

# Trends in health care utilization and costs attributable to hepatocellular carcinoma, 2002–2009: a population-based cohort study

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## ABSTRACT

**Background** The incidence of hepatocellular carcinoma (HCC) and the complexity of its diagnosis and treatment are increasing. We estimated trends in net health care utilization, costs of care attributable to HCC in Ontario, and rate ratios of resource use at various stages of care.

**Methods** This population-based retrospective cohort study identified HCC patients and non-cancer control subjects, and health care resource utilization between 2002 and 2009. Generalized estimating equations were then used to estimate net health care utilization (HCC patients vs. the matched control subjects) and net costs of care attributable to HCC. Generalized linear models were used to analyze rate ratios of resource use.

**Results** We identified 2832 HCC patients and 2808 matched control subjects. In comparison with the control subjects, HCC patients generally used a greater number of health care services. Overall, the mean net cost of care per 30 patient-days (2013 Canadian dollars) attributable to outpatient visits and hospitalizations was highest in the pre-diagnosis (1 year before diagnosis), initial (1st year after diagnosis), and end-of-life (last 6 months before death, short-term survivors) phases. Mean net homecare costs were highest in the end-of-life phase (long-term survivors). In the end-of-life phase (short-term survivors), mean net costs attributable to outpatient visits and total services significantly increased to \$14,220 from \$1,547 and to \$33,121 from \$14,450 (2008–2009 and 2002–2003 respectively).

**Conclusions** In HCC, our study found increasing resource use and net costs of care, particularly in the end-of-life phase among short-term survivors. Our findings offer a basis for resource allocation decisions in the area of cancer prevention and control.

**Key Words** Costs, cost analyses, economics, end-of-life care, health care utilization, liver cancer, survivors

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 2nd most frequent cause of cancer-related death worldwide, accounting for approximately 600,000 deaths each year<sup>1</sup>. The incidence of HCC is increasing worldwide; more than 500,000 new cases occur annually, accounting for more than 5% of all cancers<sup>1</sup>. Cirrhosis often precedes HCC, and major risk factors for HCC include hepatitis B and C infections, HIV co-infection<sup>2</sup>, alcohol- and non-alcohol-induced liver disease (typically nonalcoholic steatohepatitis), diabetes, obesity, and smoking<sup>3–8</sup>.

In Canada, the incidence of HCC has increased significantly both for men (3.6% annually between 1970 and 2007) and for women (2.4% annually between 1986 and 2007)<sup>9</sup>. The increase in the HCC incidence since the mid-1980s is related to the aging Canadian population, the significant domestic burden of hepatitis C, and the ongoing trend in immigration from high-risk HCC countries where hepatitis B and C infections are endemic<sup>1,10,11</sup>. Additionally, HCC-related mortality rates increased in both sexes between 2000 and 2009, and are likely to continue to increase given the increase in HCC incidence<sup>9</sup>. Because of a low HCC surveillance rate and the fact that HCC is generally asymptomatic

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until very late in the progression of the disease<sup>12,13</sup>, patients are often diagnosed at an advanced stage of the disease at the time of referral for treatment, leading to relatively short survival periods<sup>9,14</sup>.

Over the years, HCC has imposed a substantial burden on the Canadian health care system<sup>15</sup>. The rising incidence of HCC and cancer-related mortality has pointed to a need for additional health care services and resources to be allocated for prevention, screening, and diagnostic, therapeutic, and supportive care strategies in Canada. To inform policy decision-makers, the objectives of the present study were therefore to estimate trends in net health care utilization and costs of care attributable to HCC in Ontario between 2002 and 2009, as well as the relative risks (RRs) of health care utilization at various stages of care.

## METHODS

### Study Design and Population

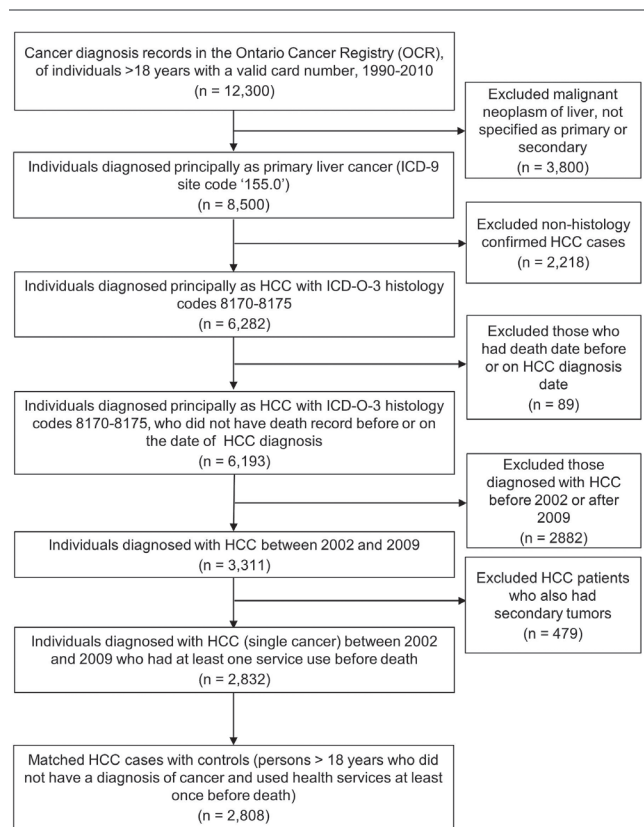
This population-based retrospective cohort study considered all eligible patients 18 years of age and older who were diagnosed with HCC in Ontario between 1 January 2002 and 31 December 2009. The study design included 3 key components and used an incidence-based approach.

Component 1 was a phase-of-care approach to estimate health care utilization and costs<sup>16-20</sup> that divided each patient's care into 3 discrete care phases: pre-diagnosis, initial, and end-of-life. The pre-diagnosis phase, often a resource-intensive component of cancer care episodes<sup>21,22</sup>, was defined as the 12 months before diagnosis. That period was chosen so as also to capture any screening that might have occurred during that period. The initial phase was defined as the first 12 months after diagnosis. The end-of-life phase was defined as the 6 months preceding death, with that analysis including only patients who died during the study period (2002–2011). Depending on length of time from diagnosis to death, patients who died were stratified into short-term survivors (survived <6 months) and long-term survivors (survived ≥6 months). A hierarchical approach (end-of-life period > initial period) was used so that all phases were mutually exclusive. For example, if a patient died 10 months after diagnosis, 6 months was allotted to the end-of-life period, and 4 months, to the initial period.

Component 2 was an estimation of the mean net health care utilization attributable to HCC (difference between HCC patients and matched non-cancer control subjects in the mean number of health services used) and of the RR for health care utilization, overall and by year of diagnosis ("index year," for the pre-diagnosis and initial phases) and year of death (for the end-of-life phase).

Component 3 was an estimation of the net cost of care attributable to HCC.

The Ontario Cancer Registry (OCR)<sup>23</sup> was used to create the study cohort. Figure 1 summarizes the selection criteria for the HCC patient sample. The site code 155.0 (*International Classification of Diseases*, 9th revision) and histology codes 8170–8175 (*International Classification of Diseases for Oncology*, 3rd edition) were used to identify primary hepatic neoplasms. All adult patients with HCC were followed from their date of diagnosis to date of death or until June 2011 (at least 18 months after diagnosis) to



**FIGURE 1** Flowchart describing the selection of the study population. ICD = International Classification of Diseases; HCC = hepatocellular carcinoma; ICD-O = International Classification of Diseases for Oncology.

capture deaths. Patients were excluded if the HCC diagnosis was recorded on or after the date of death.

Potential control subjects were selected from a 5% random sample of the reference Ontario population database (Registered Persons Database), including residents of Ontario with unique health card numbers registered for the purpose of Ontario health insurance coverage and Ontario drug benefits provided through a universally funded health care system administered by the Ontario Ministry of Health and Long-Term Care. Eligible control subjects were individuals 18 years of age and older who did not have a diagnosis of cancer and who had used health services at least once before death. Although health care services vary in some respects, the system provides free access to hospital and emergency department (ED) visits, physician services, and homecare; copayments for long-term care placements; and copayments for prescription medications for individuals 65 years of age and older.

Ethics approval for the study was granted by the University of Toronto Health Sciences Research Ethics Board. Informed consent was not obtained because this secondary analysis accessed existing de-identified data; consent was therefore deemed to be neither feasible nor necessary.

### Data Sources

The Ontario Ministry of Health and Long-Term Care routinely collects health administrative information for the

approximately 13.6 million people resident in Ontario, Canada's most populous province. Those data are housed at the Institute for Clinical Evaluative Sciences in several linked health care service utilization databases for Ontario.

The ocr is a population-based tumour registry that contains information on all new cases of cancer (except for non-melanoma skin cancers) diagnosed in Ontario since 1964. It captures about 95% of all cancers in the province and has been shown to be both accurate and reliable<sup>24–27</sup>.

To estimate comorbidities, frequency and type of hospital admissions, length of stay, and in-hospital mortality, the cancer registry cohort was linked to the Discharge Abstract Database maintained by the Canadian Institute for Health Information. Where possible, hospitalization records from the date of diagnosis were used to assign each patient and control subject a baseline Charlson–Deyo comorbidity index. If patients did not have a hospitalization record at their diagnosis date, baseline comorbidity was determined by looking 2 years back into the hospitalization data to find the most recent hospitalization record; the comorbidity score from that hospitalization was then applied<sup>15,28,29</sup>. The Charlson–Deyo comorbidity index at baseline was marked as “missing” if the individual had no hospitalization records at diagnosis or during the 2 years before diagnosis. Comorbidity was adjusted for each hospitalization after baseline.

Health care utilization and direct medical costs were determined from the perspective of the Ontario Ministry of Health and Long-Term Care. Health care utilization and costs associated with outpatient physician visits and laboratory tests were determined from the physician Claims History Database of the Ontario Health Insurance Plan. Emergency department visits and same-day surgery were determined using the National Ambulatory Care Reporting System database. Prescription medication use and costs were obtained from the Ontario Drug Benefit Program database. Client-level data for homecare services were obtained from the Ontario Home Care Administrative System (pre-2005) and the Ontario Home Care Database (post-2005).

### Study Variables

The ocr includes data for the date of hcc diagnosis, age, sex, birth location, urban or rural residence, cause of death, and date of death.

Median neighbourhood household income was determined by linking patient postal codes found in the ocr to Canadian census data, which categorizes neighbourhoods into income quintiles. The least and most well-off 20% of neighbourhoods were respectively included within the 1st and the 5th quintiles<sup>30</sup>.

The Charlson–Deyo comorbidity index was calculated using methods previously described<sup>31,32</sup>; an *International Classification of Diseases* (10th revision) coding algorithm was applied to the diagnostic field codes from the hospitalization data (excluding diagnoses for liver disease and metastatic cancer). Conditions were weighted and then totalled to provide an overall comorbidity index value for a given episode, which was then categorized into one of five groups (0, 1, 2,  $\geq 3$ , or no hospitalization record), representing varying degrees of comorbidity as already

described. Treatments for hcc—such as potentially curative treatment (surgical resection, liver transplantation, or radiofrequency ablation), noncurative treatment (chemotherapy, sorafenib, or transarterial chemoembolization), palliative care, and no treatment—were determined using databases maintained by the Canadian Institute for Health Information, the Ontario Health Insurance Plan, and the Ontario Drug Benefit Program. Sorafenib was approved by Health Canada in late 2007. The definitions of comorbidity and hcc treatments used were those established in previous studies<sup>15,28,29</sup>. Table 1 presents the codes used to identify hcc treatments.

The categories of health care utilization included family physician visits, specialist visits, ED visits, acute inpatient hospitalizations, same-day surgery, prescription medications, homecare use, and total services (the sum of the numbers for all health care utilization types). For primary care and specialist visits, health care utilization was determined by using physician and laboratory service fee codes to estimate outpatient costs (physician services and other fee-for-service practitioner services). If a patient had multiple service billings from specialists or a family physician on the same day, only 1 unique visit was counted for that day. Similarly, 1 unique homecare use was counted when there were multiple records of homecare services provided to a patient on the same day. For each phase of care, we estimated the number of health services used per 30 patient–days of follow-up, while accounting for the varying length of follow-up for each patient within each phase. The length of follow-up for each patient within each phase was calculated using the hierarchical approach already described and taking into consideration whether the patient had died by the end of study follow-up and, if dead, the length of time from date of diagnosis to death. For example, if a patient did not die during study follow-up, the patient would have 1 year in the initial phase, but would not be included in the end-of-life analysis. If a patient died at least 1 year after diagnosis, the first 365 days from diagnosis would be allotted to the initial phase, and the remaining period (from the 366th day from diagnosis) to death would be allotted to the end-of-life phase. If a patient died within 1 year after diagnosis (for instance, 10 months after diagnosis), the lengths of the follow-up periods allotted to the initial and end-of-life phases would be 4 and 6 months, respectively, and if a patient died 5 months after diagnosis, that patient would have 5 months in the end-of-life phase, but would not contribute any length of follow-up to the initial phase.

The categories of health care costs included outpatient visits, ED visits, acute inpatient hospitalizations, same-day-surgery, prescription medications, homecare visits, and total services. The costs of outpatient visits were estimated using the available 2008 unit cost for each physician and laboratory service fee code. The main costs of hospitalization, ED visits, and same-day-surgery for a particular year were estimated using the Resource Intensity Weight methodology developed by the Canadian Institute for Health Information<sup>33–36</sup>. To determine person-level costs for the hcc patients, we calculated unit costs (for example, hospitalization-specific cost per weighted case multiplied by the individual's resource intensity weight for a given hospitalization). Paralleling the calculation of net health

**TABLE 1** Treatment procedures for patients with hepatocellular carcinoma

Treatment	Code type <sup>a</sup>		
	CCP	CCI	OHIP
<i>Potentially curative therapy</i>			
Local excision or destruction of lesion or tissue of liver	62.1		
Partial hepatectomy	62.12		
Other destruction of lesion of liver	62.19		
Lobectomy of liver	62.20		
Excision partial, liver, using endoscopic (laparoscopic) approach		1OA87DA	
Excision partial, liver, using open approach		1OA87LA	
Excision partial, liver, using ultrasonic aspirator device (for dissection) and open approach		1OA87LAAZ	
Liver excision, complete left or right lobectomy			S267
Liver excision of lesion			S269
Liver excision, hepatectomy, left lateral segmental excision			S270
Liver excision, extended right lobectomy			S271
Liver excision, partial lobectomy			S275
Total hepatectomy	62.3		
Liver transplant	62.4		
Auxiliary liver transplant	62.41		
Other transplant of liver	62.49		
Transplant, liver of a deceased donor full size liver		1OA85LAXXK	
Transplant, liver of a deceased donor, multiorgan liver with intestine, pancreas, spleen, or stomach (or any combination of)		1OA85VCXXK	
Transplant, liver of a living donor, split liver		1OA85WLXXJ	
Transplant, liver of a deceased donor split liver (or reduced pediatric-size liver)		1OA85WLXXX	
Living donor orthotopic liver transplantation recipient			S266
Liver excision, liver transplant recipient			S294
Digestive system–liver, repeat liver transplant			S295
Destruction, liver endoscopic (laparoscopic) approach using radiofrequency		1OA59DAAW	
Destruction, liver percutaneous approach using radiofrequency		1OA59HAAW	
Destruction, liver open approach using radiofrequency		1OA59LAAW	
Radiofrequency ablation			J069
<i>Noncurative therapy</i>			
Percutaneous ablation			
Destruction, liver endoscopic (abdominal) approach using cryoprobe		1OA59DAAD	
Destruction, liver endoscopic (abdominal) approach using laser		1OA59DAAG	
Destruction, liver endoscopic (abdominal) approach using device NEC		1OA59DAGX	
Destruction, liver endoscopic (abdominal) approach using chemical cautery agent (for example, ethanol)		1OA59DAX7	
Destruction, liver percutaneous approach using chemical cautery agent (for example, ethanol)		1OA59HAX7	
Destruction, liver open approach using cryoprobe		1OA59LAAD	
Destruction, liver open approach using laser		1OA59LAAG	
Destruction, liver open approach using device NEC		1OA59LAGX	
Destruction, liver open approach using chemical cautery agent (for example, ethanol)		1OA59LAX7	
Chemotherapy			
Diagnostic and therapeutic injection(s) or infusion(s), test dose (bleomycin and L-asparaginase once per patient per drug)			G075
Diagnostic and therapeutic injection or infusion (intravenous chemotherapy), each additional injection			G281
Single-agent intravenous chemotherapy—that is, doxorubicin, daunorubicin, epirubicin, mitoxantrone, cisplatin, or bleomycin (>10 U/m <sup>2</sup> )			G339
[Paclitaxel], rituximab, trastuzumab, bortezomib, docetaxel administration or multiple agent intravenous chemotherapy including at least one of either doxorubicin, daunorubicin, epirubicin, mitoxantrone, cisplatin, or bleomycin (>10 U/m <sup>2</sup> )			G345
Special single agent chemotherapy utilizing either high-dose methotrexate with folinic acid rescue, methotrexate given in a dose of >1 g/m <sup>2</sup> , high dose cisplatin (>75 mg/m <sup>2</sup> given concurrently with hydration and osmotic diuresis, high dose cytosine, arabinoside (>2 g/m <sup>2</sup> ), or high dose cyclophosphamide (>1 g/m <sup>2</sup> )			G359



TABLE I Continued

Treatment	Code type <sup>a</sup>		
	CCP	CCI	OHIP
<i>Noncurative therapy</i>			
Chemotherapy			
Single injection (for agents other than doxorubicin, cisplatin, bleomycin, or high dose methotrexate)			G381
Supervision of chemotherapy (marrow suppressant) for malignant or autoimmune disease by telephone, monthly			G382
Arteries–cannulation–chemotherapy–hepatic (TACE)			R776
<i>Supportive and palliative care</i>			
General or family practice, special palliative care consultation			A945
Special palliative care consultation, hospital inpatient			C945
Palliative care			C982
Palliative care support, individual care, 0.5 hours or major part			K023

<sup>a</sup> The CCI is the new national standard for classifying health care procedures. It is the companion classification system to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Canada, and replaces the CCP and the intervention portion of the International Classification of Diseases, 9th revision, Clinical Modification, in Canada. The CCP was originally developed by Statistics Canada in 1978 to meet Canadian needs for a procedural classification to be used in conjunction with the International Classification of Diseases, 9th revision. CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CCI = Canadian Classification of Health Interventions; OHIP = Ontario Health Insurance Plan; NEC = not elsewhere classified; TACE = transarterial chemoembolization.

care utilization attributable to hcc, we calculated the total costs of care and the lengths of follow-up periods (in days) for patients and control subjects within each phase of care, taking into consideration whether the individual had died by the end of the study period.

### Matching Patients and Control Subjects

Matching on sociodemographic and clinical factors associated with resource use was performed as detailed by Thein *et al.*<sup>15</sup> Propensity scores were derived by fitting a logistic model with hcc status as the dependent variable and the index year or year of death, age, sex, urban or rural residence, income quintile, Charlson–Deyo comorbidity index, and interaction between age and comorbidity as the independent variables.

Matching for each cohort used two sets of patients and control subjects: Cohort 1 included all incident patients, who were matched 1:1 to control subjects to estimate utilization for the pre-diagnosis and initial phases. Cohort 2 included all patients who died (classified as short-term or long-term survivors). To estimate utilization for the end-of-life phase, short-term and long-term survivors were separately matched 1:1 to control subjects who had died. Each patient was matched to the closest non-cancer control subject who met these criteria: age  $\pm$  10 years at the index date; same sex; same index year (for Cohort 1) or same year of death (for Cohort 2); same Charlson–Deyo comorbidity index; and a propensity score within a caliper width of 0.2 standard deviation<sup>15</sup>.

### Statistical Analysis

Differences in sociodemographic and clinical characteristics of hcc patients by year of diagnosis (2002–2003, 2004–2005, 2006–2007, and 2008–2009) were examined using the chi-square test and Fisher exact test, as appropriate. In addition, sociodemographic and clinical information, including age, sex, urban or rural residence, income

quintile, Charlson–Deyo comorbidity index, index year, and death year are presented for matched and unmatched patients and control subjects. All statistical analyses were performed using the SAS software application (version 9.4; SAS Institute, Cary, NC, U.S.A.).

### Estimation of Health Care Utilization Attributable to HCC

To account for the matched study design, generalized estimating equations were used to estimate net health care utilization per 30 patient–days attributable to hcc for each care phase [mean with 95% confidence interval (ci)], adjusting for age, sex, urban or rural residence, income quintile, and Charlson–Deyo comorbidity index. Generalized linear models were used to analyze the RR for health care utilization, comparing hcc patients with matched control subjects, specifying a negative binomial distribution and a log-link function, and also adjusting for the same covariates. The RR was reported because that measure provides valuable insights into the differences in health care utilization between patients and control subjects on a relative scale. Mean net resource utilization and RR were determined for the overall study period (2002–2009) and by year of diagnosis (2002–2003, 2004–2005, 2006–2007, 2008–2009) for the pre-diagnosis and initial phases, and by year of death (in 2-year subgroups) for the end-of-life phase.

### Estimation of Health Care Costs Attributable to HCC

To account for the matched study design, generalized estimating equations were used to estimate the mean (95% ci) net costs of care attributable to hcc per 30 patient–days, adjusting for age, sex, urban or rural residence, income quintile, and Charlson–Deyo comorbidity index. To account for inflation, the Statistics Canada Consumer Price Index for health care and personal items for Ontario<sup>37</sup> was used to adjust all costs to 2013 Canadian dollars. As for

health care utilization, the results are reported by year of diagnosis for the pre-diagnosis and initial phases, and by year of death for the end-of-life phase.

## RESULTS

### Study Population Characteristics

Overall, 2832 patients in the OCR were identified as having a primary diagnosis of HCC between 2002 and 2009 (Table II). The number of HCC cases increased to 841 in 2008–2009 from 570 in 2002–2003. Comorbidity (one or more diseases) also increased to 46.1% from 40.5% ( $p = 0.004$ ). Radio-frequency ablations in the year after diagnosis increased significantly to 21.9% in 2008–2009 from 6.3% in 2002–2003 ( $p < 0.001$ ); however, surgical resections decreased to 15.3% from 21.2% ( $p = 0.007$ ). In addition, the use of sorafenib increased to 13.9% in 2008–2009 from 6.2% in 2006–2007 ( $p < 0.001$ ).

For the pre-diagnosis phase, 2808 of 2832 patients were able to be matched to control subjects; for the initial phase, 1914 of 1927 could be matched; and for the end-of-life phase, 686 of 902 (short-term survivors) and 947 of 1226 (long-term survivors) could be matched. Patients in the pre-diagnosis and initial phases were able to be closely matched to non-cancer controls; however, many patients who contributed time to the end-of-life phase could not be matched to suitable controls (Table III).

In the cohort used for the pre-diagnosis phase analysis, 571 patients (20.3%) and 2362 control subjects (84.1%) died during study follow-up. In the cohort used for the initial phase analysis, 571 patients (29.8%) and 1628 control subjects (85.1%) died during study follow-up.

### Health Care Utilization Attributable to HCC

Tables IV–V present the mean utilization and costs per 30 patient–days for matched HCC patients and control subjects for various sources of care, by care phase and index or death year.

#### Utilization by Resource Type

Figures 2 and 3 show the net values attributable to HCC from a comparison of the overall mean number of health care visits and of the RRs for resource use per 30 patient–days by HCC patients and by non-cancer control subjects during the various phases of care (2002–2009 or 2002–2011). In general, HCC patients received a greater number of health care services (Figures 2 and 3); exceptions were same-day surgery during the pre-diagnosis phase (utilization:  $-1.77$ ; 95% CI:  $-2.49$  to  $-1.04$ ; RR: 0.23; 95% CI: 0.20 to 0.26) and prescription medications during the end-of-life phase for short-term survivors (utilization:  $-3.02$ ; 95% CI:  $-3.93$  to  $-2.11$ ; RR: 0.60; 95% CI: 0.51 to 0.71) and for long-term survivors (utilization:  $-3.12$ ; 95% CI:  $-4.00$  to  $-2.24$ ; RR: 0.65; 95% CI: 0.58 to 0.72).

Compared with the non-cancer control subjects, HCC patients made a substantially higher number of specialist visits during the end-of-life phase for short-term survivors (average utilization: 9.69 visits; 95% CI: 8.81 to 10.57 visits), during the initial phase (utilization: 2.89 visits; 95% CI: 2.72 to 3.06 visits), and during the pre-diagnosis phase (utilization: 1.01 visits; 95% CI: 0.92 to 1.11 visits). The number

of family physician visits made by HCC patients was highest during the end-of-life phase for short-term survivors (utilization: 4.23 visits; 95% CI: 3.63 to 4.84 visits). During the initial phase, utilization was 0.87 visits (95% CI: 0.76 to 0.98 visits), and during the end-of-life phase for long-term survivors, it was 0.73 visits (95% CI: 0.50 to 0.97 visits). The number of homecare visits was highest during the end-of-life phase for long-term survivors (utilization: 2.03 visits; 95% CI: 1.53 to 2.54 visits). During the end-of-life phase for short-term survivors, utilization was 1.57 visits (95% CI: 1.00 to 2.14 visits), and during the initial phase, it was 1.10 visits (95% CI: 0.82 to 1.39 visits; Figure 2).

The HCC patients made ED visits at 24.37 times (RR) the rate of the non-cancer control subjects during the initial phase (95% CI: 20.10 to 29.55), at 4.99 times the control rate during the end-of-life phase for short-term survivors (95% CI: 4.23 to 5.89), and at 3.39 times the control rate during the pre-diagnosis phase (95% CI: 2.90 to 3.98). In addition, HCC patients were hospitalized at 14.24 times (RR) the control rate during the initial phase (95% CI: 9.62 to 21.09), at 10.77 times the control rate during the end-of-life phase for short-term survivors (95% CI: 8.57 to 13.54), and at 2.99 times the control rate during the pre-diagnosis phase (95% CI: 2.08 to 4.32). Lastly, HCC patients received same-day surgery services at 5.74 times (RR) the control rate during the initial phase (95% CI: 4.01 to 8.20), at 4.90 times the control rate during the end-of-life phase for short-term survivors (95% CI: 2.82 to 8.51), and at 1.74 times the control rate during the end-of-life phase for long-term survivors (95% CI: 1.11 to 2.73; Figure 3). In a comparison of health care utilization by short-term and long-term survivors during the end-of-life phase, rates of health care utilization by the short-term survivors were significantly higher for all services with the exception of homecare visits and prescription medications, for which service use was not significantly different.

#### Trends by Type of Resources

Tables VI–VIII present trends in health care utilization over time (to 2008–2009 and to 2010–2011 from 2002–2003). The analysis of trends over time showed that health care utilization numbers attributable to HCC remained relatively consistent for all phases of care; an exception was hospitalizations, which increased 573% to 0.10 (95% CI: 0.07 to 0.14) hospitalizations per 30 patient–days in 2010–2011 from  $-0.02$  (95% CI:  $-0.09$  to 0.05) hospitalizations per 30 patient–days in 2002–2003 during the end-of-life phase for long-term survivors. At the same time, net prescription medications use by HCC patients decreased  $-4434\%$  to  $-3.64$  (95% CI:  $-5.50$  to  $-1.77$ ) from 0.08 (95% CI:  $-2.03$  to 2.19; Table VIII) per 30 patient–days. Similarly, the RRs for resource use remained relatively consistent over time for all phases of care. Exceptions occurred in the initial phase, in which specialist visits decreased [to a 2008–2009 RR of 3.99 (95% CI: 3.56 to 4.48) from a 2002–2003 RR of 6.44 (95% CI: 5.40 to 7.67), representing a change of  $-38\%$ ], as did ED visits [to RR 11.23 (95% CI: 8.07 to 15.62) from RR 37.79 (95% CI: 20.35 to 70.18), for a change of  $-70\%$ ] and total services [to RR 2.71 (95% CI: 2.42 to 3.04) from RR 3.92 (95% CI: 3.37 to 4.56), for a change of  $-31\%$ ; Table VI]; and in the end-of-life phase for long-term survivors, in which prescription medication use

decreased over time [to a 2010–2011 RR of 0.64 (95% CI: 0.51 to 0.80; Table VIII) from a 2002–2003 RR of 1.35 (95% CI: 0.89 to 2.05), for a change of –52%].

### Health Care Costs Attributable to HCC

Figure 4 presents the overall mean net cost of care per 30 patient–days attributable to HCC for each type of service,

**TABLE II** Baseline characteristics of patients diagnosed with hepatocellular carcinoma by year of diagnosis, 2002–2009

Variable	Year of diagnosis <sup>a</sup>					p Value
	Overall	2002–2003	2004–2005	2006–2007	2008–2009	
Patients (n)	2832	570	661	760	841	
Age group [n (%)]						
<60 Years	1089 (38.5)	219 (38.4)	273 (41.3)	285 (37.5)	312 (37.1)	
60–69 Years	735 (26.0)	145 (25.4)	172 (26.0)	205 (27.0)	213 (25.3)	
70–79 Years	742 (26.2)	168 (29.5)	162 (24.5)	186 (24.5)	226 (26.9)	
≥80 Years	266 (9.4)	38 (6.7)	54 (8.2)	84 (11.1)	90 (10.7)	0.070
Male sex [n (%)]	2238 (79.0)	451 (79.1)	512 (77.5)	602 (79.2)	673 (80.0)	0.681
Residence [n (%)]						
Rural	220 (7.8)	38 (6.7)	62 (9.4)	44 (5.8)	76 (9.0)	
Urban	2609 (92.1)	532 (93.3)	599 (90.6)	713 (93.8)	765 (91.0)	
Missing	— (0.1)	0	0	— (0.4)	0	0.010 <sup>b</sup>
Income quintile [n (%)]						
Q1 (lowest)	727 (25.7)	150 (26.3)	179 (27.1)	180 (23.7)	218 (25.9)	
Q2	628 (22.2)	113 (19.8)	143 (21.6)	187 (24.6)	185 (22.0)	
Q3	565 (20.0)	125 (21.9)	146 (22.1)	134 (17.6)	160 (19.0)	
Q4	477 (16.8)	103 (18.1)	104 (15.7)	125 (16.5)	145 (17.2)	
Q5 (highest)	422 (14.9)	78 (13.7)	84 (12.7)	128 (16.8)	132 (15.7)	0.091 <sup>b</sup>
Missing	13 (0.5)	— (0.2)	— (0.8)	6 (0.8)	— (0.1)	
Charlson–Deyo comorbidity index [n (%)]						
0	1159 (40.9)	243 (42.6)	304 (46.0)	275 (36.2)	337 (40.1)	
1	612 (21.6)	113 (19.8)	121 (18.3)	188 (24.7)	190 (22.6)	
2	340 (12.0)	60 (10.5)	72 (10.9)	90 (11.8)	118 (14.0)	
≥3	292 (10.3)	58 (10.2)	69 (10.4)	85 (11.2)	80 (9.5)	
No hospitalization record	429 (15.2)	96 (16.8)	95 (14.4)	122 (16.1)	116 (13.8)	0.013
Stage at diagnosis [n (%)]						
Early (stages 0–I)	236 (10.4)		36 (5.5)	79 (10.4)	121 (14.4)	
Intermediate (stage II)	322 (14.2)		63 (9.5)	109 (14.3)	150 (17.8)	
Advanced (stages III–IV)	668 (29.5)		160 (24.2)	229 (30.1)	279 (33.2)	
Unknown	1036 (45.8)		402 (60.8)	343 (45.1)	291 (34.6)	<0.001
Type of treatment [n (%)]						
Surgical resection	480 (17.0)	121 (21.2)	118 (17.9)	112 (14.7)	129 (15.3)	0.007
Liver transplantation	381 (13.5)	70 (12.3)	93 (14.1)	113 (14.9)	105 (12.5)	0.412
Radiofrequency ablation	339 (12.0)	36 (6.3)	40 (6.1)	79 (10.4)	184 (21.9)	<0.001
Sorafenib <sup>c</sup>	181 (6.4)	8 (1.4)	9 (1.4)	47 (6.2)	117 (13.9)	<0.001
Chemotherapy	349 (12.3)	88 (15.4)	90 (13.6)	73 (9.6)	98 (11.7)	0.009
Transarterial chemoembolization	215 (7.6)	30 (5.3)	53 (8.0)	62 (8.2)	70 (8.3)	0.135
Percutaneous ethanol injection	36 (1.3)	14 (2.5)	12 (1.8)	7 (0.9)	— (0.4)	0.002 <sup>b</sup>
Palliative care	1294 (45.7)	255 (44.7)	307 (46.4)	354 (46.6)	378 (45.0)	0.852
No treatment	708 (25.0)	162 (28.4)	187 (28.3)	193 (25.4)	166 (19.7)	<0.001

<sup>a</sup> Counts less than 6 are suppressed.

<sup>b</sup> By Fisher exact test.

<sup>c</sup> Approved by Health Canada in late 2007.

**TABLE III** Baseline characteristics of matched cases (patients with hepatocellular carcinoma) and controls (non-cancer control subjects) and of unmatched cases and controls by phase of care, 2002–2009

Variable	Phase of care															
	1 Year before diagnosis				1st year after diagnosis				Last 6 months before death							
	Matched		Unmatched		Matched		Unmatched		Matched		Unmatched		Matched		Unmatched	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Patients (n)	2,808	2,808	24	171,572	1,914	1,914	13	171,969	686	686	1,442	5,042	947	947	1,181	4,781
Age group (%)																
<60 Years	38.6	38.6	16.7	82.0	41.4	41.4	23.1	81.9	31.3	31.3	33.9	12.7	30.5	30.5	35.1	11.8
60–69 Years	25.8	25.8	41.7	9.1	25.4	25.4	30.8	9.2	21.9	21.9	28.0	9.6	21.3	21.3	29.8	9.0
70–79 Years	26.1	26.1	33.3	5.6	25.4	25.4	46.2	5.7	29.7	29.7	29.4	26.5	35.0	35.0	25.2	25.3
≥80 Years	9.4	9.4	8.3	3.4	7.8	7.8	0.0	3.3	17.1	17.1	8.7	51.2	13.2	13.2	9.9	53.8
Sex (% women)	21.0	21.0	16.7	52.0	21.4	21.4	15.4	51.8	22.0	22.0	22.0	58.6	25.8	25.8	19.0	59.8
Residence																
Urban	92.6	92.6	37.5	87.6	92.7	92.7	38.5	87.6	93.3	93.4	90.7	83.8	93.1	93.4	90.3	83.3
Rural	7.4	7.4	50.0	12.1	7.3	7.3	53.9	12.1	6.7	6.6	9.2	16.1	6.9	6.7	9.7	16.7
Missing	0.0	0.0	12.5	0.3	0.0	0.0	7.7	0.3	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.1
Income quintile (%)																
1 (lowest)	25.8	25.8	12.5	19.4	24.8	24.8	7.7	19.4	27.8	24.5	26.3	24.8	25.8	25.8	27.6	24.6
2	22.3	22.4	4.2	19.9	23.4	23.5	7.7	19.9	20.3	20.9	21.6	20.7	22.6	23.3	20.0	20.2
3	20.1	20.0	8.3	20.0	20.1	20.1	15.4	20.0	19.4	20.7	21.2	19.4	20.9	23.2	20.3	18.8
4	16.9	16.8	12.5	20.2	17.2	17.2	7.7	20.2	15.0	16.3	16.9	17.7	17.4	16.0	15.3	17.8
5 (highest)	15.0	15.0	8.3	19.9	14.5	14.5	7.7	19.9	17.5	17.6	13.4	16.9	13.3	12.0	15.8	18.0
Missing	0.0	0.0	54.2	0.6	0.0	0.0	53.9	0.6	0.0	0.0	0.8	0.5	0.0	0.0	0.9	0.5
Charlson–Devo comorbidity index (%)																
0	41.1	41.1	16.7	37.6	41.5	41.5	15.4	37.7	32.2	32.2	44.9	13.5	33.5	33.5	46.7	12.2
1	21.6	21.6	20.8	5.3	26.2	26.2	15.4	5.2	13.9	13.9	20.8	24.6	25.6	25.6	13.0	22.8
2	11.9	11.9	25.0	2.2	13.7	13.7	23.1	2.2	8.6	8.6	14.2	16.1	17.0	17.0	8.7	14.8
3+	10.2	10.2	25.0	2.1	12.4	12.4	38.5	2.0	7.1	7.1	12.5	28.6	17.5	17.5	5.3	27.7
No hospitalization record (%)	15.2	15.2	12.5	53.0	6.2	6.2	7.7	52.9	38.2	38.2	7.6	17.3	6.4	6.4	26.3	22.4
Index year (%)																
2002	9.9	9.9	0.0	11.8	8.8	8.8	0.0	11.8	6.1	26.8	13.2	18.0	7.3	22.8	13.8	18.3
2003	10.4	10.4	4.2	11.9	10.5	10.5	7.7	11.9	9.5	18.8	12.1	15.9	10.6	18.5	11.9	15.8



**TABLE III** Continued

Variable	Phase of care															
	1 Year before diagnosis				1st year after diagnosis				Last 6 months before death							
	Matched		Unmatched		Matched		Unmatched		Matched		Unmatched					
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls				
<b>Index year (%)</b>																
2004	10.7	10.7	8.3	12.3	10.2	10.2	7.7	12.3	10.2	15.5	12.6	16.1	10.6	15.8	12.9	16.0
2005	12.6	12.6	16.7	12.4	12.0	12.0	23.1	12.4	13.1	13.4	13.3	13.6	11.9	12.4	14.2	13.8
2006	13.0	13.0	8.3	12.6	13.4	13.4	7.7	12.6	13.4	10.5	12.4	11.8	13.7	12.5	11.9	11.4
2007	13.7	13.7	41.7	12.9	13.9	13.9	30.8	12.9	15.6	5.7	12.6	9.9	15.2	7.3	12.3	9.8
2008	13.4	13.4	8.3	13.1	14.1	14.1	7.7	13.1	14.4	6.1	11.2	8.3	14.8	6.6	10.2	8.3
2009	16.4	16.4	12.5	13.1	17.2	17.2	15.4	13.1	17.6	3.2	12.6	6.6	16.0	4.2	12.9	6.6
<b>Death year (%)</b>																
2002	—	—	—	—	—	—	—	—	6.1	6.1	6.5	1.4	1.5	1.5	10.3	2.1
2003	—	—	—	—	—	—	—	—	9.5	9.5	7.6	3.4	4.0	4.0	11.6	4.1
2004	—	—	—	—	—	—	—	—	10.2	10.2	9.5	5.0	6.1	6.1	12.6	5.5
2005	—	—	—	—	—	—	—	—	13.1	13.1	10.3	6.5	8.5	8.5	13.5	7.1
2006	—	—	—	—	—	—	—	—	13.4	13.4	12.1	9.3	10.7	10.7	14.1	9.6
2007	—	—	—	—	—	—	—	—	15.6	15.6	10.8	11.0	12.5	12.5	12.3	11.3
2008	—	—	—	—	—	—	—	—	14.4	14.4	12.6	12.8	15.3	15.3	11.4	12.5
2009	—	—	—	—	—	—	—	—	17.6	17.6	15.1	16.0	18.5	18.5	13.8	15.8
2010	—	—	—	—	—	—	—	—	0.0	0.0	9.8	17.9	14.5	14.5	0.3	16.0
2011	—	—	—	—	—	—	—	—	0.0	0.0	5.7	16.8	8.6	8.6	0.1	16.0

**TABLE IV** Health care utilization per 30 patient-days for matched cases (hepatocellular carcinoma patients) and controls (non-cancer control subjects) by index year, 2002–2009, and by death year, 2002–2011

Variable	Index year							
	2002–2003 [mean (95% CI)]		2004–2005 [mean (95% CI)]		2006–2007 [mean (95% CI)]		2008–2009 [mean (95% CI)]	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<i>1 Year before diagnosis</i>								
Patients (n)	569	569	655	655	748	748	836	836
Family physician visits	1.27 (1.18 to 1.36)	0.75 (0.67 to 0.83)	1.18 (1.06 to 1.29)	0.65 (0.59 to 0.70)	1.20 (1.05 to 1.35)	0.68 (0.62 to 0.74)	1.26 (1.10 to 1.41)	0.73 (0.66 to 0.79)
Specialist visits	1.63 (1.50 to 1.75)	0.59 (0.51 to 0.67)	1.47 (1.34 to 1.60)	0.58 (0.52 to 0.64)	1.83 (1.64 to 2.03)	0.70 (0.61 to 0.78)	1.75 (1.56 to 1.94)	0.76 (0.69 to 0.83)
Emergency department visits	0.23 (0.11 to 0.35)	0.07 (0.02 to 0.13)	0.30 (0.16 to 0.44)	0.12 (0.05 to 0.18)	0.36 (0.21 to 0.50)	0.06 (0.05 to 0.08)	0.42 (0.23 to 0.60)	0.13 (0.07 to 0.19)
Acute inpatient hospitalizations	0.04 (0.03 to 0.05)	0.01 (0.01 to 0.02)	0.03 (0.02 to 0.04)	0.01 (0.01 to 0.01)	0.05 (0.04 to 0.06)	0.01 (0.01 to 0.02)	0.04 (0.03 to 0.05)	0.02 (0.01 to 0.02)
Same-day surgery	1.60 (-0.59 to 3.79)	2.74 (1.66 to 3.82)	0.34 (0.14 to 0.54)	3.92 (2.19 to 5.65)	0.57 (0.01 to 1.14)	2.09 (1.23 to 2.96)	0.62 (0.29 to 0.95)	1.61 (1.07 to 2.16)
Prescription medications	1.73 (1.46 to 2.01)	1.20 (0.93 to 1.47)	1.81 (1.56 to 2.07)	1.43 (1.10 to 1.76)	2.22 (1.88 to 2.55)	1.48 (1.22 to 1.74)	2.78 (2.37 to 3.18)	2.62 (2.12 to 3.12)
Homecare visits	0.41 (0.20 to 0.61)	0.27 (0.15 to 0.39)	0.38 (0.18 to 0.57)	0.46 (0.14 to 0.79)	0.76 (0.43 to 1.08)	0.25 (0.13 to 0.38)	0.47 (0.27 to 0.67)	0.47 (0.29 to 0.65)
Total services	6.92 (4.70 to 9.14)	5.64 (4.51 to 6.77)	5.51 (4.98 to 6.04)	7.17 (5.40 to 8.95)	6.99 (6.10 to 7.87)	5.28 (4.37 to 6.18)	7.33 (6.55 to 8.12)	6.34 (5.52 to 7.16)
<i>1st year after diagnosis</i>								
Patients (n)	369	369	425	425	522	522	598	598
Family physician visits	1.58 (1.33 to 1.83)	0.64 (0.55 to 0.72)	1.74 (1.48 to 2.01)	0.56 (0.50 to 0.61)	1.41 (1.21 to 1.62)	0.62 (0.57 to 0.68)	1.40 (1.24 to 1.55)	0.72 (0.65 to 0.80)
Specialist visits	3.33 (2.96 to 3.69)	0.52 (0.44 to 0.60)	3.61 (3.25 to 3.97)	0.60 (0.52 to 0.68)	3.87 (3.53 to 4.21)	0.63 (0.57 to 0.69)	3.41 (3.13 to 3.69)	0.87 (0.77 to 0.98)
Emergency department visits	1.52 (0.61 to 2.43)	0.03 (0.03 to 0.04)	3.22 (1.72 to 4.73)	0.08 (0.02 to 0.14)	2.31 (1.46 to 3.15)	0.07 (0.05 to 0.10)	1.34 (0.87 to 1.81)	0.15 (0.04 to 0.26)
Acute inpatient hospitalizations	0.21 (0.12 to 0.30)	0.01 (0.01 to 0.01)	0.27 (0.13 to 0.42)	0.01 (0.01 to 0.02)	0.18 (0.14 to 0.22)	0.01 (0.01 to 0.01)	0.16 (0.13 to 0.20)	0.02 (0.01 to 0.02)
Same-day surgery	0.15 (0.09 to 0.21)	0.01 (0.01 to 0.02)	0.09 (0.07 to 0.12)	0.02 (0.01 to 0.02)	0.09 (0.06 to 0.13)	0.02 (0.02 to 0.02)	0.10 (0.07 to 0.13)	0.02 (0.02 to 0.03)

TABLE IV Continued

Variable	Index year							
	2002-2003 [mean (95% CI)]		2004-2005 [mean (95% CI)]		2006-2007 [mean (95% CI)]		2008-2009 [mean (95% CI)]	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<i>1st year after diagnosis</i>								
Prescription medications	2.33 (1.93 to 2.74)	1.75 (1.30 to 2.19)	2.35 (1.94 to 2.76)	1.27 (0.98 to 1.56)	3.07 (2.58 to 3.55)	2.21 (1.69 to 2.73)	3.22 (2.78 to 3.66)	2.66 (2.15 to 3.17)
Homecare visits	1.35 (1.04 to 1.67)	0.22 (0.07 to 0.38)	1.25 (0.88 to 1.61)	0.48 (0.19 to 0.77)	2.14 (1.53 to 2.76)	0.70 (0.35 to 1.05)	1.70 (1.27 to 2.13)	0.67 (0.36 to 0.99)
Total services	10.48 (9.20 to 11.75)	3.18 (2.62 to 3.74)	12.54 (10.54 to 14.54)	3.01 (2.49 to 3.54)	13.07 (11.63 to 14.51)	4.27 (3.51 to 5.02)	11.33 (10.39 to 12.26)	5.13 (4.38 to 5.87)
<b>Death year</b>								
Variable	2002-2003 [mean (95% CI)]		2004-2005 [mean (95% CI)]		2006-2007 [mean (95% CI)]		2010-2011 [mean (95% CI)]	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	<i>Last 6-months before death short-term (&lt;6 months) survivors</i>							
Patients (n)	107	107	160	160	199	199	220	220
Family physician visits	6.61 (4.84 to 8.39)	2.40 (1.48 to 3.32)	6.14 (5.04 to 7.25)	2.43 (2.05 to 2.80)	6.63 (5.52 to 7.73)	1.83 (1.56 to 2.10)	6.03 (5.17 to 6.90)	1.91 (1.59 to 2.24)
Specialist visits	13.38 (11.41 to 15.35)	3.08 (1.72 to 4.43)	12.03 (10.30 to 13.76)	2.08 (1.62 to 2.53)	12.12 (10.54 to 13.70)	2.29 (1.84 to 2.74)	11.85 (10.53 to 13.17)	2.65 (2.15 to 3.16)
Emergency department visits	1.24 (0.98 to 1.51)	0.26 (0.21 to 0.32)	1.64 (1.22 to 2.05)	0.39 (0.25 to 0.53)	2.18 (1.67 to 2.70)	0.28 (0.20 to 0.36)	1.59 (1.17 to 2.01)	0.45 (0.25 to 0.65)
Acute inpatient hospitalizations	1.54 (1.13 to 1.94)	0.15 (0.11 to 0.19)	1.44 (1.01 to 1.88)	0.13 (0.10 to 0.16)	1.73 (1.22 to 2.25)	0.13 (0.07 to 0.20)	1.46 (1.05 to 1.88)	0.14 (0.11 to 0.16)
Same-day surgery	0.19 (-0.09 to 0.47)	0.01 (0 to 0.02)	0.13 (0.06 to 0.20)	0.01 (0 to 0.02)	0.10 (0.06 to 0.14)	0.04 (0.01 to 0.07)	0.07 (0.05 to 0.10)	0.02 (0.01 to 0.04)
Prescription medications	3.00 (1.99 to 4.01)	4.8 (3.34 to 6.27)	3.92 (2.88 to 4.95)	7.57 (5.73 to 9.40)	3.91 (3.09 to 4.74)	7.10 (5.69 to 8.51)	4.74 (3.72 to 5.76)	7.59 (6.03 to 9.15)
Homecare visits	2.59 (1.71 to 3.46)	1.72 (0.81 to 2.62)	3.86 (2.70 to 5.01)	1.53 (0.75 to 2.32)	3.28 (2.56 to 4.00)	1.26 (0.82 to 1.70)	3.19 (2.50 to 3.87)	2.27 (1.47 to 3.08)
Total services	28.36 (25.69 to 31.02)	12.41 (10.12 to 14.70)	29.03 (25.98 to 32.07)	14.13 (11.82 to 16.44)	29.85 (26.98 to 32.72)	12.88 (11.31 to 14.46)	28.86 (26.32 to 31.41)	15.01 (13.02 to 17.01)

TABLE IV Continued

	Death year												
	2002–2003		2004–2005		2006–2007		2008–2009		2010–2011		Cases	Controls	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls			
<i>Last 6-months before death long-term (≥6 months) survivors</i>													
Patients (n)	52	52	138	138	219	219	320	320	218	218	218	218	218
Family physician visits	3.57 (2.84 to 4.29)	2.51 (1.58 to 3.44)	3.34 (2.86 to 3.81)	3.02 (2.59 to 3.44)	2.95 (2.58 to 3.32)	2.36 (2.02 to 2.71)	3.08 (2.78 to 3.37)	2.41 (2.08 to 2.74)	3.57 (2.84 to 4.29)	3.57 (2.84 to 4.29)	3.57 (2.84 to 4.29)	3.57 (2.84 to 4.29)	2.51 (1.58 to 3.44)
Specialist visits	3.82 (3.06 to 4.58)	2.84 (2.20 to 3.49)	4.61 (3.95 to 5.26)	3.72 (3.04 to 4.39)	4.05 (3.61 to 4.50)	3.04 (2.60 to 3.48)	3.71 (3.41 to 4.01)	3.23 (2.81 to 3.65)	3.82 (3.06 to 4.58)	3.82 (3.06 to 4.58)	3.82 (3.06 to 4.58)	3.82 (3.06 to 4.58)	2.84 (2.20 to 3.49)
Emergency department visits	0.78 (0.43 to 1.14)	0.54 (0.05 to 1.02)	1.33 (1.01 to 1.66)	0.73 (0.37 to 1.08)	1.09 (0.89 to 1.30)	0.45 (0.30 to 0.61)	0.70 (0.59 to 0.82)	0.58 (0.38 to 0.78)	0.78 (0.43 to 1.14)	0.78 (0.43 to 1.14)	0.78 (0.43 to 1.14)	0.78 (0.43 to 1.14)	0.54 (0.05 to 1.02)
Acute inpatient hospitalizations	0.21 (0.16 to 0.26)	0.23 (0.17 to 0.30)	0.26 (0.22 to 0.30)	0.24 (0.20 to 0.28)	0.25 (0.22 to 0.28)	0.22 (0.16 to 0.28)	0.26 (0.23 to 0.28)	0.22 (0.16 to 0.28)	0.21 (0.16 to 0.26)	0.21 (0.16 to 0.26)	0.21 (0.16 to 0.26)	0.21 (0.16 to 0.26)	0.23 (0.17 to 0.30)
Same-day surgery	0.07 (0 to 0.15)	0.03 (0 to 0.05)	0.06 (0.04 to 0.08)	0.02 (0.01 to 0.04)	0.07 (0.04 to 0.11)	0.03 (0.02 to 0.05)	0.05 (0.04 to 0.07)	0.04 (0.02 to 0.05)	0.07 (0 to 0.15)	0.07 (0 to 0.15)	0.07 (0 to 0.15)	0.07 (0 to 0.15)	0.03 (0 to 0.05)
Prescription medications	4.70 (3.83 to 5.57)	4.77 (2.68 to 6.86)	5.03 (4.02 to 6.03)	6.96 (5.09 to 8.82)	4.93 (4.00 to 5.87)	9.42 (7.71 to 11.14)	6.23 (5.32 to 7.13)	9.13 (7.57 to 10.68)	4.70 (3.83 to 5.57)	4.70 (3.83 to 5.57)	4.70 (3.83 to 5.57)	4.70 (3.83 to 5.57)	4.77 (2.68 to 6.86)
Homecare visits	3.70 (2.20 to 5.19)	2.34 (1.15 to 3.54)	3.64 (2.81 to 4.47)	2.14 (1.23 to 3.05)	4.88 (3.98 to 5.78)	1.63 (1.05 to 2.21)	4.81 (4.08 to 5.53)	2.51 (1.81 to 3.21)	3.70 (2.20 to 5.19)	3.70 (2.20 to 5.19)	3.70 (2.20 to 5.19)	3.70 (2.20 to 5.19)	2.34 (1.15 to 3.54)
Total services	16.77 (14.57 to 18.97)	13.24 (10.23 to 16.25)	18.21 (16.62 to 19.80)	16.79 (14.45 to 19.14)	18.16 (16.58 to 19.74)	17.13 (15.12 to 19.13)	18.79 (17.46 to 20.11)	18.07 (16.16 to 19.98)	16.77 (14.57 to 18.97)	16.77 (14.57 to 18.97)	16.77 (14.57 to 18.97)	16.77 (14.57 to 18.97)	13.24 (10.23 to 16.25)

CI = confidence interval.

**TABLE V** Cost<sup>a</sup> per 30 patient-days for matched cases (hepatocellular carcinoma patients) and controls (non-cancer control subjects), by index year, 2002–2009, and by death year, 2002–2011

Variable	Index year							
	2002–2003		2004–2005		2006–2007		2008–2009	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<i>1 Year before diagnosis</i>								
Patients (n)	569	569	655	655	748	748	836	836
Outpatient visits	354 (286 to 422)	170 (113 to 228)	296 (248 to 344)	165 (102 to 227)	385 (333 to 437)	222 (154 to 289)	437 (347 to 526)	243 (190 to 296)
Emergency department visits	94 (18 to 171)	10 (4 to 15)	145 (49 to 242)	39 (13 to 64)	242 (85 to 399)	22 (15 to 28)	324 (134 to 514)	51 (26 to 76)
Acute inpatient hospitalizations	285 (191 to 379)	84 (53 to 115)	224 (156 to 291)	94 (39 to 149)	391 (281 to 501)	192 (79 to 305)	303 (233 to 372)	147 (99 to 196)
Same-day surgery	39 (33 to 46)	10 (7 to 13)	32 (26 to 39)	10 (7 to 12)	34 (28 to 39)	17 (13 to 21)	37 (31 to 43)	22 (16 to 29)
Prescription medications	73 (62 to 84)	49 (41 to 56)	120 (93 to 147)	64 (54 to 75)	110 (92 to 128)	71 (57 to 86)	121 (105 to 138)	103 (89 to 116)
Homecare visits	25 (15 to 36)	19 (10 to 28)	21 (13 to 28)	31 (8 to 55)	60 (37 to 83)	21 (11 to 30)	46 (33 to 59)	49 (24 to 75)
Total services	881 (720 to 1,042)	349 (264 to 434)	848 (702 to 995)	411 (305 to 516)	1,235 (1,008 to 1,462)	554 (379 to 728)	1,282 (1,029 to 1,536)	628 (520 to 736)
<i>1st year after diagnosis</i>								
Patients (n)	369	369	425	425	522	522	598	598
Outpatient visits	4,325 (2,984 to 5,666)	151 (73 to 230)	3,557 (2,677 to 4,436)	273 (160 to 387)	4,362 (3,121 to 5,604)	240 (132 to 349)	2,931 (2,475 to 3,387)	382 (272 to 492)
Emergency department visits	186 (88 to 285)	11 (7 to 16)	394 (252 to 536)	27 (4 to 50)	244 (185 to 304)	18 (14 to 22)	139 (108 to 169)	27 (11 to 43)
Acute inpatient hospitalizations	3,696 (1,727 to 5,664)	89 (49 to 129)	5,297 (1,959 to 8,635)	133 (82 to 185)	4,147 (1,825 to 6,469)	129 (74 to 184)	2,527 (1,281 to 3,774)	207 (103 to 311)
Same-day surgery	186 (66 to 305)	11 (7 to 14)	85 (35 to 136)	13 (9 to 17)	76 (43 to 108)	19 (15 to 24)	83 (39 to 126)	21 (16 to 27)
Prescription medications	256 (189 to 323)	85 (67 to 104)	249 (181 to 317)	69 (56 to 82)	258 (216 to 300)	91 (75 to 107)	379 (313 to 446)	102 (88 to 116)
Homecare visits	124 (94 to 154)	17 (5 to 29)	133 (96 to 170)	29 (12 to 46)	337 (92 to 581)	49 (28 to 70)	256 (165 to 346)	62 (38 to 87)



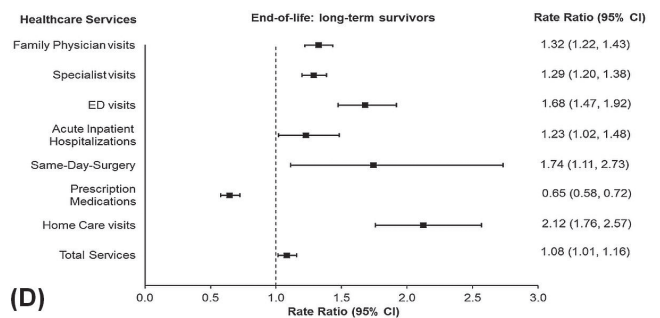
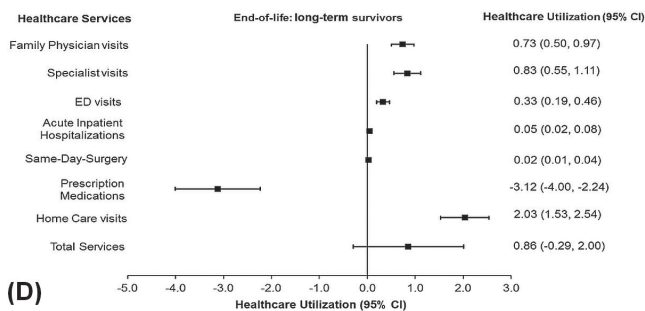
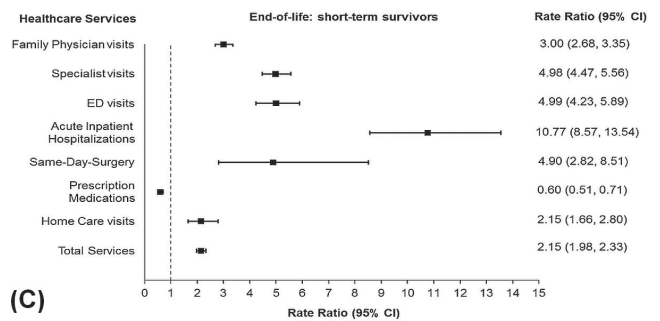
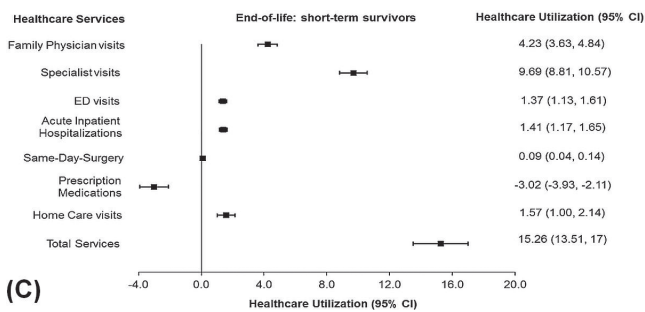
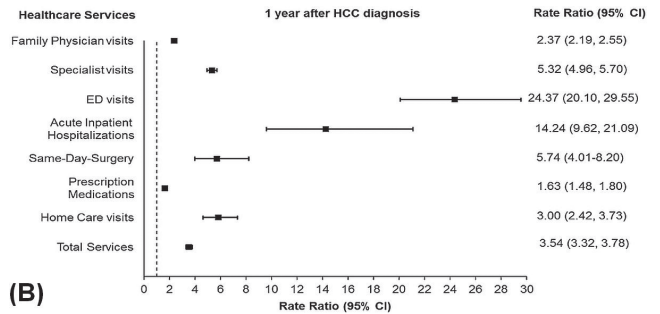
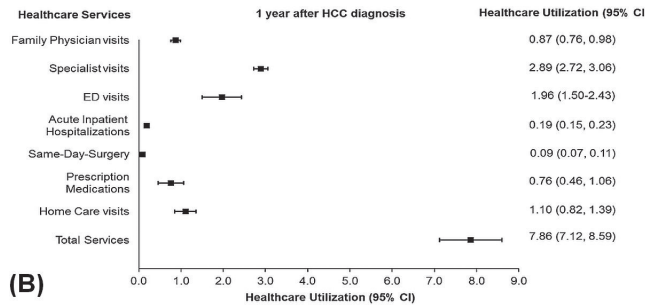
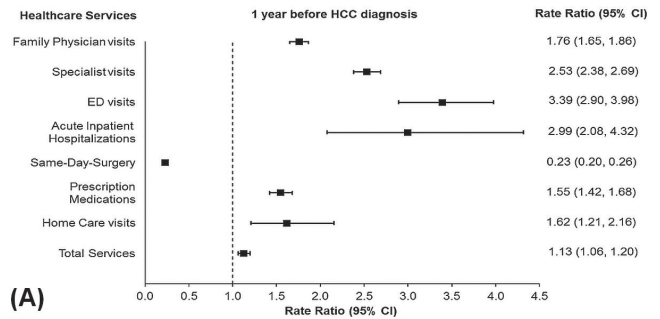
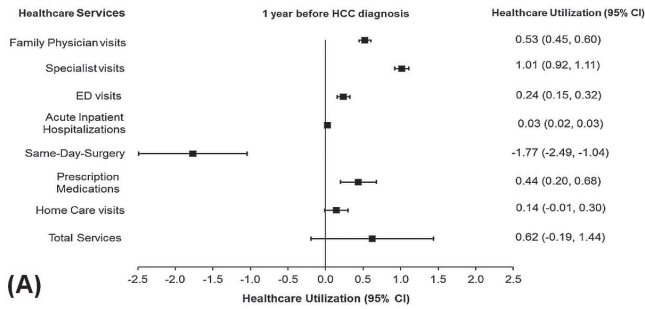
TABLE V Continued

Variable	Index year							
	2002–2003		2004–2005		2006–2007		2008–2009	
	[mean \$ (95% CI)]		[mean \$ (95% CI)]		[mean \$ (95% CI)]		[mean \$ (95% CI)]	
Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
<i>1st year after diagnosis</i>								
Total services	8,789 (5,713 to 11,866)	375 (263 to 487)	9,734 (5,780 to 13,688)	553 (398 to 707)	9,453 (5,709 to 13,196)	558 (410 to 707)	6,338 (4,893 to 7,782)	813 (618 to 1,008)
<i>Death year</i>								
2002–2003		2004–2005		2006–2007		2008–2009		2010–2011
[mean \$ (95% CI)]		[mean \$ (95% CI)]		[mean \$ (95% CI)]		[mean \$ (95% CI)]		[mean \$ (95% CI)]
Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
<i>Last 6 months before death, short-term (&lt;6 months) survivors</i>								
Patients (n)	107	107	160	160	199	199	220	220
Outpatient visits	3,304 (2,263 to 4,345)	1,768 (430 to 3,107)	7,396 (1,479 to 13,313)	1,154 (402 to 1,907)	12,546 (1,319 to 23,773)	1,560 (609 to 2,511)	15,544 (5,923 to 25,166)	1,420 (950 to 1,890)
Emergency department visits	676 (508 to 844)	151 (116 to 185)	1,219 (325 to 2,114)	201 (141 to 261)	1,365 (895 to 1,835)	161 (102 to 220)	1,096 (697 to 1,494)	195 (131 to 259)
Acute inpatient hospitalizations	13,197 (10,481 to 15,912)	1,509 (1,046 to 1,972)	13,743 (10,326 to 17,160)	2,006 (1,297 to 2,714)	17,573 (13,456 to 21,689)	2,312 (1,515 to 3,109)	19,990 (15,753 to 24,227)	2,483 (1,730 to 3,235)
Same-day surgery	98 (–40 to 237)	9 (–2 to 19)	96 (36 to 156)	20 (–2 to 42)	65 (38 to 92)	31 (13 to 49)	50 (29 to 70)	19 (7 to 30)
Prescription medications	147 (88 to 206)	134 (94 to 175)	209 (143 to 275)	188 (147 to 230)	183 (132 to 234)	176 (141 to 211)	300 (217 to 382)	177 (141 to 214)
Homecare visits	491 (228 to 754)	164 (70 to 257)	536 (378 to 693)	168 (76 to 261)	967 (680 to 1,254)	177 (111 to 243)	899 (654 to 1,145)	323 (204 to 442)
Total services	17,928 (14,724 to 21,133)	3,804 (2,248 to 5,361)	23,215 (13,472 to 32,959)	3,759 (2,409 to 5,109)	32,720 (19,654 to 45,787)	4,439 (2,904 to 5,974)	37,901 (25,012 to 50,791)	4,637 (3,509 to 5,765)
<i>Last 6 months before death, long-term (≥6 months) survivors</i>								
Patients (n)	52	52	138	138	219	219	320	218

TABLE V Continued

	Death year											
	2002–2003		2004–2005		2006–2007		2008–2009		2010–2011			
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<i>Last 6 months before death, long-term (≥6 months) survivors</i>												
Outpatient visits	1,362 (209 to 2,516)	1,261 (298 to 2,223)	1,090 (746 to 1,434)	2,350 (1,213 to 3,487)	1,460 (1,012 to 1,909)	2,228 (1,304 to 3,152)	1,032 (743 to 1,321)	1,442 (1,043 to 1,842)	1,409 (833 to 1,985)	1,407 (901 to 1,913)		
Emergency department visits	277	262	458	358	403	256	273	267	11	10		
Acute inpatient hospitalizations	2,291 (1,099 to 3,484)	2,247 (1,448 to 3,046)	2,614 (2,067 to 3,160)	3,295 (2,405 to 4,185)	3,191 (2,585 to 3,796)	3,842 (2,906 to 4,779)	2,105 (1,820 to 2,390)	3,104 (2,364 to 3,844)	310 (−10 to 630)	105 (8 to 202)		
Same-day surgery	42 (2 to 83)	60 (−26 to 146)	32 (18 to 46)	33 (6 to 59)	60 (25 to 96)	38 (11 to 65)	27 (17 to 37)	39 (10 to 68)	1 (0 to 3)	0 (0 to 0)		
Prescription medications	345 (214 to 476)	169 (97 to 241)	275 (203 to 347)	188 (152 to 224)	281 (205 to 357)	253 (191 to 315)	489 (396 to 581)	204 (173 to 235)	412 (301 to 523)	215 (167 to 263)		
Homecare visits	480 (257 to 704)	202 (85 to 320)	441 (326 to 556)	269 (136 to 402)	754 (608 to 900)	214 (151 to 278)	745 (642 to 848)	367 (251 to 483)	417 (301 to 534)	190 (120 to 260)		
Total services	4,818 (2,656 to 6,981)	4,218 (2,812 to 5,625)	4,930 (4,143 to 5,718)	6,514 (4,647 to 8,380)	6,172 (5,209 to 7,136)	6,859 (5,215 to 8,504)	4,693 (4,238 to 5,148)	5,446 (4,367 to 6,526)	2,581 (1,898 to 3,264)	1,952 (1,438 to 2,467)		

<sup>a</sup> In 2013 Canadian dollars. CI = confidence interval.



**FIGURE 2** Net health care utilization attributable to hepatocellular carcinoma (HCC) patients (A) at 1 year before diagnosis (2002–2009), (B) during the 1st year after diagnosis (2002–2009), (C) during the last 6 months before death for short-term (<6 months) survivors (2002–2011), and (D) during the last 6 months before death for long-term ( $\geq 6$  months) survivors (2002–2011). Net health care utilization was calculated as the difference between the mean number of health care services attributed to HCC patients and to propensity-score-matched non-cancer control subjects. Values are expressed as means with 95% confidence intervals per 30 patient–days. Error bars indicate the 95% confidence intervals.

**FIGURE 3** Rate ratios for resource use attributable to hepatocellular carcinoma (HCC) patients (A) at 1 year before diagnosis (2002–2009), (B) during the 1st year after diagnosis (2002–2009), (C) during the last 6 months before death for short-term (<6 months) survivors (2002–2011), and (D) during the last 6 months before death for long-term ( $\geq 6$  months) survivors (2002–2011). Rate ratios are shown for HCC patients compared with propensity-score-matched non-cancer control subjects. Rates were measured from 2002 to 2009 or to 2011 (inclusive), assuming a negative binomial distribution. Error bars indicate 95% confidence intervals.

**TABLE VI** Net health care utilization per 30 patient-days and rate ratio of resource use attributable to hepatocellular carcinoma care, by index year of service, 2002–2009

Variable	Index year											
	2002–2003			2004–2005			2006–2007			2008–2009		
	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Net HCU change <sup>c</sup> (%)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Net HCU change <sup>c</sup> (%)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Net HCU change <sup>c</sup> (%)	
<i>1 Year before diagnosis</i>												
Matched cases (n)	569		655		748		836					
Family physician visits	0.52 (0.40 to 0.64)	1.69 (1.50 to 1.91)	0.53 (0.41 to 0.66)	1.82 (1.61 to 2.06)	2	0.52 (0.36 to 0.68)	1.77 (1.58 to 2.00)	0	0.53 (0.36 to 0.70)	1.73 (1.54 to 1.94)	2	
Specialist visits	1.04 (0.88 to 1.19)	2.74 (2.40 to 3.13)	0.89 (0.76 to 1.02)	2.54 (2.24 to 2.87)	-14	1.14 (0.93 to 1.34)	2.66 (2.36 to 2.99)	10	0.99 (0.78 to 1.19)	2.30 (2.06 to 2.57)	-5	
Emergency department visits	0.16 (0.03 to 0.29)	3.13 (2.14 to 4.60)	0.18 (0.03 to 0.34)	2.61 (1.88 to 3.61)	15	0.29 (0.14 to 0.44)	5.10 (3.64 to 7.17)	84	0.29 (0.09 to 0.48)	3.09 (2.32 to 4.12)	81	
Acute inpatient hospitalizations	0.03 (0.02 to 0.04)	3.75 (1.58 to 8.92)	0.02 (0.01 to 0.03)	2.81 (1.22 to 6.51)	-35	0.03 (0.02 to 0.05)	3.71 (1.82 to 7.56)	11	0.02 (0.01 to 0.03)	2.28 (1.24 to 4.22)	-28	
Same-day surgery	-1.14 (-3.58 to 1.30)	0.30 (0.21 to 0.42)	-3.58 (-5.32 to -1.84)	0.10 (0.08 to 0.14)	-215	-1.52 (-2.55 to -0.49)	0.18 (0.14 to 0.24)	-33	-0.99 (-1.63 to -0.35)	0.43 (0.34 to 0.55)	13	
Prescription medications	0.53 (0.17 to 0.89)	1.75 (1.46 to 2.10)	0.38 (0 to 0.76)	1.56 (1.30 to 1.86)	-29	0.74 (0.35 to 1.12)	1.59 (1.36 to 1.85)	38	0.15 (-0.46 to 0.76)	1.48 (1.27 to 1.74)	-71	
Homecare visits	0.14 (-0.10 to 0.37)	1.21 (0.64 to 2.27)	-0.09 (-0.47 to 0.29)	2.05 (1.00 to 4.22)	-164	0.50 (0.16 to 0.84)	3.61 (1.97 to 6.60)	265	0	1.31 (0.78 to 2.19)	-97	
Total services	1.28 (-1.23 to 3.78)	1.20 (1.05 to 1.37)	-1.67 (-3.51 to 0.18)	0.84 (0.74 to 0.96)	-231	1.71 (0.45 to 2.96)	1.30 (1.16 to 1.45)	34	0.99 (-0.11 to 2.10)	1.28 (1.15 to 1.42)	-22	
<i>1st year after diagnosis</i>												
Matched cases (n)	369		425		522		598					
Family physician visits	0.94 (0.69 to 1.20)	2.51 (2.11 to 2.99)	1.19 (0.92 to 1.45)	3.12 (2.64 to 3.69)	26	0.79 (0.58 to 1.00)	2.24 (1.94 to 2.60)	-17	0.67 (0.50 to 0.85)	1.93 (1.69 to 2.20)	-29	
Specialist visits	2.81 (2.44 to 3.18)	6.44 (5.40 to 7.67)	3.01 (2.64 to 3.37)	6.01 (5.16 to 7.01)	7	3.24 (2.90 to 3.58)	6.19 (5.41 to 7.08)	15	2.54 (2.24 to 2.84)	3.99 (3.56 to 4.48)	-10	
Emergency department visits	1.49 (0.59 to 2.39)	37.79 (20.35 to 70.18)	3.14 (1.65 to 4.64)	43.42 (28.19 to 66.89)	111	2.23 (1.39 to 3.07)	30.45 (20.79 to 44.59)	50	1.19 (0.70 to 1.67)	11.23 (8.07 to 15.62)	-20	
Acute inpatient hospitalizations	0.20 (0.11 to 0.29)	20.95 (7.36 to 59.64)	0.26 (0.11 to 0.40)	17.82 (7.87 to 40.33)	30	0.17 (0.13 to 0.21)	16.67 (7.16 to 38.80)	-14	0.14 (0.11 to 0.18)	8.59 (4.65 to 15.85)	-27	

TABLE VI Continued

Variable	Index year											
	2002–2003		2004–2005		2006–2007		2008–2009		Net HCU change <sup>c</sup> (%) <sup>b</sup>		Net HCU change <sup>c</sup> (%) <sup>b</sup>	
	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)	Mean net HCU <sup>a</sup> (95% CI)	Mean rate ratio <sup>b</sup> (95% CI)
<i>1st year after diagnosis</i>												
Same-day surgery	0.14 (0.08 to 0.20)	11.56 (4.50 to 29.71)	0.08 (0.05 to 0.10)	5.97 (2.62 to 13.64)	0.07 (0.04 to 0.11)	4.65 (2.39 to 9.06)	0.08 (0.05 to 0.11)	4.36 (2.42 to 7.86)	–44	–46	–44	–44
Prescription medications	0.58 (0 to 1.16)	1.55 (1.24 to 1.94)	1.08 (0.60 to 1.56)	2.12 (1.72 to 2.61)	0.85 (0.25 to 1.46)	1.98 (1.65 to 2.39)	0.56 (–0.08 to 1.19)	1.43 (1.21 to 1.70)	46	28	46	–5
Homecare visits	1.13 (0.79 to 1.47)	12.13 (6.62 to 22.20)	0.77 (0.31 to 1.23)	5.70 (3.30 to 9.83)	1.44 (0.86 to 2.03)	6.30 (4.14 to 9.58)	1.02 (0.55 to 1.50)	6.84 (4.43 to 10.55)	28	21	28	–9
Total services	7.29 (5.92 to 8.66)	3.92 (3.37 to 4.56)	9.52 (7.50 to 11.55)	4.75 (4.11 to 5.49)	8.80 (7.39 to 10.22)	3.88 (3.44 to 4.38)	6.20 (5.11 to 7.29)	2.71 (2.42 to 3.04)	21	21	21	–15

<sup>a</sup> Difference between the mean number of health services allocated to patients with hepatocellular carcinoma and to matched non-cancer control subjects.

<sup>b</sup> Estimated by modelling count, using negative binomial regression. Control subjects constituted the reference population.

<sup>c</sup> Compared with 2002–2003.

HCU = health care utilization; CI = confidence interval.

and the net cost of all services for each phase of care (2002–2009 or 2002–2011). Table ix summarizes trends in the net costs of care attributable to HCC over time (to 2008–2009 or 2010–2011 from 2002–2003)—that is, the estimate of the difference in costs for HCC patients compared with non-cancer control subjects over time. Overall, the mean net costs per 30 patient–days of outpatient visits and hospitalizations were the highest in the pre-diagnosis, initial, and end-of-life for short-term survivors phases [Figure 4(A–C)]. Mean net homecare costs were highest during the end-of-life for long-term survivors phase [Figure 4(D)].

For HCC patients, the net average total health care cost per 30 patient–days was \$586 (95% CI: \$464 to \$709) in the pre-diagnosis phase, which increased in the initial phase to \$7,812 (95% CI: \$6,286 to \$9,338) and increased markedly in the end-of-life phase for short-term survivors to \$25,613 (95% CI: \$19,456 to \$31,771), but which decreased substantially in the end-of-life phase for long-term survivors to –\$452 (95% CI: –\$1,119 to \$216; Figure 4).

Outpatient visits accounted for approximately 29% of the net total cost during the pre-diagnosis phase [\$169 (95% CI: \$125 to \$213)], 44% during the initial phase [\$3,454 (95% CI: \$2,963 to \$3,945)], and 37% during the end-of-life phase for short-term survivors [\$9,460 (95% CI: \$4,753 to \$14,167)]. Those costs contributed 11% in cost savings (fewer costs than were incurred by control subjects) during the end-of-life phase for long-term survivors [–\$500 (95% CI: –\$871 to –\$129)]. The net total cost of outpatient visits was highest during the end-of-life phase for short-term survivors.

Visits to the ED accounted for approximately 31% of the net total cost during the pre-diagnosis phase [\$182 (95% CI: \$106 to \$258)], 3% during the initial phase [\$212 (95% CI: \$170 to \$254)], and 4% during the end-of-life phase for short-term survivors [\$963 (95% CI: \$676 to \$1,251)]. Such visits contributed 12% during the end-of-life phase for long-term survivors [\$52 (95% CI: \$4 to \$100)]. Short-term survivors in the end-of-life phase incurred the highest costs associated with ED visits.

Hospitalizations accounted for approximately 29% of the net total cost during the pre-diagnosis phase [\$170 (95% CI: \$114 to \$226)], 47% during the initial phase [\$3,662 (95% CI: \$2,555 to \$4,770)], and 57% during the end-of-life phase for short-term survivors [\$14,545 (95% CI: \$12,466 to \$16,624)]. They contributed 15% in cost savings during the end-of-life phase for long-term survivors [–\$520 (95% CI: –\$919 to –\$120)]. Short-term survivors in the end-of-life phase incurred the highest costs associated with hospitalizations.

Mean net costs attributable to outpatient visits and total services significantly increased to \$14,220 (95% CI: \$4,473 to \$23,966) in 2008–2009 from \$1,547 (95% CI: –\$71 to \$3,165) in 2002–2003 and to \$33,121 (95% CI: \$19,966 to \$46,275) in 2008–2009 from \$14,450 (95% CI: \$10,872 to \$18,027) in 2002–2003 respectively, during the end-of-life phase for short-term survivors.

## DISCUSSION

Our study demonstrated that in all phases of care, compared with non-cancer control subjects, HCC patients used a greater number of health care services (exceptions were



**TABLE VII** Net health care utilization per 30 patient-days and rate ratio of resource use attributable to hepatocellular carcinoma care at end-of-life<sup>a</sup> among short-term survivors<sup>b</sup> by death year of service, 2002–2009

Variable	Death year									
	2002–2003		2004–2005		2006–2007		2008–2009		Net HCU change <sup>e</sup> (%)	
	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Net HCU change <sup>e</sup> (%)	Net HCU change <sup>e</sup> (%)
Matched cases (n)	107		160		199		220			
Family physician visits	4.10 (2.05 to 6.15)	2.75 (2.03 to 3.73)	3.72 (2.59 to 4.84)	2.50 (2.01 to 3.11)	4.75 (3.62 to 5.87)	3.43 (2.79 to 4.22)	4.12 (3.17 to 5.07)	3.15 (2.60 to 3.82)	16	0
Specialist visits	10.39 (8.09 to 12.69)	4.88 (3.74 to 6.37)	9.91 (8.05 to 11.77)	6.04 (4.78 to 7.64)	9.91 (8.19 to 11.63)	5.26 (4.31 to 6.43)	9.14 (7.68 to 10.61)	4.82 (3.97 to 5.86)	-5	-12
Emergency department visits	1.00 (0.73 to 1.27)	4.82 (3.18 to 7.32)	1.23 (0.80 to 1.66)	4.18 (3.04 to 5.73)	1.92 (1.39 to 2.44)	7.77 (5.60 to 10.79)	1.16 (0.69 to 1.63)	4.16 (3.08 to 5.60)	92	16
Acute inpatient hospitalizations	1.42 (0.98 to 1.86)	9.98 (5.87 to 16.98)	1.30 (0.87 to 1.74)	10.35 (6.43 to 16.66)	1.61 (1.09 to 2.14)	11.98 (7.73 to 18.58)	1.33 (0.91 to 1.75)	10.36 (6.92 to 15.49)	14	-6
Same-day surgery	0.20 (-0.11 to 0.50)	16.31 (1.95 to 136.60)	0.12 (0.05 to 0.19)	12.67 (2.56 to 62.69)	0.06 (0.01 to 0.10)	2.35 (1.02 to 5.38)	0.05 (0.02 to 0.08)	3.13 (1.17 to 8.40)	-71	-75
Number of prescription medications	-2.04 (-3.82 to -0.26)	0.62 (0.39 to 0.99)	-3.62 (-5.68 to -1.56)	0.52 (0.36 to 0.74)	-3.18 (-4.59 to -1.76)	0.56 (0.42 to 0.75)	-2.89 (-4.72 to -1.06)	0.68 (0.51 to 0.92)	-56	-42
Homecare visits	0.82 (-0.36 to 2.00)	2.98 (1.37 to 6.50)	2.36 (0.92 to 3.79)	3.94 (2.17 to 7.16)	2.01 (1.17 to 2.86)	3.19 (1.97 to 5.16)	1.04 (-0.01 to 2.09)	1.62 (1.03 to 2.56)	147	27
Total services	15.69 (12.18 to 19.20)	2.42 (2.01 to 2.91)	14.89 (11.05 to 18.73)	2.14 (1.79 to 2.55)	17.02 (13.95 to 20.10)	2.34 (2.03 to 2.71)	13.90 (10.57 to 17.24)	2.01 (1.72 to 2.34)	9	-11

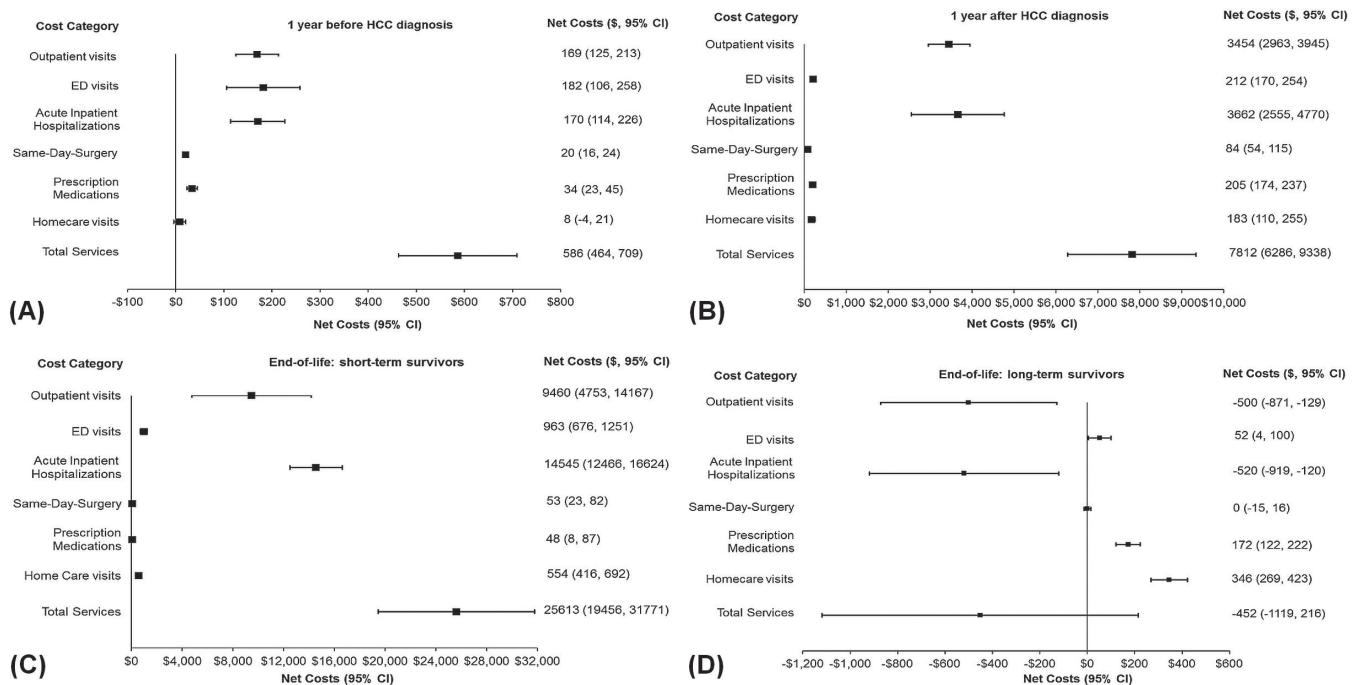
<sup>a</sup> Last 6 months before death.  
<sup>b</sup> Survived less than 6 months.  
<sup>c</sup> Difference between the mean number of health services allocated to patients with hepatocellular carcinoma and to matched non-cancer control subjects.  
<sup>d</sup> Estimated by modelling count, using negative binomial regression. Control subjects constituted the reference population.  
<sup>e</sup> Compared with 2002–2003.  
 HCU = health care utilization; CI = confidence interval.

**TABLE VIII** Net health care utilization per 30 patient-days and rate ratio of resource use attributable to hepatocellular carcinoma care at end-of-life<sup>a</sup> among long-term survivors<sup>b</sup> by death year of service, 2002–2011

Variable	Death year											
	2002–2003		2004–2005		2006–2007		2008–2009		2010–2011		Net HCU change <sup>e</sup> (%)	Net HCU change <sup>e</sup> (%)
	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)	Mean net HCU <sup>c</sup> (95% CI)	Mean rate ratio <sup>d</sup> (95% CI)
Matched cases (n)	52		138		219		320		218			
Family physician visits	0.85 (-0.16 to 1.87)	1.44 (1.04 to 2.00)	0.32 (-0.25 to 0.90)	1.11 (0.92 to 1.34)	0.59 (0.08 to 1.09)	1.28 (1.08 to 1.51)	-31 (-1.08 to 1.48)	0.65 (0.23 to 1.07)	1.29 (1.12 to 1.48)	1.17 (0.70 to 1.64)	-24 (-1.36 to 1.90)	1.61 (1.36 to 1.90)
Specialist visits	0.95 (0 to 1.90)	1.31 (1.01 to 1.70)	1.04 (0.26 to 1.82)	1.37 (1.15 to 1.64)	1.03 (0.47 to 1.59)	1.37 (1.18 to 1.59)	9 (-1.18 to 1.31)	0.47 (-0.03 to 0.98)	1.15 (1.01 to 1.31)	1.04 (0.47 to 1.61)	-50 (-1.21 to 1.63)	1.40 (1.21 to 1.63)
Emergency department visits	0.31 (-0.28 to 0.91)	1.82 (1.00 to 3.32)	0.58 (0.12 to 1.05)	2.14 (1.52 to 3.02)	0.64 (0.39 to 0.90)	2.46 (1.89 to 3.20)	105 (-1.89 to 3.20)	0.13 (-0.11 to 0.36)	1.34 (1.06 to 1.69)	0.17 (-0.05 to 0.40)	-59 (-1.07 to 1.86)	1.41 (1.07 to 1.86)
Acute inpatient hospitalizations	-0.02 (-0.09 to 0.05)	0.93 (0.40 to 2.14)	0.02 (-0.03 to 0.07)	1.10 (0.68 to 1.77)	0.04 (-0.03 to 0.10)	1.17 (0.79 to 1.72)	269 (0.79 to 1.72)	0.04 (-0.02 to 0.11)	1.19 (0.87 to 1.64)	0.10 (0.07 to 0.14)	290 (1.06 to 2.41)	1.60 (1.06 to 2.41)
Same-day surgery	0.04 (-0.02 to 0.10)	2.23 (0.27 to 18.31)	0.04 (0.01 to 0.06)	2.61 (0.71 to 9.57)	0.04 (0.01 to 0.08)	2.35 (0.96 to 5.76)	11 (-0.01 to 0.03)	0.01 (-0.01 to 0.03)	1.38 (0.65 to 2.90)	0.01 (-0.01 to 0.02)	-62 (-0.42 to 3.30)	1.17 (0.42 to 3.30)
Number of prescription medications	0.08 (-2.03 to 2.19)	1.35 (0.89 to 2.05)	-1.87 (-3.85 to 0.12)	0.75 (0.56 to 1.00)	-4.51 (-6.37 to -2.65)	0.53 (0.42 to 0.66)	-5479 (-5479 to 0)	-2.89 (-4.54 to -1.24)	0.69 (0.56 to 0.84)	-3.64 (-5.50 to -1.77)	-3545 (-5.50 to -1.77)	0.64 (0.51 to 0.80)
Homecare visits	1.44 (-0.43 to 3.31)	2.59 (1.18 to 5.68)	1.36 (0.10 to 2.62)	2.06 (1.25 to 3.38)	3.22 (2.16 to 4.29)	3.80 (2.67 to 5.39)	124 (2.67 to 5.39)	2.35 (1.37 to 3.33)	2.04 (1.49 to 2.79)	0.91 (0.09 to 1.74)	63 (0.09 to 1.74)	1.72 (1.04 to 2.82)
Total services	3.62 (-0.06 to 7.30)	1.39 (1.08 to 1.78)	1.46 (-1.22 to 4.14)	1.13 (0.97 to 1.31)	1.01 (-1.37 to 3.39)	1.10 (0.96 to 1.25)	-72 (-1.37 to 1.25)	0.75 (-1.48 to 2.98)	1.08 (0.96 to 1.21)	-0.24 (-2.42 to 1.95)	-79 (-2.42 to 1.95)	1.02 (0.90 to 1.17)

<sup>a</sup> Last 6 months before death.<sup>b</sup> Survived 6 months or more.<sup>c</sup> Difference between the mean number of health services allocated to patients with hepatocellular carcinoma and to matched non-cancer control subjects.<sup>d</sup> Estimated by modelling count, using negative binomial regression. Control subjects constituted the reference population.<sup>e</sup> Compared with 2002–2003.

HCU = health care utilization; CI = confidence interval.



**FIGURE 4** Mean net cost of care attributable to hepatocellular carcinoma (HCC), by cost category, (A) at 1 year before diagnosis (2002–2009), (B) during the 1st year after diagnosis (2002–2009), (C) during the last 6 months before death for short-term (<6 months) survivors (2002–2011), and (D) during the last 6 months before death for long-term ( $\geq 6$  months) survivors (2002–2011). Net costs were generated using generalized estimating equations. Values are expressed as means with 95% confidence intervals per 30 patient–days and reflect 2013 Canadian dollars. Error bars indicate the 95% confidence intervals. CI = confidence interval; ED = emergency department.

same-day surgery during the pre-diagnosis phase and prescription medications during the end-of-life phase for both short-term and long-term survivors). Mean net costs attributable to outpatient visits and total services significantly increased in 2008–2009 from 2002–2003 by 819% and 129% respectively in the end-of-life phase for short-term survivors. Those increases might reflect increases in the intensity of treatment with newer technologies—in particular, radiofrequency ablation (increased by a factor of 5) and sorafenib (increased by a factor of 15). Overall, health care utilization and costs attributable to HCC were high for specialist and outpatient visits, ED visits, and hospitalizations in the pre-diagnosis, initial, and end-of-life phases for short-term survivors, which could represent the increasing costs associated with HCC diagnosis. In many cases, HCC does not present with any severe symptoms until very late in the course of the disease<sup>9,12,13</sup>. Thus, the resource utilization and costs incurred are significant even before diagnosis.

Very few studies have determined differences in health care resource utilization between cancer patients and matched non-cancer control subjects over time. Studies from Denmark<sup>21</sup> and the United States<sup>22</sup> using matched patients and control subjects have reported that the pre-diagnosis phase is a resource-intensive component in cancer care episodes, with large-factor increases in the use of general practice visits, diagnostic investigations, ED visits, and hospital services. In addition, the Danish study<sup>21</sup> reported a marked use of hospital services in the year after diagnosis.

The high treatment costs for HCC<sup>15</sup> and the complexity in managing the disease present both financial and clinical challenges. The increasing prevalence of cirrhosis and its complications in Canada<sup>38</sup> means that surveillance, diagnosis, and care for individuals with HCC is further complicated. Furthermore, the very early stage of HCC—for example, a single asymptomatic lesion measuring less than 2 cm in diameter, with no vascular or distant metastasis—is difficult to diagnose<sup>12</sup>. Although ultrasound surveillance of populations at risk for HCC has been considered by the hepatology community both in Canada and internationally to be the standard of care, such surveillance has not been widely promoted by Canadian health agencies<sup>39–43</sup>.

Given the ineffectiveness or low rates of community surveillance for cirrhosis or identification of patients at high risk for HCC, the incidence of HCC continues to increase<sup>14</sup>. Consequently, demand for screening, diagnosis, care, and curative treatment is also increasing. Outpatient visits contributed a significant proportion of the net health care utilization and costs incurred in the pre-diagnosis care phase, the initial care phase, and the end-of-life care phase for short-term survivors, presenting significant policy implications given the national shortage of liver disease specialists.

With respect to gastroenterologists, Canada has, at 1.83 per 100,000 population, one of the lowest specialist-to-population ratios in the G8 countries, and that ratio is expected to drop by one third as current gastroenterologists approach retirement age over the next 5 years<sup>44,45</sup>. Wait times for referred individuals are substantial, and according to one review, fewer than 33% of patients referred for a

**TABLE IX** Net cost of care<sup>a</sup> attributable to hepatocellular carcinoma per 30 patient–days by cost category, disease phase, and index year or death year of service

Variable	Index year						
	2002–2003 [mean \$ (95% CI)]	2004–2005 [mean \$ (95% CI)]	Net cost change (%)	2006–2007 [mean \$ (95% CI)]	Net cost change (%)	2008–2009 [mean \$ (95% CI)]	Net cost change (%)
<i>Costs during 1 year before diagnosis</i>							
Matched cases (n)	569	655		748		836	
Outpatient visits	184 (95 to 272)	131 (52 to 211)	-29	163 (84 to 242)	-11	194 (96 to 291)	5
Emergency department visits	85 (8 to 162)	107 (8 to 206)	26	220 (63 to 377)	159	273 (82 to 464)	221
Acute inpatient hospitalizations	201 (104 to 298)	130 (42 to 218)	-35	199 (42 to 356)	-1	155 (73 to 237)	-23
Same-day surgery	29 (22 to 36)	23 (16 to 29)	-22	17 (10 to 24)	-42	15 (6 to 24)	-49
Prescription medications	25 (13 to 37)	56 (29 to 82)	125	39 (17 to 60)	57	19 (-2 to 39)	-24
Homecare visits	6 (-7 to 19)	-11 (-36 to 14)	-269	39 (15 to 63)	517	-4 (-32 to 25)	-156
Total services	532 (354 to 711)	438 (261 to 615)	-18	681 (404 to 960)	28	654 (382 to 926)	23
<i>Costs in the 1st year after diagnosis (\$)</i>							
Matched cases (n)	369	425		522		598	
Outpatient visits	4,174 (2,837 to 5,512)	3,283 (2,406 to 4,161)	-21	4,123 (2,881 to 5,364)	-1	2,549 (2,082 to 3,015)	-39
Emergency department visits	175 (77 to 273)	367 (223 to 510)	110	227 (168 to 286)	30	111 (77 to 146)	-36
Acute inpatient hospitalizations	3,606 (1,646 to 5,566)	5,163 (1,845 to 8,481)	43	4,018 (1,723 to 6,313)	11	2,321 (1,094 to 3,547)	-36
Same-day surgery	175 (56 to 294)	73 (22 to 124)	-58	56 (24 to 87)	-68	62 (18 to 105)	-65
Prescription medications	171 (101 to 240)	180 (112 to 247)	5	167 (122 to 211)	-2	278 (211 to 344)	63
Homecare visits	107 (76 to 139)	104 (65 to 144)	-3	288 (44 to 531)	169	193 (105 to 282)	81
Total services	8,414 (5,348 to 11,480)	9,180 (5,277 to 13,083)	9	8,894 (5,183 to 12,605)	6	5,524 (4,100 to 6,948)	-34
<i>Death year</i>							
Matched cases (n)	107	160		199		220	
Outpatient visits	1,547 (-71 to 3,165)	6,325 (374 to 12,276)	309	11,732 (-974 to 24,437)	659	14,220 (4,473 to 23,966)	819
Emergency department visits	537 (357 to 718)	1,010 (124 to 1,897)	88	1,214 (731 to 1,696)	126	906 (502 to 1,310)	69
Acute inpatient hospitalizations	11,999 (9,165 to 14,834)	11,742 (8,195 to 15,289)	-2	15,239 (11,060 to 19,419)	27	17,237 (12,950 to 21,525)	44
Same-day surgery	97 (-54 to 248)	76 (12 to 140)	-22	34 (2 to 66)	-65	32 (7 to 57)	-67
Prescription medications	8 (-58 to 74)	25 (-55 to 106)	209	7 (-51 to 64)	-18	120 (32 to 208)	1376
Homecare visits	320 (43 to 597)	372 (185 to 559)	16	810 (496 to 1,123)	153	603 (326 to 881)	88
<i>Costs in the 6 months before death, short-term survivors<sup>b</sup> (\$)</i>							
Matched cases (n)	107	160		199		220	
Outpatient visits	1,547 (-71 to 3,165)	6,325 (374 to 12,276)	309	11,732 (-974 to 24,437)	659	14,220 (4,473 to 23,966)	819
Emergency department visits	537 (357 to 718)	1,010 (124 to 1,897)	88	1,214 (731 to 1,696)	126	906 (502 to 1,310)	69
Acute inpatient hospitalizations	11,999 (9,165 to 14,834)	11,742 (8,195 to 15,289)	-2	15,239 (11,060 to 19,419)	27	17,237 (12,950 to 21,525)	44
Same-day surgery	97 (-54 to 248)	76 (12 to 140)	-22	34 (2 to 66)	-65	32 (7 to 57)	-67
Prescription medications	8 (-58 to 74)	25 (-55 to 106)	209	7 (-51 to 64)	-18	120 (32 to 208)	1376
Homecare visits	320 (43 to 597)	372 (185 to 559)	16	810 (496 to 1,123)	153	603 (326 to 881)	88

TABLE IX Continued

	Death year									
	2002–2003 [mean \$ (95% CI)]	2004–2005 [mean \$ (95% CI)]	Net cost change (%)	2006–2007 [mean \$ (95% CI)]	Net cost change (%)	2008–2009 [mean \$ (95% CI)]	Net cost change (%)	2010–2011 [mean \$ (95% CI)]	Net cost change (%)	
<i>Costs in the 6 months before death, long-term survivors<sup>a</sup> (\$)</i>										
Matched cases (n)	52	138		219		320		218		
Outpatient visits	-46 (-1,649 to 1,557)	-1,232 (-2,313 to -150)	-2587	-761 (-1,776 to 254)	-1560	-426 (-888 to 36)	-829	-18 (-780 to 743)	60	
Emergency department visits	40 (-171 to 250)	93 (-68 to 254)	133	148 (43 to 254)	272	7 (-86 to 100)	-82	1 (-9 to 12)	-97	
Acute inpatient hospitalizations	-34 (-1,394 to 1,325)	-573 (-1,492 to 345)	-1564	-639 (-1,751 to 474)	-1753	-1,003 (-1,744 to -263)	-2812	204 (-135 to 543)	691	
Same-day surgery	-30 (-132 to 71)	-1 (-28 to 25)	96	22 (-20 to 64)	173	-12 (-42 to 19)	62	1 (0 to 3)	104	
Prescription medications	175 (39 to 311)	95 (7 to 183)	-46	28 (-71 to 126)	-84	284 (191 to 378)	63	200 (79 to 320)	14	
Homecare visits	283 (49 to 518)	138 (-42 to 318)	-51	537 (377 to 697)	89	385 (232 to 538)	36	230 (98 to 361)	-19	
Total services	390 (-2,197 to 2,977)	-1,480 (-3,239 to 278)	-480	-671 (-2,525 to 1,184)	-272	-764 (-1,868 to 340)	-296	612 (-252 to 1,477)	57	

<sup>a</sup> Generated using generalized estimating equations. Values reflect 2013 Canadian dollars.

<sup>b</sup> Survived less than 6 months.

<sup>c</sup> Survived 6 months or more.

probable cancer were seen by a gastroenterologist within the target wait time<sup>45</sup>. Compounding that difficulty is the fact that only a minority of gastroenterologists routinely see patients with liver disease<sup>46</sup>. Lack of timely care could therefore affect the survival prognosis for patients with HCC and could increase the number of ED visits and hospitalizations. Because ED visits represent a significant burden to the health care system, the likely contribution to the patient load resulting from HCC emphasizes the need for prevention and early diagnosis.

This retrospective matched case-control population-based study had a large sample size and used rigorous propensity scoring to match HCC patients with non-cancer control subjects by sociodemographic characteristics and comorbidity. It therefore provides a comprehensive and accurate estimation of the net health care utilization and net costs of care in Ontario between 2002 and 2009. It builds on previous work by calculating net health care utilization and costs, exploring a longer pre-diagnosis care phase to capture routine surveillance for diagnosis, and reporting on cost trends over time. It also includes analyses of important contributors to costs—namely, hospitalizations, drugs, physician services, and homecare services, which account for the largest health care expenditures.

The study has some limitations, however.

First, HCC stage data in the OCR to differentiate utilization by cancer stage are limited, and cancer treatment, health care utilization, and costs can vary by stage at diagnosis<sup>47,48</sup>. Classification of malignant tumours based on TNM staging [extent of the tumour (T), extent of spread to the lymph nodes (N), and presence of metastasis (M)<sup>49,50</sup>] was used in the OCR from 2004 onwards; the most common stage grouping (45.8%) was “unknown”; 29.5% of cases were designated advanced-stage (III–IV), 14.2% were designated intermediate-stage (II), and 10.4% were designated early-stage (0–I). The 5-year relative survival rate for liver cancer in Canada is 20%<sup>9</sup>, and yet that rate varies with both age and stage at diagnosis. Nevertheless, compared with long-term survivors, short-term survivors, who can be hypothesized to have more aggressive-stage disease, had significantly higher health care utilization and costs during the end-of-life phase.

Second, the Ontario Drug Benefit Program covers only patients 65 years of age and older or patients with special circumstances. Thus, the estimated cost of prescription medications is an underestimate. Nevertheless, prescription medication costs were higher for HCC patients than for non-cancer control subjects in all care phases.

Third, we were not able to estimate indirect costs (including caregiver time costs; out-of-pocket costs; costs of lost production because of short-term absence from work, permanent disability, and death before 65 years of age), which are important for reaching an understanding of the cost of an illness to society and patients.

Fourth, because of the relatively small sample of patients in the end-of-life phase, we were not able to conduct subgroup analyses or examine predictors of increased costs and health care system utilization. Our cohort is now several years old, and some secular trends in practice could have occurred; however, all current modalities of treatment, including sorafenib, were available by the end of our study period.



Finally, a generalized linear model specifying a negative binomial distribution was assumed for all health services utilization. However, that model might not have been completely appropriate for every service analysis, given that, in some situations, a large proportion of the control subjects used no services. The resulting differences might have contributed to the large RRS reached in the negative binomial regression.

## CONCLUSIONS

Our study found increasing resource use and net costs of care during the study period for HCC patients, particularly for short-term survivors during the end-of-life phase. The combination of the growing HCC incidence in Canada and possible new, but expensive, future treatments mean that HCC will continue to place a significant burden on the health care system. Additional information that will contribute to effective prevention and early detection is needed so that the costs incurred from late diagnosis and the terminal period of life can be remediated. The information presented here can assist in policy decision-making with respect to resource allocation for cancer prevention and control, and can serve as a foundation for economic and health outcomes evaluations to improve survival and reduce costs within the context of the health care system.

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## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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