Health Care Costs Associated With Hepatocellular Carcinoma: A Population-Based Study

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Although the burden of hepatocellular carcinoma (HCC) is an escalating public health problem, it has not been rigorously estimated within a Canadian context. We conducted a population-based study using Ontario Cancer Registry linked administrative data. The mean net costs of care due to HCC were estimated using a phase of care approach and generalized estimating equations. Using an incidence approach, the mean net costs of care were applied to survival probabilities of HCC patients to estimate 5-year net costs of care and extrapolated to the Canadian population of newly diagnosed HCC patients in 2009. During 2002-2008, 2,341 HCC cases were identified in Ontario. The mean (95% confidence interval [CI]) net costs of HCC care per 30 patient-days (2010 US dollars) were $3,204 ($2,863-$3,545) in the initial phase, $2,055 ($1,734-$2,375) in the continuing care phase, and $7,776 ($5,889-$9,663) in the terminal phase. The mean (95% CI) 5-year net cost of care was $77,509 ($60,410-$94,607) and the 5-year aggregate net cost of care was $106 million ($83-$130 million) (undiscounted). The net costs of patients receiving liver transplantation only and those undergoing surgical resection only were highest in the terminal phase. The net cost of patients receiving radiofrequency ablation as the only treatment was relatively low in the initial phase, and there were no significant differences in the continuing and terminal phases. Conclusion: Our findings suggest that costs attributable to HCC are significant in Canada and expected to increase. Our findings of phase-specific cost estimates by resource categories and type of treatment provide information for future cost-effectiveness analysis of potential innovative interventions, resource allocation, and health care budgeting, and public health policy to improve the health of the population. (HEPATOLOGY 2013;58:1375-1384)

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The burden of illness associated with hepatocellular carcinoma (HCC) is an escalating public health problem worldwide.1 Studies using population-based registries have shown an increase in HCC incidence and mortality in many countries over the past 30 years.1-6 In Canada, HCC incidence is expected to continue to increase over the next decade,4-6 with an average increase in the age-adjusted incidence of 3.4% per year in men and 2.2% per year in women.7 The increases in HCC incidence in some

Abbreviations: CCI, Charlson-Deyo Comorbidity Index; CI, confidence interval; HCC, hepatocellular carcinoma; ICD-9, International Statistical Classification of Diseases and Related Health Problems, 9th Revision; OCR, Ontario Cancer Registry; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Patients and Methods

Full details of methodological descriptions regarding data sources, estimation of health care costs associated with HCC, and 5-year net costs of HCC care can be found in the Supporting Information.

Study Design. We conducted a population-based retrospective cohort study using Ontario Cancer Registry (OCR) linked administrative data and a reference Ontario population to estimate the net costs of care for HCC from January 1, 2002, through December 31, 2008. Individuals were followed from the day of diagnosis until death or until 12 months after the end of the study period to capture deaths. The study design included three key elements. The first element was a phase of care (initial, continuing care, and terminal phases) approach to costing. The initial phase of cancer care includes services normally provided within the first few months at the time of diagnosis, which commonly include diagnostic services and curative treatments. The continuing care phase includes surveillance activities for detecting recurrences, medications to prevent cancer recurrence, and treatment of complications deriving from the initial therapy. The terminal phase applies to care received at the end of life, often palliative in nature. The second element was an estimation of the net costs of care due to HCC (difference between the mean costs for HCC patients and for matched controls without HCC). The third element was a construction of estimates of the 5-year net costs of care due to HCC (using an incidence approach estimating cumulative costs from the date of diagnosis to death and by aggregating the costs of the three phases). Approval for the study was granted by the University of Toronto Health Sciences Research Ethics Board.

Study Population. The study population included all diagnosed cases of HCC in Ontario recorded in the OCR between January 1, 2002, and December 31, 2008, in individuals aged >18 years who did not have a second cancer. We used the International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) site code 155.0 and the International Classification of Diseases for Oncology, 3rd Edition histology codes 8170-8175 to identify cases of HCC. Selection criteria for the patient sample are summarized in Supporting Table 1. Potential controls were selected from a 5% random sample of the reference Ontario population database (Registered Persons Database), including all persons with unique health card numbers registered for the purposes of Ontario health insurance coverage and Ontario drug benefits. All eligible controls were persons aged >18 years who did not have a diagnosis of HCC.
Residents of Ontario with a valid health card have access to health services within a universal, publically funded health care system administered by the Ontario Ministry of Health and Long-Term Care. Although there are certain exceptions within the different services, the system provides free access to hospital and emergency room visits, physician services, home care, copayments for long-term care placements, and prescription medications for those aged >65 years.

**Data Sources.** The OCR is a population-based tumor registry consisting of information on all new cases of cancer in Ontario (except non-melanoma skin cancers) since 1964. Using the perspective of the Ontario Ministry of Health and Long-Term Care, direct medical costs were determined. Costs associated with outpatient visits in Ontario were determined from the Physician's Claims History Database of the Ontario Health Insurance Plan. The Canadian Institute for Health Information Discharge Abstract Database was used to estimate comorbidity, frequency and type of hospital admissions, length of stay, and in-hospital mortality. Costs associated with radiofrequency ablation (RFA), surgical resection, liver transplantation, transarterial chemoembolization (TACE), percutaneous ethanol injection, chemotherapy, and sorafenib were determined using the Canadian Institute for Health Information and Ontario Health Insurance Plan databases. Costs for emergency room visits and same-day surgery were determined using the National Ambulatory Care Reporting System Database. Medication costs were obtained from the Ontario Drug Benefit Program Database. Costs associated with home care, continuing care, and long-term care were determined using the Ontario Home Care Database, Continuing Care Reporting System, and Ontario Drug Benefit Program Database.

**Phases of Cancer Care.** To determine the duration of the initial phase and the terminal phase of our linked cohort, we performed a joinpoint regression of the log-linear trends in the average cost of HCC care per 30 patient-days from HCC diagnosis to death.\(^{29,30}\) This allows the identification, through regression modelling of the observed data, of the points at which statistically significant changes occur in the slope of the longitudinal cost function.\(^{30}\) This suggested that a significant trend started to emerge 3 months prior to HCC diagnosis and declined 1 month after diagnosis. Models of patients surviving 3, 6, 12, and 86 months after diagnosis of HCC showed that all four cohorts had markedly increased average total cost per 30 patient-days in the months leading up to diagnosis, with very high costs in the month of diagnosis, and decreased costs after diagnosis (Fig. 1). For 6-, 12-, and 86-month survivors, costs gradually increased again as the month of death approached although there was no significant trend. Based on these findings, we defined the phases of care as follows: initial phase, between 3 months prior to HCC diagnosis and 1 month after diagnosis; terminal phase, 6 months preceding death; and continuing care phase, the intermediate observation time. For instance: for patients who died within 1 month after diagnosis of HCC, the costs for 3 months

### Table 1. Characteristics of Individuals With HCC by Year of Diagnosis

| Year | n    | % Aged ≤ 60 Years | % Aged ≥ 60 Years | % with CCI ≥ 3 | Treatment in Year After Diagnosis, % | Survival After Diagnosis, % |
|------|------|------------------|------------------|---------------|-------------------------------------|-----------------------------|
|      |      |                  |                  |               | Surgical Resection | Liver Transplantation | RFA | TACE | Chemotherapy | Sorafenib* | 1 Year | 3 Years | 5 Years |
| Overall | 2,341 | 41.9             | 6.9              | 9.2           | 15.9                  | 9.7             | 8.5 | 4.9 | 8.3         | NA       | 51     | 24     | 13      |
| 2002   | 275  | 41.8             | 3.6              | 6.6           | 20.0                  | 5.8             | 5.1 | 1.8 | 8.7         | 48       | 26     | 14     |         |
| 2003   | 293  | 40.6             | 6.5              | 11.3          | 18.8                  | 7.2             | 7.5 | 2.4 | 12.0        | 50       | 24     | 14     |         |
| 2004   | 307  | 42.7             | 6.5              | 10.1          | 13.4                  | 10.8            | 2.9 | 2.6 | 8.5         | 48       | 23     | 12     |         |
| 2005   | 355  | 44.8             | 6.2              | 9.9           | 19.4                  | 9.0             | 6.5 | 7.9 | 9.0         | 50       | 25     | NA     |         |
| 2006   | 364  | 42.6             | 7.7              | 8.8           | 13.5                  | 11.8            | 8.8 | 4.7 | 6.0         | 52       | 21     | NA     |         |
| 2007   | 382  | 41.4             | 8.6              | 10.0          | 13.4                  | 11.5            | 8.4 | 6.5 | 5.8         | 0.3      | 51     | NA     | NA      |
| 2008   | 365  | 39.2             | 8.2              | 8.0           | 14.3                  | 10.1            | 18.6| 6.9 | 9.0         | 6.6      | 52     | NA     | NA      |

Abbreviation: NA, not applicable.
*Sorafenib was approved by Health Canada in late 2007.*

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**Fig. 1.** Joinpoint regression of the log-linear trends in the average total cost per 30 patient-days from 3 months before diagnosis to death for persons surviving 3 (black solid line), 6 (black dashed line), 12 (black dotted line), and 86 (gray solid line) months after diagnosis of HCC.
before diagnosis were attributed to the initial phase and the costs within 1 month after diagnosis were attributed to the terminal phase; for patients who died 7 months after diagnosis, the costs for 3 months before diagnosis and 1 month after diagnosis were attributed to the initial phase and the remaining costs after diagnosis were attributed to the terminal phase. For patients who did not die during the study period, all observation time (and costs) was sequentially allocated to the initial and continuing care phases.\textsuperscript{13} For costing purposes, all incident cases were referred to as cohort 1 (the incident cohort) and the incident cases who died were referred to as cohort 2 (the death cohort).

\textbf{Matching Cases and Controls.} The “net cost” method\textsuperscript{12,15} involves matching cases and controls on socio-demographic and clinical factors associated with resource use. For each case and control, we calculated the income quintile,\textsuperscript{31} Charlson-Deyo Comorbidity Index (CCI)\textsuperscript{26,27} and propensity score.\textsuperscript{32,33} The household neighborhood income was calculated using the Statistics Canada Postal Code Conversion file and the 2001 and 2006 Canadian census data. The first quintile represents the lower 20% of neighborhoods with the poorest median neighborhood income. The fifth quintile represents the upper 20% of neighborhoods with the most affluent median neighborhood income.\textsuperscript{31} The CCI was calculated using the methods described by Charlson et al.\textsuperscript{26} and Deyo et al.,\textsuperscript{27} applying an ICD-9 coding algorithm to the 14 diagnostic field codes in our hospitalization data (excluding diagnoses for liver disease and metastatic cancer). Baseline comorbidity was determined using the hospitalization record at diagnosis date. Conditions were weighted and then summed up to provide an overall CCI which reflected the number and severity of comorbid diseases reflecting the cumulative increased likelihood of 1-year mortality. The summed weights for a given episode were then categorized into one of five groups (CCI of 0, 1, 2, >3, or no hospital record) representing different degrees of comorbidity. If cases did not have a hospitalization record at diagnosis date, we determined baseline comorbidity by looking back 2 years into the hospitalization data to find the most recent hospitalization record and applying the CCI from that hospitalization.\textsuperscript{28} Patients were assigned as having a missing CCI at baseline if they had no hospitalization records at diagnosis or 2 years prior to diagnosis. The propensity score for an individual is the conditional probability of assignment to a diagnosis of HCC given the observed individual covariates.\textsuperscript{32,33} This was derived by fitting a logistic model with HCC status as dependent variable and the index year, age, sex, income quintile, rurality, CCI, and the interaction between age and comorbidity as independent variables.

We performed matching for each cohort using two sets of cases and controls: in cohort 1, all cases were matched 1:1 to controls to estimate costs for the initial and continuing care phases; and in cohort 2, cases who died as a result of HCC were matched 1:1 to controls who died from other causes to estimate costs for the terminal phase. For each case, the closest non-HCC control was selected that matched the following criteria: age \(\pm 10\) years at the index date; same sex; diagnosed in the same year; CCI, and a propensity score within a caliper width (i.e., the difference in propensity scores between matched cases and controls differs by at most a fixed distance) of 0.2 SD.\textsuperscript{34}

\textbf{Estimation of Health Care Costs Associated With HCC.} Because of regional variations in reimbursements, the median 2008 cost for each physician and laboratory service fee code was used to estimate outpatient costs. The mean costs of hospitalization, emergency room visits, and same-day surgery for a particular year were estimated using the Resource Intensity Weight methodology. All costs were adjusted for inflation to 2010 Canadian dollars using the Statistics Canada Consumer Price Index for health care and personal items for Ontario. Purchasing Power Parities for Gross Domestic Product was used to convert 2010 Canadian dollars to 2010 U.S. dollars.

\textbf{Net Costs of HCC Care.} Within each phase of care, we calculated total costs of care and total months of observation for cases and controls. For each phase of care, we estimated mean (and 95% confidence interval [CIs]) net costs of care due to HCC (per 30 patient-days) using generalized estimating equations to account for the matched study design. CIs for the predicted costs for each phase were reproduced by applying bootstrap resampling of the data 1,000 times.

\textbf{5-Year Net Costs of HCC Care.} We applied the incidence approach\textsuperscript{16,25} that involves using the mean net costs of HCC care per 30 patient-days by phase, in conjunction with survival probabilities after HCC diagnosis accounting for competing risks\textsuperscript{35} (using cancer registry statistics from 2002 to 2008), to estimate 5-year net costs of care in diagnosed HCC patients. The lower and upper bound of the 95% CI for phase-specific net costs of care were used to estimate a plausible range of 5-year net costs of care.\textsuperscript{16} Costs were discounted at 3% and 5% annually.

\textbf{Aggregate 5-Year Net Costs of HCC Care in the Canadian Population.} We applied 5-year net cost of care estimates to the number of newly diagnosed HCC patients in the Ontario population in 2009.
from the OCR (~36% of the total HCC in the Canadian population) to estimate the aggregate 5-year net costs of care due to HCC. To extrapolate to the total Canadian population of newly diagnosed HCC patients in 2009, we divided the estimated number of newly diagnosed HCC patients in Ontario by 0.36. We assumed that the cost of care and survival for patients diagnosed in 2009 would approximate our estimates derived over a period 2002-2008.

Sensitivity Analysis. A sensitivity analysis was performed where the initial phase was defined as the first 12 months after diagnosis of HCC, the terminal phase was defined as the final 12 months of life, and the continuing care phase was defined as all months between the initial and terminal phases of care. For patients surviving <24 months after diagnosis, the final 12 months of observation and costs of care were allocated first to the terminal phase, consistent with other studies.

Results

Characteristics of the Study Population. Overall, 2,341 cases were identified with a principal diagnosis of HCC in the OCR during the study period 2002-2008 (Table 1). Over the period, the number of new HCC cases increased, and the proportion of those aged 80 and above increased. Patients receiving treatment with liver transplantation, RFA, or TACE in the year after HCC diagnosis increased over time; in contrast, those receiving surgical resection decreased. The overall 1-, 3-, and 5-year survival was 51%, 24%, and 13%, respectively.

Both sets of cases and controls (cohort 1 and cohort 2) were well matched except for birth location, because this information was missing for the controls (Table 2). Cases that contributed person-time to the initial phase (110 days) were closely matched to the controls (119 days); however, many cases that contributed person-time to the continuing care (826 versus 1,493 days) and terminal (129 versus 169 days) phases could not be matched with suitable controls.

Health Care Costs Associated With HCC. The average total health care costs per 30 patient-days among HCC patients was relatively high in the initial phase ($3,660), declined during the continuing care phase ($2,745), and increased markedly in the terminal phase ($12,036) (Table 3). Estimates of the average net costs of HCC care per 30 patient-days were highest in the terminal phase ($7,776, 65% of the total costs in this phase), followed by the initial phase ($3,204, 88% of the total costs) and continuing care phase ($2,055, 75% of the total costs) (Table 4). We only reported 95% CIs derived from the generalized estimating equations since they were practically the same as the bootstrap CIs. Liver failure or potential complications of cirrhosis accounted for approximately 30% of the total net costs in the initial phase ($957; 95% CI, $800 to $1,115), 18% in the continuing care phase ($379; 95% CI, $315 to $444), and 52% in the terminal phase ($4,022; 95% CI, $3,179 to $4,864). The net costs of patients that received liver transplantation only, and those undergoing surgical resection only were highest in the terminal phase. The net costs of patients receiving RFA as the only treatment were relatively low in the initial phase, and no significant cost differences were observed in the continuing care and terminal phases.

In the sensitivity analysis (Table 5) assigning 12 months after the diagnosis to the initial phase and 12 months preceding death to the terminal phase, there was a significant increase (83%) in the total net costs of care in the initial phase and a slight increase (8%) in the terminal phase compared with the total net costs of care in the primary analysis (Table 4). The net costs of care were about halved (54%) in the continuing care phase.

The net costs of outpatient visits due to HCC (69%-93% of the total costs of outpatient visits), acute inpatient care due to HCC (72%-91% of the total costs of acute inpatient visits), and emergency room visits due to HCC (62%-75% of the total costs of emergency room visits) accounted for the highest cost categories across all three phases.

Estimates of 5-Year Net Costs of HCC Care. Estimates of the mean (95% CI) 5-year net costs of HCC care were $77,509 ($60,410 to $94,607) (undiscounted), $52,959 ($41,435 to $64,482) (3% discount), and $48,602 ($38,152 to $59,052) (5% discount) (Table 6). Year 1 net costs of care accounted for 49% of the 5-year net costs of care. In the sensitivity analysis, the respective 5-year estimates were: $103,688 ($77,636 to $129,740), $65,225 ($49,162 to $81,288), and $57,559 ($43,525 to $71,592).

Aggregate 5-Year Net Costs of HCC Care in the Canadian Population. When the mean 5-year net costs were applied to the newly diagnosed HCC cases in the Canadian population in 2009, the 5-year aggregate net costs of care were approximately $106.4 million (undiscounted; 95% CI, $82.9 to $129.9 million), $72.7 (3% discount; 95% CI, $56.9 to $88.5 million), and $66.7 million (5% discount; 95% CI, $52.4 to $81.1 million). In the sensitivity analysis, the respective 5-year aggregate net costs of care were: $142.3 million ($106.6, $178.1 million), $89.5
Table 3. Mean Health Care Costs Among HCC Cases and Controls According to Cost Category and Disease Phase

| Cost Category                      | Disease Phase | Cases      | Controls    | Cases      | Controls    | Cases      | Controls    | Cases      | Controls    |
|-----------------------------------|---------------|------------|-------------|------------|-------------|------------|-------------|------------|-------------|
|                                   |               | Initial    | Continuing  | Terminal   |              | Initial    | Continuing  | Terminal   |              |
| N                                 | 2,320         | 2,320      | 156,009     | 1,478      | 2,285       | 156,009    | 1,103       | 1,103      | 579         | 2,879       |
| Mean ± SD time spent, days        | 110 ± 14      | 119 ± 8    | 119 ± 14    | 826 ± 71   | 1,493 ± 74  | 1,517 ± 762| 129 ± 65    | 169 ± 36   | 132 ± 61    | 172 ± 30    |
| Outpatient visits, $               | 2,024 (1,803 - 2,245) | 135 (106 - 164) | 1,182 (1,000 - 1,365) | 242 (217 - 268) | 3,059 (2,050 - 4,067) | 944 (780 - 1,108) |        |            |            |
| Emergency room visits, $           | 120 (109 - 132) | 34 (22 - 45) | 161 (135 - 187) | 40 (27 - 52) | 551 (423 - 678) | 211 (180 - 241) |        |            |            |
| Same-day surgery, $                | 45 (41 - 50) | 13 (10 - 16) | 37 (31 - 44) | 24 (21 - 26) | 46 (32 - 61) | 22 (18 - 28) |        |            |            |
| Acute inpatient care, $            | 1,283 (1,140 - 1,426) | 112 (95 - 117) | 827 (678 - 976) | 163 (139 - 188) | 7,075 (6,189 - 7,960) | 1,970 (1,697 - 2,243) |        |            |            |
| Medications, $                     | 106 (95 - 117) | 65 (59 - 70) | 280 (246 - 313) | 84 (77 - 91) | 207 (184 - 230) | 149 (136 - 162) |        |            |            |
| Home care, $                       | 52 (43 - 60) | 22 (16 - 28) | 175 (124 - 226) | 34 (27 - 41) | 492 (433 - 551) | 215 (171 - 260) |        |            |            |
| Continuing Care, $                 | 8 (-2 - 19) | 32 (8 - 56) | 38 (13 - 64) | 31 (10 - 52) | 526 (206 - 846) | 331 (227 - 435) |        |            |            |
| Long-term care, $                  | 10 (4 - 16) | 35 (23 - 46) | 22 (11 - 32) | 61 (44 - 78) | 64 (44 - 84) | 40 (350 - 450) |        |            |            |
| Total cost, $                      | 3,660 (3,329 - 3,990) | 456 (380 - 532) | 2,745 (2,426 - 3,063) | 690 (631 - 748) | 12,036 (10,214 - 13,857) | 4,260 (3,880 - 4,639) |        |            |            |

All costs reflect 2010 US$ per 30 patient-days. Values are expressed as the mean (95% CI).
million ($67.5, $111.6 million), and $79.0 million ($59.8, $98.3 million).

**Discussion**

In the face of limited health care resources and an increasing national health burden, it is reasonable to consider cost when making policy decisions for an increasing number of cancer patients. Our population-based study using an incidence approach suggests that costs associated with HCC are significant and rising and accountable for approximately $25 million per year in Canada. Notably, the first year net costs accounted for approximately half of the 5-year net costs. The total net costs of HCC care accounted for at least two-thirds of the total health care costs across all three phases, with the highest

### Table 4. Mean Net Costs of Care Due to HCC According to Cost Category, Treatment Type and Disease Phase

| Cost Category                  | Initial                  | Continuing Care           | Terminal                  |
|-------------------------------|--------------------------|---------------------------|---------------------------|
| Outpatient visits, $          | 1,889 (1,665 - 2,112)    | 940 (756 - 1,123)         | 2,115 (1,090 - 3,139)     |
| Emergency room visits, $      | 87 (71 - 102)            | 122 (93 - 150)            | 340 (209 - 472)           |
| Same-day surgery, $           | 32 (27 - 37)             | 13 (6 - 20)               | 24 (8 - 40)               |
| Acute inpatient care, $       | 1,171 (1,021 - 1,320)    | 664 (515 - 813)           | 5,105 (4,158 - 6,052)     |
| Medications, $                | 42 (30 - 53)             | 196 (161 - 230)           | 58 (32 - 83)              |
| Home care, $                  | 30 (19 - 40)             | 141 (90 - 192)            | 277 (204 - 350)           |
| Continuing care, $            | −24 (−50 - 3)            | 7 (−26 - 41)              | 195 (−142 - 532)          |
| Long-term care, $             | −25 (−38 - 12)           | −39 (−60 - 19)            | −336 (−389 - −283)        |
| Total net costs, $            | 3,204 (2,863 - 3,545)    | 2,055 (1,734 - 2,375)     | 7,776 (5,889 - 9,663)     |
| Type of HCC treatment, $      |                          |                           |                           |
| Curative treatment            |                          |                           |                           |
| RFA only                      | 1,684 (717 - 2,652)      | 1,285 (518 - 3,089)       | −881 (−3,280 - 1,519)     |
| Surgical resection only       | 7,337 (5,455 - 9,219)    | 1,811 (481 - 3,142)       | 32,712 (1,954 - 63,469)   |
| Liver transplantation only    | 11,454 (9,059 - 13,849)  | 3,016 (2,247 - 3,786)     | 29,865 (1,243 - 58,487)   |
| RFA + surgical resection      | 7,971 (4,687 - 11,256)   | 1,437 (780 - 2,095)       | 4,241 (−3,490 - 11,973)   |
| RFA + liver transplantation   | 2,114 (529 - 3,699)      | 3,967 (3,014 - 4,919)     | 13,267 (−47,431 - 73,966) |
| Surgical resection + liver transplantation | 11,249 (5,771 - 16,729) | 3,395 (497 - 6,294)       | 13,267 (−47,431 - 73,966) |
| RFA + surgical resection + liver transplantation | 1,961 (−842 - 4,764) | 2,791 (1,696 - 3,886) |  |
Table 6. Five-Year Net Costs of Care Due to HCC

| Period | Survival After Diagnosis, % | Discount | Mean (95% CI), $ |
|--------|----------------------------|----------|-----------------|
| 1 Year | 51                         | Undiscounted | $37,931 (28,661 - 47,201) |
| 2 Years| 33                         | Undiscounted | $51,824 (39,710 - 63,939) |
| 3 Years| 24                         | 3% discount  | $42,469 (32,673 - 52,265) |
|        | 5% discount                | $38,966 (30,055 - 47,875) |
| 4 Years| 17                         | Undiscounted | $62,503 (48,249 - 76,759) |
|        | 3% discount                | $46,937 (36,373 - 57,501) |
|        | 5% discount                | $42,746 (33,220 - 52,272) |
| 5 Years| 13                         | Undiscounted | $70,609 (54,804 - 86,414) |
|        | 3% discount                | $50,262 (39,164 - 61,358) |
|        | 5% discount                | $45,926 (35,898 - 55,956) |
|        | 3% discount                | $52,959 (41,435 - 64,482) |
|        | 5% discount                | $48,602 (38,152 - 59,052) |
| 6 Years| 10                         | Undiscounted | $77,509 (60,410 - 94,607) |
|        | 3% discount                | $52,959 (41,435 - 64,482) |
|        | 5% discount                | $48,602 (38,152 - 59,052) |

Costs reflect 2010 US$. Costs are likely increasing relatively faster than estimated HCC incidence because sorafenib was only being introduced in the last couple of years of the study period. Increased use of this medication, and possibly other expensive medications for the future, will compound the economic burden of HCC. Consequently, programs to screen for and treat viral hepatitis may attenuate the rise in HCC incidence; and programs to screen for HCC among patients with high-risk chronic hepatitis or cirrhosis may reduce costs by early detection of cancer, at which point it is amenable to less costly treatment (e.g., RFA).

Management of HCC patients may have been suboptimal in some settings, and our estimated costs may have been underestimated. A recent United States study among a Medicare population aged ≥65 years reported underutilization of potentially curative therapy, even among those with favorable tumor features. Treatment options may differ or may be applied differently in different settings; this is a relevant aspect because the end point of surveillance is the application of effective therapy. There are limited data on population-based HCC surveillance in Canada, although screening rates are likely to be low. Barriers to effective care include low rates of community surveillance in patients with cirrhosis or those at high risk of HCC (13%-29%) due to the difficulty in the implementation of regular surveillance, complicated diagnostic evaluation, limited access to specialized multidisciplinary care and high cost of potentially curative therapy. Improved management of HCC may therefore further increase the costs associated with HCC care.

Our study is one of the few studies to examine costs associated with HCC care. Compared with published cost analyses of HCC in the United States and Taiwan using a similar approach, we discovered that our Canadian mean 5-year net costs of care due to HCC ($77,509, undiscounted) were higher than in these studies (United States 5-year net costs, $45,000; Taiwan 10-year net costs, $17,000 in 2010 US$). It is difficult, however, to compare our results with other studies conducted on the subject of HCC due to different patient populations, data sources, methods used regarding the time spent in the initial and terminal phases, as well as the different study period, health care systems, treatment guidelines, treatment practice patterns, and reimbursement policies. Our estimates of per-patient 5-year net costs of care for HCC (3% discount, $52,959), were also higher than the per-patient lifetime costs of lung, breast, and colon cancer care ($22,970-$27,890 in 2010 US$) in Canada, regardless of their prognosis.

Our findings are consistent with cancer studies that followed a temporal pattern of diagnosis and death wherein the net costs of care were highest in the initial and terminal phases and lower in the continuing care phase. However, in our study, it is likely that the relatively higher costs in the continuing phase of care include costs associated with late treatment after the diagnosis as well as care for recurrences. This was revealed in the sensitivity analysis where the initial phase included the first 12 months after the diagnosis of HCC and the net costs of care were almost doubled in the initial phase and halved in the continuing care phase. Although the initial phase of 12 months may fully capture the intensity of treatment that occurs, the actual intervals of the initial and terminal phases may depend on the disease of interest as well as treatment effectiveness. Notably, the sensitivity analyses performed on the definition of the duration of the three phases also have an impact on the long-term and aggregate net costs of care due to HCC. Our findings highlight the important implications for identification and measurement of differential costs of each different phase of care in light of its potential use in policy decision models—designed to explicitly include resource consequences and health outcomes in a health economic evaluation framework in order to evaluate whether particular health care technologies should be provided within the context of an organized health care system.

Our study has some limitations. First, HCC stage data was not available from the OCR in order to differentiate costs by cancer stage, since the costs of...
cancer care may vary by stage at diagnosis. However, in the study by Yabroff et al., 16 for esophageal and liver cancers, the net costs of care were similar by stage at initial diagnosis. Second, medication costs were not available for most patients aged <65 years. The effect on our results should not be substantial, because medication costs due to HCC represented relatively low in the initial (39%) of the total medication costs) and terminal (28%) phases. Third, we estimated direct health care costs only and not direct non-health care costs or indirect costs (e.g., lost productivity), which are important for the cost of illness for society and individuals. Finally, there was lack of information on risk factors for developing HCC to estimate cause-specific costs.

The strengths of our study include comprehensive cost estimation and rigorous methodology not considered in other studies. 16, 40, 44 Our study included an adult population aged >18 years and important cost categories such as medications and long-term care. The restriction to those aged >65 years in other studies 16 may miss some younger patients who could receive more aggressive care at a younger age. Additionally, we used a rigorous propensity score matching between cases and controls, including sociodemographics and comorbidity to provide unbiased estimation of net costs of care.

In conclusion, our findings suggest that the burden of HCC in Canada is significant and is expected to continue to increase due to the growth and aging of the Canadian population, the peaking incidence of HCC related to chronic hepatitis B and C infections, and the potentially expensive medications of the future. Our research provides value-added scientific rigor for future innovative technology appraisals of prevention and treatment interventions, leading to better health care decision-making and mitigation of the burden of disease in this population for HCC as well as for other diseases.

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References

1. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004;127:S5-S16.

2. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817-823.

3. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485-1491.

4. el-Saadany S, Tepper M, Mao Y, Semenciw R, Giulivi A. An epidemiologic study of hepatocellular carcinoma in Canada. Can J Public Health 2002;93:443-446.

5. Pocobelli G, Cook LS, Brant R, Lee SS. Hepatocellular carcinoma incidence trends in Canada: analysis by birth cohort and period of diagnosis. Liver Int 2008;28:1272-1279.

6. Dyer Z, Peletskian K, van Zanten SV. Review article: the changing epidemiology of hepatocellular carcinoma in Canada. Aliment Pharmacol Ther 2005;22:17-22.

7. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-2576.

8. Okada K, Ohtsuki T, Obata H, Tomimitsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-928.

9. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.

10. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365: 1118-1127.

11. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379:1245-1255.

12. Brown ML, Riley GF, Potosky AL, Ettzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. Med Care 1999;37:1249-1259.

13. Brown ML, Riley GF, Schussler N, Ettzioni R. Estimating health care costs related to cancer treatment from SEER-Medicare data. Med Care 2002;40:IV-104-117.

14. Baker MS, Kessler LG, Urban N, Smucker RC. Estimating the treatment costs of breast and lung cancer. Med Care 1991;29:40-49.

15. Taplin SH, Barlow W, Urban N, Mandelson MT, Timlin DJ, Ichikawa L, et al. Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. J Natl Cancer Inst 1995;87:417-426.

16. Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 2008;100:630-641.

17. Doyle C, Stockler M, Pintilie M, Panesar P, Ward P, Sturgeon J, et al. Resource implications of palliative chemotherapy for ovarian cancer. J Clin Oncol 1997;15:1000-1007.

18. Evans WK, Will BP, Berthelot JM, Wolfson MC. The economics of lung cancer management in Canada. Lung Cancer 1996;14:19-29.

19. Fassbender K, Fainsinger R, Brenneis C, Brown P, Braun T, Jacobs P. Utilization and costs of the introduction of system-wide palliative care in Alberta, 1993–2000. Palliat Med 2005;19:513-520.

20. Grover SA, Coupal L, Zowall H, Rajan R, Trachtenberg J, Elhilali M, et al. The economic burden of prostate cancer in Canada: forecasts from the Montreal Prostate Cancer Model. CMAJ 2000;162:987-992.

21. Maroun J, Ng E, Berthelot JM, Le Petit C, Dahrouge S, Flanagan WM, et al. Lifetime costs of colon and rectal cancer management in Canada. Chronic Dis Can 2003;24:91-101.

22. Wai ES, Trevian CH, Taylor SCM, Mates D, Jackson JS, Olivotto IA. Health system costs of metastatic breast cancer. Breast Cancer Res Treat 2001;65:233-240.

23. Will BP, Berthelot JM, Le Petit C, Tomiak EM, Verma S, Evans WK. Estimates of the lifetime costs of breast cancer treatment in Canada. Eur J Cancer 2000;36:724-735.

24. Will BP, Le Petit C, Berthelot JM, Tomiak EM, Verma S, Evans WK. Diagnostic and therapeutic approaches for nonmetastatic breast cancer in Canada, and their associated costs. Br J Cancer 1999;79:1428-1436.

25. Hartunian NS, Smart CN, Thompson MS. The incidence and economic costs of cancer, motor vehicle injuries, coronary heart disease, and stroke: a comparative analysis. Am J Public Health 1980;70:1249-1260.

26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-619.

28. Jembere N, Campitelli MA, Sherman M, Feld JJ, Lou W, Peacock S, et al. Influence of socioeconomic status on survival of hepatocellular carcinoma in the Ontario population: a population-based study, 1990–2009. PLoS One 2012;7:e40917.

29. Joinpoint regression program (version 3). National Cancer Institute. http://srab.cancer.gov/joinpoint/. Accessed September 16, 2011.

30. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335-351.

31. Wilkins R. Automated geographic coding based on the Statistics Canada Postal Code Conversion Files, including postal codes to December 2005. Ottawa: Health Analysis and Measurement Group, Statistics Canada; 2004. abacus.library.ubc.ca/bitstream/10573/41318/1/msword-pccfx6.pdf. Accessed October 13, 2011.

32. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score J Am Stat Assoc 1984;79:516-524.

33. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33-38.

34. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies, Pharm Stat 2011;10:150-161.

35. Kalbfeisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: Wiley; 1980.

36. Statistics Canada. Available at: http://www.statcan.gc.ca/estat/estat-eng.htm. Accessed Jan 31, 2012.

37. El-Serag HB, Siegel AB, Davila JA, Shaib YH, Cayton-Woody M, McBride R, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. J Hepatol 2006;44:158-166.

38. Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med 2011;154:85-93.

39. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. HEPATOLOGY 2010;52:132-141.

40. Lang HC, Wu JC, Yen SH, Lan CF, Wu SL. The lifetime cost of hepatocellular carcinoma: a claims data analysis from a medical centre in Taiwan. Appl Health Econ Health Policy 2008;6:55-65.

41. Progress Report on Cancer Control in Canada. www.phac-aspc.gc.ca. Accessed February 25, 2012.

42. Riley GF, Potosky AL, Lubitz JD, Kessler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. Med Care 1995;33:828-841.

43. Krahn MD, Zagorski B, Laporte A, Aliabhai SM, Bremner KE, Tomlinson G, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. BJU Int 2010;105:338-346.

44. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol 2009;50:89-99.