-1975 (1971)
	0.63	0.72	0.79	0.87	1.00	1.29	1.63	1.88	2.13	2.26	3.38	4.42	5.29	5.29	5.29	5.29
40-44									0.80 (27)[d]	0.84 (32)	1.0 (49)	1.5 (82)	1.8 (112)			
0.34									0.72 (24)[e]	0.77 (29)	1.2 (58)	1.5 (83)	1.8 (114)	1.8 (122)	1.8 (114)	1.8 (106)
45-49								1.6 (51)	1.7 (56)	1.5 (56)	2.8 (134)	3.5 (194)				
0.79								1.5 (48)	1.7 (55)	1.8 (67)	2.6 (124)	3.5 (195)	4.2 (264)	4.2 (281)	4.2 (267)	
50-54							3.0 (91)	3.1 (99)	3.4 (109)	3.5 (131)	5.6 (264)					
1.64							2.7 (82)	3.1 (97)	3.5 (112)	3.7 (138)	5.6 (266)	7.3 (399)	8.7 (540)	8.7 (575)		
55-59						4.2 (114)	5.4 (160)	6.9 (213)	7.5 (236)	8.5 (307)						
3.56						4.6 (125)	5.8 (170)	6.7 (206)	7.6 (238)	8.0 (292)	12.0 (559)	15.7 (853)	18.8 (1144)			
60-64					7.0 (155)	7.8 (199)	10.3 (287)	12.6 (372)	13.9 (419)							
6.49					6.5 (145)	8.4 (213)	10.6 (295)	12.9 (382)	13.8 (418)	14.6 (509)	22.0 (963)	28.7 (1496)				
65-69				9.0 (167)	11.2 (224)	14.1 (328)	19.3 (496)	19.9 (542)								
11.03				9.6 (178)	11.0 (221)	14.2 (331)	18.0 (462)	20.7 (566)	23.5 (658)	24.9 (813)	37.3 (1528)					
70-74			11.9 (156)	13.8 (211)	16.8 (286)	21.2 (426)	24.7 (548)									
15.82			12.5 (163)	13.8 (212)	15.8 (268)	20.4 (410)	25.8 (573)	29.7 (712)	33.7 (844)	35.7 (1036)						
75-79		16.1 (134)	16.9 (166)	18.2 (214)	18.9 (250)	27.5 (434)										
20.80		15.0 (125)	16.4 (161)	18.2 (213)	20.8 (275)	26.8 (423)	34.0 (607)	39.1 (750)	44.3 (911)							
80-84	14.7 (66)	15.2 (81)	18.8 (121)	21.9 (172)	22.7 (203)											
23.31	14.7 (66)	16.8 (90)	18.4 (118)	20.4 (160)	23.3 (209)	30.1 (334)	38.0 (483)	43.8 (609)								

[a] Fitted incidence rates and number of HCC cases are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (incidence per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed incidence rate (per 100,000 person-years) and the observed number of HCC cases.
[e] The second row for each age group is the fitted incidence rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of HCC deaths and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].

Appendix P. Observed and fitted[a] HCC incidence rate per 100,000 person-years and number of HCC cases (n) by age at diagnosis and birth-cohort (mid-year of birth-cohort), among females aged 40-84 years in Canada from 1976-1980 through 2011-2015.

Birth-cohort (mid-year)[b]/ Age group (5-year)[c]	1892-1900 (1896)	1897-1905 (1901)	1902-1910 (1906)	1907-1915 (1911)	1912-1920 (1916)	1917-1925 (1921)	1922-1930 (1926)	1927-1935 (1931)	1932-1940 (1936)	1937-1945 (1941)	1942-1950 (1946)	1947-1955 (1951)	1952-1960 (1956)	1957-1965 (1961)	1962-1970 (1966)	1967-1975 (1971)
	0.66	0.86	0.85	0.93	1.00	1.17	1.30	1.82	1.63	1.93	1.85	2.00	2.66	2.33	2.33	2.33
40-44									0.23 (8)[d]	0.46 (17)	0.33 (16)	0.30 (17)	0.47 (30)			
0.18									0.29 (9)[e]	0.35 (13)	0.32 (15)	0.35 (19)	0.47 (30)	0.42 (29)	0.42 (26)	0.42 (24)
45-49								0.70 (22)	0.43 (14)	0.55 (21)	0.61 (29)	0.71 (40)				
0.33								0.59 (18)	0.53 (17)	0.64 (24)	0.61 (29)	0.65 (36)	0.87 (55)	0.77 (51)	0.77 (49)	
50-54							0.71 (22)	1.2 (37)	1.2 (38)	1.2 (45)	1.2 (57)					
0.64							0.84 (26)	1.2 (37)	1.1 (33)	1.2 (46)	1.2 (57)	1.3 (71)	1.7 (107)	1.5 (98)		
55-59						1.6 (47)	1.5 (47)	2.0 (61)	1.8 (58)	2.2 (83)						
1.16						1.4 (40)	1.5 (47)	2.1 (66)	1.9 (60)	2.2 (83)	2.2 (102)	2.3 (129)	3.1 (192)			
60-64					2.4 (59)	2.7 (78)	2.3 (71)	4.0 123)	3.6 (114)							
2.17					2.2 (53)	2.6 (73)	2.8 (86)	3.9 (121)	3.5 (111)	4.2 (153)	4.0 (184)	4.3 (236)				
65-69				3.5 (74)	3.4 (80)	3.8 (105)	4.6 (134)	6.2 (185)								
3.44				3.2 (67)	3.4 (81)	4.0 (112)	4.5 (131)	6.3 (185)	5.6 (170)	6.6 (234)	6.4 (281)					
70-74			5.2 (84)	5.1 (99)	4.9 (108)	5.7 (147)	7.6 (207)									
5.41			4.6 (75)	5.0 (97)	5.4 (119)	6.4 (164)	7.0 (191)	9.8 (271)	8.8 (252)	10.5 (344)						
75-79		6.8 (79)	5.6 (79)	6.2 (104)	8.2 (156)	9.4 (212)										
7.60		6.5 (76)	6.5 (91)	7.0 (119)	7.6 (145)	8.9 (200)	9.9 (237)	13.8 (335)	12.4 (315)							
80-84	6.2 (46)	7.6 (68)	8.1 (89)	9.1 (120)	9.0 (136)											
9.31	6.2 (46)	8.0 (71)	7.9 (87)	8.6 (114)	9.3 (141)	10.9 (199)	12.1 (237)	16.9 (338)								

[a] Fitted incidence rates and number of HCC cases are based on an age-cohort Poisson regression model.
[b] Poisson regression estimates of the birth-cohort relative rates are displayed beneath the birth years in the first row (the 1916 birth-cohort is the referent group).
[c] Poisson regression estimates of the age-specific rates (incidence per 100,000 person-years) are displayed beneath the 5-year age groups in the first column.
[d] The first row for each age group is the observed incidence rate (per 100,000 person-years) and the observed number of HCC cases.
[e] The second row for each age group is the fitted incidence rate and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate)] and in parentheses is the fitted number of HCC cases and it is equal to [(birth-cohort-specific relative rate) x (age-specific rate) x (person-years of observation)].