Brief Report

Factors Associated With Opioid Use in Long-term Cancer Survivors

Lisa Barbera, MD, Rinku Sutradhar, PhD, Doris Howell, RN, PhD, Elyse Corn, MSc, Mary Ann O'Brien, PhD, Hsien Seow, MD, Deb Dudgeon, MD, Clare Atzema, MD, Craig C. Earle, MD, Carlo DeAngelis, PharmD, and Jonathan Sussman, MD

Tom Baker Cancer Centre (L.B.), Calgary, Alberta; Institute for Clinical Evaluative Sciences (L.B., R.S., E.C., C.A., C.C.E.), Toronto, Ontario; University Health Network (D.H.), Princess Margaret Cancer Centre, Toronto, Ontario; University of Toronto (M.A.O'B.), Department of Family and Community Medicine, Toronto, Ontario; McMaster University (H.S., J.S.), Department of Oncology, Hamilton, Ontario; Queen's University Department of Medicine and Oncology (D.D.), Kingston, Ontario; Sunnybrook Health Sciences Centre (C.A.), Department of Emergency Services, Toronto, Ontario; Odette Cancer Centre (C.C.E.), Sunnybrook Health Sciences Centre, Department of Medicine, Toronto, Ontario; and Odette Cancer Centre (C.D.), Sunnybrook Health Sciences Centre, Department of Pharmacy, Toronto, Ontario, Canada

Abstract

Purpose. To evaluate factors associated with opioid use in patients with cancer surviving more than five years without recurrence. We evaluated exposures of opioid use before cancer diagnosis, opioid use between cancer diagnosis and five-year anniversary, surgeries, and chemotherapy.

Methods. We conducted a retrospective cohort study using linked provincial administrative data. Patients were aged 24−70 years and eligible for government-funded pharmacare. The index date was the five-year anniversary from diagnosis. Patients were accrued between 2010 and 2015. The main outcome was opioid prescription rate after index date. The main exposures were opioid use before diagnosis, opioid use between diagnosis and index, surgeries, and chemotherapy. A negative binomial regression model was used to estimate relative rates (RR) of opioid use after index date.

Results. Our cohort included 7431 individuals. The overall crude prescription rate after the index date was 2 per person-year. The factor most strongly associated with a higher rate of opioid use after index was continuous opioid use between diagnosis and index (RR 46.1, 95% confidence interval 34.8−61.2). Opioid use before diagnosis was also a factor (RR = 1.8, 95% confidence interval 1.44−2.19). A history of depression, comorbidity, and more than two years of diabetes were also associated with higher risk of post−index date opioid use. Significant interactions were identified between prior opioid use and opioid use between diagnosis and index. Most prescriptions are from family physicians.

Conclusion. Patients who use opioids continuously between diagnosis and index date are at increased risk of continued use after five years of survival. Safe and appropriate pain management is an important survivorship issue. J Pain Symptom Manage 2019;58:100−107. © 2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words
Cancer, opioids, survivorship

Introduction

Opioid use is currently the subject of intense scrutiny. Scientific publications have raised concerns about inappropriate use, diversion, morbidity and mortality,[1−5] and the lay press report on the opioid crisis daily. These reports and discussions are typically in reference to individuals without cancer.

Recently, concerns have been raised about chronic opioid use in patients with cancer.[6,7] Our prior work has described the use of opioids in patients with

cancer, including comparisons with patients without cancer and those with remote cancer diagnoses.[8,9] In one study, we compared opioid use in long-term cancer survivors (beyond five years from diagnosis) with age- and sex-matched controls without cancer.[6] Those with evidence of recurrence or a new cancer before five years were excluded. Those with evidence of recurrence or a new cancer after attaining survivorship were censored. We found that in spite of addressing recurrent cancer in our cohort, the rate of opioid use was significantly higher by 22% in cancer survivors when compared with controls.

Knowing that cancer survivors have a higher rate of opioid use, the aim of this current work was to explore possible reasons for this finding, including opioid use before cancer diagnosis, opioid use between cancer diagnosis and five-year anniversary, cancer surgeries, and chemotherapy.

Methods
Study Design
This was a retrospective analysis of observational data using linked administrative health care data in Ontario, Canada. Linkage was conducted using a unique encoded identifier. The study was approved by the Sunnybrook Health Science Centre Research Ethics Board and compliant with the privacy and confidentiality policies of the Institute for Clinical Evaluative Sciences.

Study Population
Our cohort includes all individuals aged 24−70 years at the date of their five-year anniversary after diagnosis (index date). Each individual had to be eligible for government-sponsored pharmacare, which is based on financial need in this age group. This is the same age group of our prior work.[6] In addition, the analysis was repeated separately for those aged 71 years or older at the index date as all patients over 65 years qualify for pharmacare regardless of income or wealth. Age 71 was chosen to allow adequate look back on each individual for opioid use before their index date. Drug information is only available from the provincial pharmacare data set.

The index date was defined as five years after the diagnosis date. Patients were accrued if their index date was between April 1, 2010, and March 31, 2015. Patients were excluded if they had stage IV disease at presentation, developed recurrence before their index date, or developed a new primary cancer before the index date. Recurrent disease was defined as receiving chemotherapy, radiation treatment, or palliative care services more than 12 months after diagnosis date or evidence of metastatic disease coded during any hospital admissions, same day surgery visits, or emergency room visits.

Data Sources and Variables
The population-based Ontario Cancer Registry (OCR) was used to identify individuals with a history of cancer and their stage and diagnosis date.[10] The Ontario Registered Persons Database (RPDB)[11] contains basic demographic information and mortality about anyone who has ever had an Ontario health card number. The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)[12] documents diagnoses and procedures from discharge abstracts of acute, chronic, and rehabilitative care hospitals in Ontario. The Same Day Surgery (SDS) and National Ambulatory Care Reporting System (NACRS) data sets document visits for same day surgery and to the emergency department. The Ontario Mental Health Recording System analyzes and reports on information submitted to CIHI about adults receiving mental health services in an inpatient setting. The Ontario Health Insurance Plan (OHIP) claims document physician services, including home visits. Activity-level reporting (ALR) data are used by the provincial cancer agency to track the delivery of chemotherapy and radiation treatment across the province. The New Drug Funding Program (NDFP) is a special mechanism for funding newer expensive systemic agents. The Homecare Database captures nonphysician services delivered at home, including nursing and personal support workers. The Ontario Drug Benefit (ODB) database contains information on all claims for prescription drugs paid to pharmacies by the program. Residents eligible for the program are either over 65 years of age or under 65 years and economically disadvantaged (e.g., on disability or welfare, https://www.ontario.ca/page/get-coverage-prescription-drugs). It was used to identify specific drugs of interest in this study. Drugs prescribed in an inpatient setting are not captured in the ODB.

Exposures
We evaluated four exposure variables (Fig. 1): 1) opioid use before cancer diagnosis was a binary variable, flagged when there was at least one prescription from 12 months before diagnosis up to three months before diagnosis; 2) opioid group describing opioid use between diagnosis and index date: coded categorically as no use at all, initial use only (from −3 months to +3 months of diagnosis data), continuous use (at least one prescription in every six-month interval of time from three months after diagnosis until index date), or other (patients who did not fall into one of the other three categories); 3) use of chemotherapy agents (paclitaxel, oxaliplatin, nab-paclitaxel, eribulin,
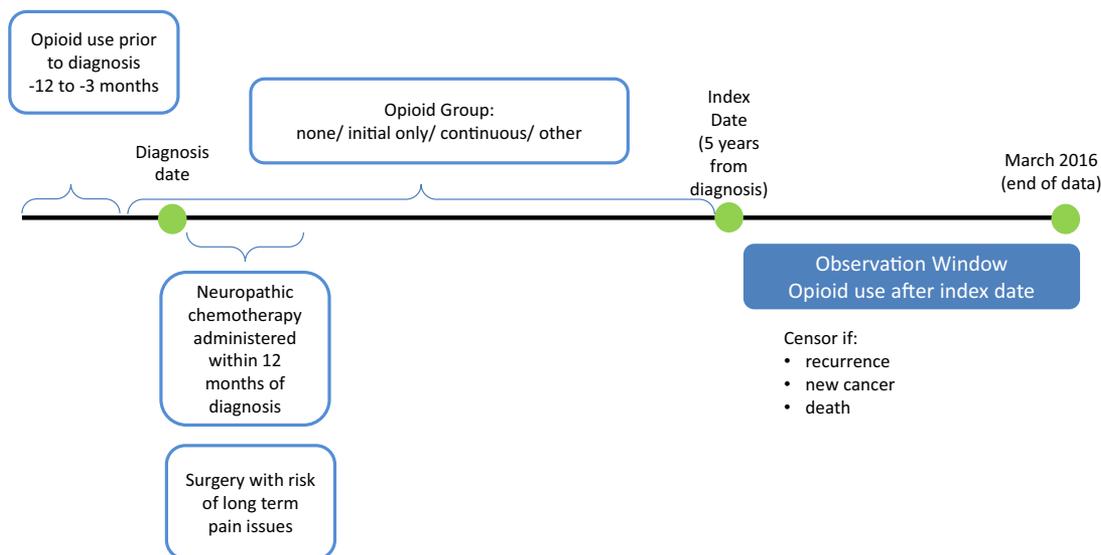
Fig. 1. Exposure and outcome variables.

docetaxel, cabazitaxel, brentuximab, bortezomib, cisplatin, carboplatin, vincristine, etoposide) known to cause neuropathy administered within 12 months of diagnosis was captured as a binary variable; and 4) record of surgical procedures at risk of long-term pain issues (mastectomy, axillary lymph node dissection, abdominal perineal resection, total mesorectal excision, thoracotomy) was captured as a binary variable. The surgical procedures chosen were felt to be those at highest risk of chronic pain difficulties.[13–23] Opioid variables were derived from ODB. Surgical variables were derived from CIHI-DAD and SDS. Chemotherapy variables were derived from ALR and NDFP.

Covariates

Basic demographics were determined from RPDB. Neighborhood income quintile was derived from postal code linkage.[24] Comorbidity was defined using a Charlson-Deyo comorbidity score using a one-year look-back window.[25] Individuals with no hospital admission or procedures during the look-back window were scored as zero. Radiotherapy use was identified in ALR and OHIP. Chemotherapy drugs were identified in OHIP, ALR, or NDFP. Palliative care was identified from OHIP, CIHI-DAD, and Home Care Database. Metastatic disease was identified in CIHI-DAD, SDS, and NACRS. Diabetes was defined using an algorithm developed and validated at the Institute for Clinical Evaluative Sciences.[26] Diabetes was specifically included because of the risk of chronic pain from peripheral neuropathy. Depression was identified using CIHI-DAD, NACRS, or Ontario Mental Health Recording System for emergency department visits or inpatient admissions for mood disorders in the year before diagnosis.[27]

Outcome

The outcome for each individual was measured as the rate of opioid prescriptions, where the numerator was the number of all opioid prescriptions from the index date to the date of last follow-up and the denominator was the duration of the follow-up time. This outcome has been used in our prior work.[6,8,9] Follow-up ended at the date of death, recurrence, development of a new primary cancer, or study end, whichever occurred first (Fig. 1).

Statistical Analysis

Distributions of the cohort characteristics and the main exposures were examined using descriptive statistics. Mean (and standard deviation) and median (and interquartile range) were used to assess continuous measures; counts (and proportions) were used for categorical measures. As an initial analysis, the crude rate of opioid prescriptions during the follow-up window was computed for the entire cohort overall and by each level of the exposure variables. To examine factors associated with the rates of opioid prescriptions after survivorship, a multivariable negative binomial regression model was implemented. The natural logarithm of each individual's follow-up time was incorporated as an offset term in the regression model. In addition to the four exposure variables mentioned previously, additional covariates included in the model were age (continuous), sex, index year (continuous), cancer diagnosis (categorical), region of residence (categorical), neighborhood income quintile, rurality (binary), Charlson Comorbidity Index (binary), a history of diabetes (none, less than two years, more than two years), and a history of depression (binary). The value of each covariate was

measured at the index date. As the association between a covariate and the opioid prescription rate may vary for different levels of another covariate, a priori, we decided to explore 2 two-way interactions: between opioid group and prediagnosis opioid use and between depression and sex. All analyses were completed using SAS, version 9.3.

Results

We identified 7431 individuals aged 24–70 years who were eligible for cohort inclusion at their index date. The median age was 67 years, and 51% were male. Prostate cancer was the most common cancer. A larger proportion of patients were in the poorest income quintile, which is expected given the financial need criteria for ODB eligibility. The distributions of all characteristics of these individuals are presented in Table 1.

Table 2 reports the frequency of each exposure variable. 12.6% of individuals had an opioid prescription before their cancer diagnosis. 47.7% had no opioid use between their diagnosis date and index, whereas 6.8% had continuous use during that time. In the year after diagnosis, 12.8% had one of the surgical procedures of interest and 7% had received the chemotherapy drugs of interest.

Table 3 reports crude opioid prescription rates after index date overall and by exposure variables. The overall crude prescription rate was two per person-year. The relative rate (RR) of opioid prescriptions for those with opioid use before diagnosis compared with those without was 8.5. The rate of opioid prescriptions for those who had opioid prescriptions continuously between diagnosis date and index date was 77 times that of those with no use at all during the same interval. The RR was 2 and 11.5, respectively, for those with initial use only or other. The rate for those with a surgery flag was 1.2 times of those without. The rate for those with a chemotherapy flag was 0.9 times of those without. Approximately one-third of patients alive in each month of follow-up had an opioid prescription, and 12% of patients ($n = 263$) had an opioid prescription in each consecutive month of follow-up (data not shown).

Table 4 reports the results of the multivariable model examining factors associated with the rate of opioid use after index date. This model consisting of main effects only (without interactions) provides the average effect of each characteristic on the rate of opioid use. The rate of opioid prescriptions after index date was 1.76 times (95% confidence interval [CI] 1.36–2.29) higher for those with a history of depression than those without and 1.3 times higher for those with at least a two-year history of diabetes than those without. Individuals who

Table 1
Distributions of Cohort Characteristics (N = 7431)

Age at index	
Mean ± SD	63.00 ± 9.05
Median (IQR)	67 (59–70)
Sex	
Female	3600 (48.4%)
Male	3831 (51.6%)
Most recent cancer diagnosis	
Brain	59 (0.8%)
Breast	967 (13.0%)
Colorectal	825 (11.1%)
Gynecological	639 (8.6%)
Head and neck	238 (3.2%)
Hematology	507 (6.8%)
Lung	328 (4.4%)
Other	1314 (17.7%)
Other gastrointestinal	114 (1.5%)
Other genitourinary	754 (10.1%)
Prostate	1686 (22.7%)
Region	
1	473 (6.4%)
2	622 (8.4%)
3	362 (4.9%)
4	876 (11.8%)
5	315 (4.2%)
6	414 (5.6%)
7	738 (9.9%)
8	734 (9.9%)
9	908 (12.2%)
10	410 (5.5%)
11	670 (9.0%)
12	300 (4.0%)
13	482 (6.5%)
14	127 (1.7%)
Income quintile	
1 (low)	2238 (30.1%)
2	1524 (20.5%)
3	1273 (17.1%)
4	1267 (17.1%)
5 (high)	1093 (14.7%)
Unknown	36 (0.5%)
Rural	
Urban	6268 (84.3%)
Rural	1163 (15.7%)
Charlson score	
0	6071 (81.7%)
1+	1360 (18.3%)
Diabetes	
No	4661 (62.7%)
Yes	2770 (37.3%)
Years since diabetes diagnosis	
Mean ± SD	9.70 ± 6.10
Median (IQR)	9 (5–14)
Depression	
No	6997 (94.2%)
Yes	434 (5.8%)

SD = standard deviation; IQR = interquartile range.

received surgical procedures of interest near the time of diagnosis were not at increased risk of opioid use after index. There was variation by region and cancer type. More than 80% of prescriptions were written by family physicians, and this was observed in the time period before diagnosis, between diagnosis and index and after diagnosis (data not shown).

On adding interactions to the model, we noticed a significant interaction between opioid use before cancer diagnosis and opioid use between diagnosis and

Distributions of Exposure Variables Among the Cohort
(N = 7431)

Variable	Value	
Opioids before diagnosis	No	6493 (87.4%)
	Yes	938 (12.6%)
Opioid group	Initial use only	682 (9.2%)
	Continuous use	506 (6.8%)
	No use	3544 (47.7%)
	Other	2699 (36.3%)
Record of surgical procedure	No	6478 (87.2%)
	Yes	953 (12.8%)
Record of chemo	No	6914 (93.0%)
	Yes	517 (7.0%)

index. Among those with no opioid use before diagnosis, the rate of opioid use after index was 63.3 times higher (95% CI 39.3–102.0) for individuals who had continuous use between their diagnosis and index date compared with individuals who had no opioid use between their diagnosis and index date. On the other hand, among those with opioid use before diagnosis, the rate of opioid use after index was 76.7 times higher (95% CI 40.8–144.27) for individuals who had continuous use between their diagnosis and index date compared with individuals who had no opioid use between their diagnosis and index date. Those with no opioid use before diagnosis and initial opioid use only were not at increased risk of opioid use after index date.

The interaction between sex and depression was modest. Both men and women with depression had a higher RR of opioid use after the index date compared with those without depression.

The analysis was repeated in its entirety for patients aged 71 years and older. In this age group, the eligibility for government-funded pharmacare is age-based only, so the entire population is included. The cohort size was 50,887. Because of the differences in cohort ascertainment, the two age groups are not directly comparable; however, the model findings were similar in the older group of patients. Family physicians again prescribed more than 80% of the prescriptions at all intervals. The results tables for the group aged 71 years and older are provided in the appendix.

Discussion

We have demonstrated that long-term cancer survivors, who have not had a cancer recurrence, have increased opioid use after their five-year anniversary. Factors associated with this risk are opioid use before the cancer diagnosis and continuous opioid use between diagnosis and index date (i.e., at least one opioid prescription in every six-month interval between diagnosis and index). We were unable to demonstrate increased risk with the type of initial cancer treatment. Prescriptions were predominantly from family physicians.

There is growing concern that the increasing regulation/restriction on opioid prescribing may have an unintended impact on patients with cancer.[28,29] Our prior work suggests this may be the case.[8,9,30] Recent guidelines and editorials have tried to highlight the care that is required to ensure patients with cancer have adequate pain management and that prescribing is done in a safe way.[31,32] Our data support the role of universal precautions. It is vital that patients with cancer continue to have access to opioids when they are indicated, although recent reviews demonstrate a lack of data supporting efficacy for long-term use and risks that go beyond misuse.[33,34]

Family physicians are the most frequent provider of opioid prescriptions along the entire trajectory of care, with oncologists providing only a small

Table 3
Crude Opioid Prescription Rates Overall and by Exposure Variables

Exposure Variable	Number of Patients	Opioid Prescriptions During Follow-up Period			Total Follow-up (years)	Crude Rate (per person-year)	Crude Relative Rate
		Mean ± SD	Median (IQR)	Number			
Crude rate (overall)	N = 7431	5.84 ± 22.56	0 (0–1)	43,434	22,122	2.0	—
Opioid prescription before diagnosis							
No	6493 (87.4%)	3.13 ± 16.11	0 (0–0)	20,329	19,406	1	—
Yes	938 (12.6%)	24.63 ± 42.79	7 (0–33)	23,105	2716	8.5	8.5
Opioid group							
Initial use only	682 (9.2%)	1.07 ± 8.67	0 (0–0)	728	1983	0.4	2
Continuous use	506 (6.8%)	43.9 ± 49.67	30 (16–57)	22,212	1440	15.4	77
No use at all	3544 (47.7%)	0.70 ± 5.46	0 (0–0)	2468	10,741	0.2	—
Other	2699 (36.3%)	6.68 ± 23.84	0 (0–2)	18,026	7958	2.3	11.5
Record of surgical procedure							
No	6478 (87.2%)	5.76 ± 22.97	0 (0–1)	37,283	19,353	1.9	—
Yes	953 (12.8%)	6.45 ± 19.49	0 (0–1)	6151	2769	2.2	1.2
Record of chemo							
No	6914 (93.0%)	5.90 ± 22.88	0 (0–1)	40,806	20,648	2	—
Yes	517 (7.0%)	5.08 ± 17.65	0 (0–1)	2628	1475	1.8	0.9

SD = standard deviation; IQR = interquartile range.

Table 4
Multivariable Model Results for Rate of Opioid Prescription After Five Years of Survival, Main Effects Model

Variable	Value	Reference	Relative Rate	Lower Confidence Limit	Upper Confidence Limit
Age			0.99	0.98	1.00
Sex	Female	Male	0.86	0.72	1.03
Year of index			**0.94**	**0.90**	**0.99**
Most recent cancer diagnosis	Brain	Lung	0.62	0.26	1.47
	Breast		**0.63**	**0.45**	**0.90**
	Colorectal		**0.61**	**0.43**	**0.87**
	Gynecological		0.80	0.54	1.19
	Head and neck		0.65	0.41	1.04
	Hematology		**0.58**	**0.39**	**0.87**
	Other		0.72	0.51	1.02
	Other gastrointestinal		1.52	0.86	2.69
	Other genitourinary		1.10	0.76	1.60
	Prostate		**0.62**	**0.43**	**0.89**
Region	1	14	1.67	0.97	2.87
	2		**2.31**	**1.36**	**3.92**
	3		1.62	0.93	2.81
	4		1.57	0.94	2.62
	5		0.77	0.43	1.38
	6		0.98	0.56	1.71
	7		1.15	0.68	1.94
	8		0.71	0.42	1.21
	9		1.14	0.68	1.90
	10		1.51	0.87	2.63
	11		0.84	0.50	1.41
	12		1.25	0.70	2.22
	13		**1.76**	**1.03**	**3.01**
Income quintile	2	1 (low)	**0.79**	**0.66**	**0.95**
	3		1.03	0.84	1.25
	4		**0.81**	**0.67**	**0.99**
	5 (high)		0.90	0.73	1.11
	Unknown		0.58	0.24	1.37
Urban/rural	Urban	Rural	0.86	0.70	1.05
Charlson score	1+	0	1.30	1.09	1.54
Diabetes	0–2 years	Never	0.80	0.57	1.11
	≥2 years		**1.33**	**1.15**	**1.54**
Depression	Yes	No	**1.76**	**1.36**	**2.29**
Record of surgical procedure	Yes	No	0.84	0.67	1.05
Record of chemotherapy	Yes	No	**0.68**	**0.52**	**0.88**
Prediagnosis opioid use	Yes	No	**1.78**	**1.44**	**2.19**
Opioid group	Initial only	None	1.08	0.85	1.39
	Continuous		**46.13**	**34.75**	**61.24**
	Other		**8.41**	**7.22**	**9.79**

Statistically significant values are shown in bold.

proportion of the prescriptions. Any interventions, education, or polices aimed at improving pain management and safe opioid prescribing would need to target this group of physicians. Survivorship care plans should address the issue of pain management and opioid use. Cancer survivors see their family physicians much more often than matched controls.[35]

Most studies of opioid use have focused on individuals without cancer because cancer-related pain is a common and legitimate indication for prescribing opioids.[32,36] In this study, we have taken care to exclude individuals who had metastatic disease at the time of diagnosis or had evidence of recurrent disease (such as resuming anticancer treatment). This would ensure the cohort included only individuals who were disease free and presumably without disease-related pain. We did consider possible treatment-related causes of chronic pain such as certain surgeries

or chemotherapy agents; however, we did not find an increased risk for these exposures. Lee et al. made an opposing observation that patients receiving chemotherapy were at increased risk of ongoing opioid use.[7] It should be noted that their group was looking at outcomes much closer to the time of treatment than our study that was five years out from diagnosis.

Strengths of this article include a detailed evaluation of opioid use before the index date, methods to exclude those with recurrent disease, and an outcome that accounts for varying amounts of follow-up time. Also, population-level data were available for the older age group and the analysis was repeated for that group. The provincial formulary includes a comprehensive range of opioids, and it is unlikely that we have underestimated or overestimated the opioid prescription rate. Limitations include limited generalizability for the 24- to 71-year-olds. Results seen here

may not be the same in those of the same age group but who do not meet the eligibility criteria for government-assisted access to the provincial formulary. The list of chemotherapy agents and surgeries was determined with clinical input and is consistent with what has been identified in the literature[34,37]; however, there may be other causes of chronic pain related to cancer treatment that we were unable to properly identify with administrative data. Also, we have assumed that the reason for opioid use before cancer diagnosis is not related to cancer, but it is not possible to describe the actual reasons for opioid use before cancer diagnosis with our data. Finally, our data do not provide more detailed information about specific drugs or doses and the definitions used (e.g., for continuous) may obscure certain practices or patterns of use.

A small number of long-term cancer survivors who are free of disease continue to use opioids in the long term. The strongest factors associated with this are opioid use before cancer diagnosis and continuous opioid use between diagnosis and the five-year anniversary. A measured and thoughtful approach to effective pain management, opioid prescribing, and use of multimodal approaches for cancer management is essential to enhance quality of life.[37] Safe and appropriate pain management is an important survivorship issue during and after cancer treatment.

Disclosures and Acknowledgments

References

1. Dhalla IA, Mamdani MM, Gomes T, Juurlink DN. Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. Can Fam Physician 2011;57:e96.

2. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. BMJ: Br Med J (Online) 2011:343.

3. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health 2015; 36:559−574.

4. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171: 686−691.

5. Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Med 2011;5:e22.

6. Sutradhar R, Lokku A, Barbera L. Cancer survivorship and opioid prescribing rates: a population-based matched cohort study among individuals with and without a history of cancer. Cancer 2017;123:4286−4293.

7. Lee JS, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. J Clin Oncol United States 2017;35:4042−4049.

8. Barbera L, Sutradhar R, Chu A, et al. Opioid prescribing among cancer and non-cancer patients: time trend analysis in the elderly using administrative data. J Pain Symptom Manage 2017;54:484−492.

9. Barbera L, Sutradhar R, Chu A, et al. Comparison of opioid prescribing among cancer and noncancer patients aged 18-64: analysis using administrative data. J Pain Symptom Manage 2018;56:72−79.

10. Clarke EA, Marrett LD, Kreiger N. Cancer registration in ontario: a computer approach. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, eds. Lyon, France: IARC Pub, 1991:246−257.

11. Iron K, Zagorski BM, Sykora K, Manuel DG. Living and dying in ontario: An opportunity for improved health information. ICES investigative report. Toronto: Institute for Clinical Evaluative Sciences, 2008.

12. Canadian Institute for, Health Information. Data quality of the discharge abstract database following the first year implementation of ICD-10-CA/CCI-final report. Ottawa: CIHI, 2004.

13. Feddern ML, Jensen TS, Laurberg S. Chronic pain in the pelvic area or lower extremities after rectal cancer treatment and its impact on quality of life: a population-based cross-sectional study. Pain 2015;156:1765−1771.

14. Johannsen M, Christensen S, Zachariae R, Jensen AB. Socio-demographic, treatment-related, and health behavioral predictors of persistent pain 15 months and 7-9 years after surgery: a nationwide prospective study of women treated for primary breast cancer. Breast Cancer Res Treat 2015;152:645−658.

15. De Oliveira GSJ, Chang R, Khan SA, et al. Factors associated with the development of chronic pain after surgery for breast cancer: a prospective cohort from a tertiary center in the United States. Breast J 2014;20:9−14.

16. Bruce J, Thornton AJ, Powell R, et al. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. Pain 2014;155:232−243.

17. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a cochrane systematic review and meta-analysis. Br J Anaesth 2013;111:711−720.

18. Hopkins KG, Rosenzweig M. Post-thoracotomy pain syndrome: assessment and intervention. Clin J Oncol Nurs 2012;16:365−370.

19. Chapman S. Chronic pain syndromes in cancer survivors. Nurs Stand 2011;25:35−41.

20. Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011;55:60−68.

21. Guastella V, Mick G, Soriano C, et al. A prospective study of neuropathic pain induced by thoracotomy: Incidence, clinical description, and diagnosis. Pain 2011;152:74−81.

22. Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. Eur J Pain 2009;13: 478−485.

23. Steegers MA, Wolters B, Evers AW, Strobbe L, Wilder-Smith OH. Effect of axillary lymph node dissection on prevalence and intensity of chronic and phantom pain after breast cancer surgery. J Pain 2008;9:813−822.

24. Wilkins R. PCCF + version 3G users guide: Automated geographic coding based on the statistics canada postal code conversions files. Ottawa: Statistics Canada, 2001.

25. 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.

26. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in ontario. Diabetes Care 2002;25:512−516.

27. Maria C, Evgenia G, Simone NV, et al. Temporal trends in mental health service utilization across outpatient and acute care sectors: a population-based study from 2006 to 2014. Can J Psychiatry 2018;63:94−102.

28. Paice JA. Under pressure: the tension between access and abuse of opioids in cancer pain management. J Oncol Pract 2017;13:595−596.

29. Haider A, Zhukovsky DS, Meng YC, et al. Opioid prescription trends among patients with cancer referred to outpatient palliative care over a 6-year period. J Oncol Pract United States 2017;13:e981.

30. Barbera L, Seow H, Husain A, et al. Opioid prescription after pain assessment: a population-based cohort of elderly patients with cancer. J Clin Oncol 2012;30:1095−1099.

31. Paice JA. Cancer pain management and the opioid crisis in America: How to preserve hard earned gains in improving the quality of cancer pain management. Cancer 2018;124: 2491−2497.

32. Paice JA, Portenoy R, Lacchetti C, et al. Management of chronic pain in survivors of adult cancers: American society of clinical oncology clinical practice guideline. J Clin Oncol 2016;34:3325−3345.

33. Bennett M, Paice JA, Wallace M. Pain and opioids in cancer care: Benefits, risks, and alternatives. Am Soc Clin Oncol Educ Book 2017;37:705−713.

34. Carmona-Bayonas A, Jimenez-Fonseca P, Castagnon E, et al. Chronic opioid therapy in long-term cancer survivors. Clin Translational Oncol 2017;19:236−250.

35. McBride ML, Lorenzi MF, Page J, et al. Patterns of physician follow-up among young cancer survivors: report of the childhood, adolescent, and young adult cancer survivors (CAYACS) research program. Can Fam Physician 2011;57: e490.

36. World HO. WHO's pain ladder. Available from http://www.who.int/cancer/palliative/painladder/en/.

37. Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. J Clin Oncol 2014;32:1739−1747.

Appendix

Table A1
Distribution of Cohort Characteristics for the 71+ Age Group Cohort (N = 50,887)

Age at Index	
Mean ± SD	79.13 ± 5.97
Median (IQR)	78 (74−83)
Sex	
Female	20,974 (41.2%)
Male	29,913 (58.8%)
Most recent cancer diagnosis	
Brain	100 (0.2%)
Breast	6465 (12.7%)
Colorectal	8397 (16.5%)
Gynecological	2280 (4.5%)
Head and neck	1266 (2.5%)
Hematology	3128 (6.1%)
Lung	2065 (4.1%)
Other	6081 (12.0%)
Other gastrointestinal	764 (1.5%)
Other genitourinary	4492 (8.8%)
Prostate	15,849 (31.1%)
Region	
1	2915 (5.7%)
2	4312 (8.5%)
3	2680 (5.3%)
4	6535 (12.8%)
5	2107 (4.1%)
6	3729 (7.3%)
7	4072 (8.0%)
8	6103 (12.0%)
9	5959 (11.7%)
10	2276 (4.5%)
11	4490 (8.8%)
12	2139 (4.2%)
13	2606 (5.1%)
14	964 (1.9%)
Income quintile	
1 (low)	8989 (17.7%)
2	10,164 (20.0%)
3	10,048 (19.7%)
4	10,479 (20.6%)
5 (high)	11,025 (21.7%)
Unknown	182 (0.4%)
Rural	
Urban	43,739 (86.0%)
Rural	7147 (14.0%)
Charlson score	
0	41,771 (82.1%)
1+	9116 (17.9%)
Diabetes	
No	34,380 (67.6%)
Yes	16,507 (32.4%)
Years since diabetes diagnosis	
Mean ± SD	10.16 ± 6.38
Median (IQR)	9 (5−15)
Depression	
No	49,870 (98.0%)
Yes	1017 (2.0%)

SD = standard deviation; IQR = interquartile range.

Table A2
Distribution of Exposure Variables Among the 71+ Age Group Cohort (N = 50,887)

Variable	Value	
Opioids before diagnosis	No	47,547 (93.4%)
	Yes	3340 (6.6%)
Opioid group	Initial use only	4251 (8.4%)
	Continuous use	743 (1.5%)
	No use	31,450 (61.8%)
	Other	14,443 (28.4%)
Record of surgical procedure	No	43,897 (86.3%)
	Yes	6990 (13.7%)
Record of chemo	No	49,166 (96.6%)
	Yes	1721 (3.4%)

Table A3
Crude Opioid Prescription Rates Overall and by Exposure Variable

| Exposure Variable | Number of Patients | Unique Opioid Prescriptions During Follow-up Period | | | Total Follow-up (years) | Crude Rate | Relative Rate |
		Mean ± SD	Median (IQR)	Number			
Crude rate (overall)	N = 50,887	2.32 ± 13.07	0 (0−0)	118,162	146,396	0.8	—
Opioid prescription before diagnosis							
No	47,547 (93.4%)	1.69 ± 10.76	0 (0−0)	80,355	137,429	0.6	—
Yes	3340 (6.6%)	11.32 ± 29.46	0 (0−7)	37,807	8967	4.2	7
Opioid group							
Initial use only	4251 (8.4%)	0.83 ± 6.32	0 (0−0)	3512	12,216	0.3	1.5
Continuous use	743 (1.5%)	38.1 ± 46.46	22 (10−45)	28,311	1853	15.3	76.5
No use at all	31,450 (61.8%)	0.71 ± 6.08	0 (0−0)	22,483	91,992	0.2	—
Other	14,443 (28.4%)	4.42 ± 17.96	0 (0−1)	63,856	40,336	1.6	8
Record of surgical procedure							
No	43,897 (86.3%)	2.26 ± 12.88	0 (0−0)	99,069	126,068	0.8	—
Yes	6990 (13.7%)	2.73 ± 14.21	0 (0−0)	19,093	20,328	0.9	1.1
Record of chemo							
No	49,166 (96.6%)	2.34 ± 13.21	0 (0−0)	115,120	141,813	0.8	—
Yes	1721 (3.4%)	1.77 ± 8.17	0 (0−0)	3042	4583	0.7	0.9

Table A4
Multivariable Model Results for Rate of Opioid Prescription After Five Years of Survival, Main Effects Model

Variable	Value	Reference	Relative Rate	Lower Confidence Limit	Upper Confidence Limit
Age			**1.07**	**1.07**	**1.08**
Sex	F	M	**1.49**	**1.36**	**1.63**
Year of index			**0.92**	**0.90**	**0.94**
Most recent cancer diagnosis	Brain	Lung	1.29	0.66	2.54
	Breast		0.95	0.80	1.14
	Colorectal		0.84	0.71	1.00
	Gynecological		1.02	0.82	1.27
	Head and Neck		1.23	0.95	1.59
	Hematology		0.85	0.69	1.04
	Other		0.97	0.80	1.17
	Other GI		0.85	0.63	1.16
	Other GU		0.97	0.80	1.18
	Prostate		0.88	0.73	1.06
Region	1	14	1.26	0.98	1.64
	2		**1.40**	**1.10**	**1.79**
	3		**1.48**	**1.14**	**1.92**
	4		1.20	0.95	1.53
	5		1.06	0.81	1.40
	6		1.07	0.83	1.38
	7		0.88	0.69	1.14
	8		0.87	0.68	1.11
	9		1.06	0.83	1.35
	10		**1.61**	**1.23**	**2.10**
	11		**1.36**	**1.06**	**1.74**
	12		**1.37**	**1.05**	**1.79**
	13		**1.57**	**1.21**	**2.03**
Income quintile	2	1 (low)	0.95	0.85	1.05
	3		0.91	0.82	1.01
	4		0.92	0.83	1.02
	5 (high)		0.85	0.77	0.94
	U		**1.71**	**1.04**	**2.81**
Urban/rural	Urban	Rural	**0.87**	**0.79**	**0.96**
Charlson score	1+	0	**1.57**	**1.45**	**1.71**
Diabetes	0−2 years	Never	1.06	0.90	1.25
	≥2 years		**1.21**	**1.13**	**1.30**
Depression	Yes	No	**2.87**	**2.32**	**3.54**
Record of surgical procedure	Yes	No	0.99	0.89	1.10
Record of chemo	Yes	No	**0.73**	**0.61**	**0.87**
Prediagnosis opioid use	Yes	No	**1.98**	**1.74**	**2.25**
Opioid group	Initial only	None	1.07	0.95	1.21
	Continuous		**37.74**	**29.31**	**48.61**
	Other		**6.12**	**5.71**	**6.57**

Statistically significant values are shown in bold.
SD = standard deviation; IQR = interquartile range.