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ORIGINAL ARTICLE

Patient-level factors associated with chronic opioid use in cancer: a population-based cohort study

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Abstract

Purpose Concerns around chronic opioid use (COU), misuse, and harms have led to increased scrutiny of opioid prescribing in oncology. There is lack of research examining patient-level factors associated with COU. Our aim was to examine patient-level factors associated with COU in newly diagnosed cancer patients.

Methods Population-based retrospective cohort study using administrative health data of patients in Alberta, Canada, diagnosed between February 2016 and October 2017. Adult cancer patients who completed a symptom survey within ± 60 days of diagnosis were included. Patients were divided into two groups: COU (defined as continuous opioid prescriptions for at least 90 days post-diagnosis) and non-chronic opioid use (NCOU). Logistic regression was used to evaluate factors associated with COU.

Results We included 694 patients (mean age 65 years; 51% female). Most had breast (20%), colorectal (13%), and lung (33%) cancers. Of the 14% with COU, 79% were opioid naïve at diagnosis. Those in the COU group were more often diagnosed with advanced cancer (66% versus 40%), had lung cancer (47%), and were opioid tolerant (> 90 days of continuous opioids within one-year pre-diagnosis). A total of 64% of COU versus 27% of NCOU had moderate to severe pain at diagnosis ($p < 0.001$). Irrespective of treatment type or stage, those with moderate to severe pain, were opioid tolerant at diagnosis, or had multiple prescribers were at greater risk for COU.

Conclusions Specific patient groups were at increased risk of COU and should be the focus of adaptive prescribing approaches to ensure that opioid use is appropriate.

Keywords Opioids · Cancer · Symptom management · Cohort study · Chronic opioid use

Background

The incidence of pain in cancer patients is estimated to be 50–70% [1]. Pain is a symptom that can occur throughout the cancer trajectory secondary to the cancer or its treatments [1]. To address this distressing symptom, organizations have developed clinical practice guidelines for pain management to ensure patients do not suffer from cancer pain [2–4]. A mainstay of these recommendations is the use of opioids for pain when it is not adequately managed by non-opioid analgesics [2–4]. Because of recent public health concerns about opioid misuse and growing scrutiny around opioid prescribing [5], the use of opioids in cancer populations is being increasingly examined [5–15]. Of interest is chronic opioid use defined by the Canadian Pain Society as the continuous use of opioids for at least 90 days [16]. A number of long-term health complications from chronic opioid use have recently been described in non-cancer populations. These include increased risk of mortality, increased potential of misuse, immune system alterations, endocrine dysfunction, increased rates of depression, and osteoporosis [17]. Recent evidence has demonstrated that cancer patients may be at higher risk for opioid misuse than previously thought [18]. Given improved survival rates from cancer and the estimated prevalence of pain in cancer survivors [1], careful consideration of opioid prescribing is now

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recommended to mitigate the complications associated with chronic opioid use [17].

Studies suggest that some cancer patients may be at increased risk for chronic opioid use, including certain post-surgical cancer patients [12] and older cancer survivors [11, 14]. In these studies, risk factors such as older age, having a surgical procedure, being on chemotherapy, the stage and type of tumor, and prior opioid use were associated with chronic opioid use. Patient-reported pain scores and comorbidities including mental illnesses have only been infrequently evaluated as risk factors for chronic opioid use in cancer populations, likely due to lack of available data. These factors are important to consider since poorly controlled pain at diagnosis and comorbid mental illness have been associated with chronic opioid use in other populations [19]. More studies on factors associated with chronic opioid therapy are required in cancer populations to guide opioid prescribing in clinical practice and to help mitigate any potential harms from chronic opioid therapy [15]. Considering the limitations in the current literature, the specific objectives of the current study were

1. To describe the prevalence of chronic opioid use before and after a cancer diagnosis
2. To describe average daily dose of opioids (morphine equivalent daily dose) before and after a cancer diagnosis
3. To determine factors associated with chronic opioid therapy in cancer patients

We hypothesized that patients with high pain scores at diagnosis or those with a history of chronic opioid use prior to diagnosis would be at greater risk for chronic opioid use after a cancer diagnosis compared with those patients with no or low pain scores and those who were opioid naïve at diagnosis.

Methods

We undertook a population-based study using provincial cancer registry and administrative data to define a cohort of adults diagnosed with any cancer. We included patients aged 18 years or older from the province of Alberta, Canada, diagnosed between February 2016 and October 2017. Alberta's cancer system is a part of Canada's publicly funded health care and thus represents the sole provider of cancer care in the province. Patients were included if they had a diagnosis of solid or hematological malignancy and had prospectively completed a comprehensive patient-reported outcome survey within 60 days of diagnosis. Patients who did not complete a symptom survey within 60 days of diagnosis were excluded (see Fig. 1, inclusion of patients in cohort). This study received approval from the Health Research Ethics Board of Alberta (HREBA.CC-17-0238). Study findings are reported according to Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

Data sources and variables

Data from Alberta Health Services and Cancer Control Alberta repositories were used to define demographic and clinical variables. Demographic data included age at diagnosis and sex. Racial data were not available, but more than 85% of the Alberta population is White [21]. Cancer stage was coded using the Collaborative Staging System to derive American Joint Commission on Cancer (AJCC) Tumor Node Metastasis (TNM) stage [22]. Cancer stage was subsequently categorized as early (stages I–III) or advanced stage (stage IV) or unknown (hematological malignancies). Initial cancer treatment was obtained from Alberta Health Services pharmacy records. We divided type of treatment into four distinct categories: those who received no treatment (no surgery, chemotherapy, radiation or other treatment), those who received surgery alone, those who received surgery plus adjuvant treatment (either chemotherapy, radiation, or both), and those who received other treatment (single-modality chemotherapy or radiation, hormonal therapy, or immunotherapy).

Prescription opioid information

Our primary study outcome was chronic opioid use. We obtained opioid prescription information from provincial Pharmacy Information Network (PIN) data. PIN data capture out-patient drug dispensing information for all residents in Alberta and contains the date of prescription, drug identification number, total dosage amount, daily dosage, and distinct prescriber number (a random number assigned to each individual prescriber). The PIN data are routinely maintained and assessed for quality by Alberta Health Services (the provincial health system of which cancer care is embedded) analytic team. These datasets have been widely used and validated in previous studies [23–25]. We defined chronic opioid use as the dispensing of daily opioids for at least 90 days [16] after the date of diagnosis (index date). Patients were assigned to one of two mutually exclusive groups: those who were chronic opioid users and those who were non-chronic opioid users.

We also evaluated opioid use prior to diagnosis. Opioid-naïve patients were defined as those with fewer than 90 days of continuous opioid prescriptions (e.g., dispensing of consecutive prescriptions) at any time during a one-year look-back period prior to the date of diagnosis. Opioid-tolerant patients were defined as those having at least one period of 90 days of continuous opioid prescriptions at any time during the one-year look-back period [16]. We identified the number of opioid prescribers associated with each patient during a 90-day period post-diagnosis by using the unique opioid prescriber

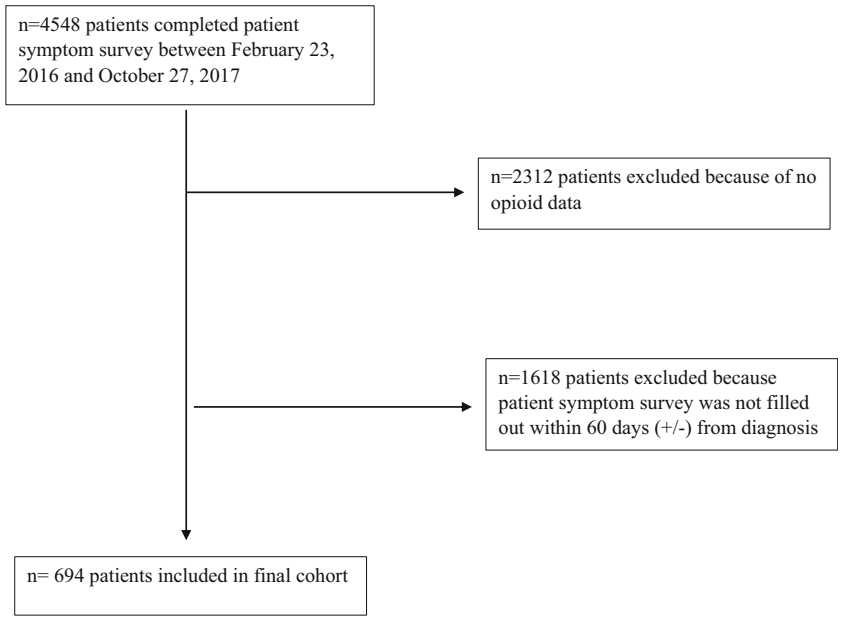

Fig. 1 Inclusion of patients in the cohort study

number. The total daily morphine equivalent dose was calculated using the drug identification numbers (a unique number assigned to identify the type of opioid) and then converting the opioid dose to be equivalent to that of oral morphine using standard opioid conversions [26]. Mean oral morphine equivalent opioid daily dose was calculated pre-diagnosis (including up to 1 year prior to diagnosis) and post-diagnosis (up to 1 year after diagnosis).

Patient-reported factors

Patient-reported factors included items from the Cancer Control Alberta "Putting Patients First" (PPF) Survey. This is a patient-reported outcome survey that was initiated in the province in 2016 with available data for analysis up to October 2017. The survey items and our team's ongoing research initiatives with these data have been described elsewhere [27]. Patient-reported levels of pain, anxiety, and depression at diagnosis were gathered using the ESASr, a well-validated questionnaire [28–30] used in a variety of cancer populations to screen for common symptoms experienced by cancer patients (pain, tiredness, nausea, fatigue, depression, anxiety, drowsiness, appetite, lack of well-being, and shortness of breath) [28]. Patients rate the severity of their symptoms using a numeric scale, with 0 representing the absence of symptoms and 10 representing the most severe symptoms. Symptom severity is typically categorized as mild (scores from 0 to 3), moderate (scores from 4 to 7), or severe (scores of > 7) [30]. The ESASr has been used to describe symptoms in cancer patients at different phases of the cancer trajectory [31], including to identify symptom clusters and symptom severity [32]. Further, it has been used to explore associations between cancers, patient variables, and symptom experiences [33].

We considered other variables including comorbidities identified from inpatient hospital data and physician billing claims by using the Charlson comorbidity index (CCI) and included conditions diagnosed within 6 months prior to or after cancer diagnosis. The CCI is a widely used comorbidity classification system and has been broadly applied to cancer populations [34–36]. We used the Deyo adaptation of the CCI [37]. Community-level socioeconomic status including educational attainment (proportion of residents with high school or higher degree) and average annual income at the dissemination area were retrieved from census data.

Statistical analysis

Descriptive statistics were used to characterize demographic, clinical, and opioid use. The *t* test, the chi-squared test, one-way ANOVA, or Fisher's exact test was used to evaluate for differences across opioid use groups.

Multivariate logistic regression models were used to evaluate associations between chronic opioid use and patient-level factors including cancer type, stage and treatment, patient-reported outcomes (pain, depression, and anxiety), and opioid use pre- and post-diagnosis. Age, CCI, sex, education, and income level were also included as covariates. Age and number of opioid prescribers were treated as continuous variables. Sex, stage (advanced or unknown versus early), treatment type (other, surgery alone, or surgery plus adjuvant treatment versus no treatment), pain, anxiety or depression level (moderate or severe versus mild), opioid use pre-diagnosis (tolerant versus naïve), CCI (1, 2 or 3+ versus 0), education level, and

income level were analyzed as categorical variables. Missing data for the patient-reported variables (ESASr) were considered to be missing at random. Two-sided p value < 0.05 was defined a priori as statistically significant. All analyses were conducted using SAS v.9.4 [38].

Results

We identified 694 patients. Characteristics of the cohort are detailed in Table 1. The majority had breast (20.6%), colorectal (12.7%), or lung cancer (32.7%). The mean age was 65 years (12.5 SD) and there were more women (51%) versus men (49%). More patients had early-stage disease (47%) and the majority received other treatments (single-agent chemotherapy, radiation, immunotherapy, or hormonal therapy) with only 11% receiving surgery alone, and 28% receiving surgery plus adjuvant treatment. Nearly half of the cohort (42%) had no comorbidities. For those with comorbidity, the most common were COPD, diabetes, and cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, or stroke). The majority were opioid naïve at diagnosis (94%).

Opioid use subgroups

Of the 694 patients, 14% were classified as chronic opioid users among whom 21% were opioid tolerant at diagnosis. There were no differences between the two groups with respect to age, sex, CCI, or socioeconomic status. There were statistically significant differences between the chronic opioid users and the non-chronic opioid users with respect to a number of variables (Table 1). Chronic opioid users were more often male (57%); had lung; prostate, or pancreas cancer; and more frequently had advanced-stage disease and received other treatments compared with non-chronic opioid users. Chronic opioid users had much higher mean daily morphine equivalent doses prior to diagnosis and post-diagnosis as compared with non-chronic opioid users.

Patient-reported factors

The patient-reported outcomes are described in Table 2. The majority of patients experienced mild symptoms (pain (68%), depression (74%), and anxiety (74%)). However, there were statistically significant differences between the groups with respect to severity of pain, anxiety, and depression. Chronic opioid users more often had moderate to severe pain (64%), moderate to severe anxiety (51%), or moderate to severe depression (38%) compared with non-chronic opioid users. Of note, 19% of chronic opioid users reported severe pain at diagnosis.

Factors related to chronic opioid use

Results of the multivariate logistic regression are represented by the forest plot (Fig. 2). Patients with moderate (OR = 1.96, 95% CI 1.07–3.56) or severe pain (OR = 2.55, 95% CI 1.07–6.06) had greater odds of becoming chronic opioid users compared with patients with mild pain. Similarly, patients who were opioid tolerant at diagnosis compared with opioid-naïve at diagnosis had greater odds of becoming chronic opioid users (OR = 3.34, 95% CI 1.31–8.50). Finally, as the number of opioid prescribers increased, so did the odds of being a chronic opioid user (OR 2.28, 95% CI 1.79–2.91).

Discussion

We conducted a population-based cohort study of cancer patients to examine the prevalence of and factors related to chronic opioid use. Our study adds to the literature for several reasons. We examined patient-reported outcomes in relation to chronic opioid use, we included robust opioid data which captured prescription information at a population level, and our study incorporated a diverse spectrum of cancer types. In addition, our study included measurement of cancer pain at diagnosis, which has not been well described in past studies.

We observed that nearly one-third of adults with cancer experienced moderate to severe pain at diagnosis. Similar findings in other cancer populations have been reported, with a recent systematic review demonstrating that at least one-third of cancer patients will experience moderate to severe pain at some point during the cancer trajectory [1]. This highlights that a significant proportion of patients encountered in oncology clinical practice will need advanced management strategies for pain. Current clinical practice guidelines for pain management [2–4] outline that opioids are indicated for many of these cases. If appropriate, referral to pain management specialists could be considered for these patients.

Clinicians should be aware of the risk that some patients may become chronic opioid users and that prescribing practices may need to be adjusted to ensure that opioid use is appropriate. Similar to previous studies, we found 11% of our cohort became chronic opioid users after being diagnosed with cancer. The incidence of chronic opioid use in cancer populations is reported in the literature to range between 2 and 16% depending on the definition of "chronic" used by the researchers and the population included [7, 9, 12]. While evidence regarding the consequences of chronic opioid use is lacking in cancer populations, the outcomes in non-cancer populations are well documented and include the potential for misuse and aberrant

Table 1 Demographic and clinical characteristics of cohort $n = 694$ categorized by opioid use

Variable	Total cohort Mean (STD)	Chronic opioid user ($n = 98$) Mean (STD)	Non-chronic opioid user ($n = 596$) Mean (STD)	p value
Age	65 (12.9)	65.1 (12.3)	65 (13)	0.9522
	n (%)	*n* (%)	*n* (%)	
Gender				0.0713
Female	356 (51.3%)	42 (42.9%)	314 (52.7%)	
Male	338 (48.7%)	56 (57.1%)	282 (47.3%)	
Tumor type				0.0001
Bladder/kidney/other GU	57 (8.2%)	5 (5.1%)	52 (8.7%)	
Breast	143 (20.6%)	7 (7.1%)	136 (22.8%)	
Colorectal	88 (12.7%)	8 (8.2%)	80 (13.4%)	
Gastric/esophageal	41 (5.9%)	6 (6.1%)	35 (5.9%)	
Head and neck	3 (0.4%)	1 (1%)	2 (0.3%)	
Hepatobiliary	16 (2.3%)	1 (1%)	15 (2.5%)	
Lung	227 (32.7%)	46 (46.9%)	181 (30.4%)	
Other	31 (4.4%)	3 (3%)	28 (4.7%)	
Pancreas	26 (3.7%)	10 (10.2%)	16 (2.7%)	
Prostate	62 (8.9%)	11 (11.2%)	51 (8.6%)	
Stage				< 0.0001
Advanced	306 (44.1%)	65 (66.3%)	241 (40.4%)	
Early	328 (47.3%)	28 (28.6%)	300 (50.3%)	
Unknown	60 (8.6%)	5 (5.1%)	55 (9.2%)	
Treatment type				< 0.0001
No treatment	96 (13.8%)	15 (15.3%)	81 (13.6%)	
Other treatment	326 (47%)	71 (72.4%)	255 (42.8%)	
Surgery only	76 (11%)	5 (5.1%)	71 (11.9%)	
Surgery plus adjuvant treatment	196 (28.2%)	7 (7.1%)	189 (31.7%)	
CCI score				0.5254
0	293 (42.2%)	36 (36.7%)	257 (43.1%)	
1	183 (26.4%)	30 (30.6%)	153 (25.7%)	
2	74 (10.7%)	9 (9.2%)	65 (10.9%)	
3+	144 (20.7%)	23 (23.5%)	121 (20.3%)	
Educational level				0.0469
≤ 80	380 (54.8%)	59 (60.2%)	321 (53.9%)	
> 80	245 (35.3%)	36 (36.7%)	209 (35.1%)	
Unknown	69 (9.9%)	3 (3.1%)	66 (11.1%)	
Median Income				0.0412
≤ 46,000	425 (61.2%)	65 (66.3%)	360 (60.4%)	
> 46,000	188 (27.1%)	29 (29.6%)	159 (26.7%)	
Unknown	81 (11.7%)	4 (4.1%)	77 (12.9%)	
Vital statistic				< 0.0001
Alive	403 (58.1%)	36 (36.7%)	367 (61.6%)	
Dead	291 (41.9%)	62 (63.3%)	229 (38.4%)	

*Median income is obtained from census data and represents median income per postal code area not patient-level income. **Education level is obtained from census data and represents proportion of patients who have education over high school and not patient-level education data. Not applicable cancer stages include those patients with hematological malignancies. Other cancers included melanoma, endocrine tumors, non-colorectal GI (excluding gastric and esophageal), bones and soft tissue, brain, gynecological, hematology, and unknown primary. Other treatments included chemotherapy only, radiation therapy only, immunotherapy, or hormonal therapy

Table 2 Baseline pain, anxiety, and depression scores and opioid information categorized by opioid use $n = 694$

Variable		Total cohort	Chronic opioid user ($n = 98$)	Non-chronic opioid user ($n = 596$)	p value
Pain score	Mild pain	470 (67.7%)	35 (35.7%)	435 (73%)	< 0.0001
	Moderate pain	171 (24.6%)	44 (44.9%)	127 (21.3%)	
	Severe pain	53 (7.6%)	19 (19.4%)	34 (5.7%)	
Anxiety score	Mild anxiety	429 (61.8%)	48 (49%)	381 (63.9%)	0.004
	Moderate anxiety	200 (28.8%)	42 (42.9%)	158 (26.5%)	
	Severe anxiety	65 (9.4%)	8 (8.2%)	57 (9.6%)	
Depression score	Mild depression	511 (73.6%)	61 (62.2%)	450 (75.5%)	0.0041
	Moderate depression	146 (21%)	33 (33.7%)	113 (19%)	
	Severe depression	37 (5.3%)	4 (4.1%)	33 (5.5%)	
Opioid use pre-diagnosis	Opioid naive	654 (94.2%)	77 (78.6%)	577 (96.8%)	< 0.0001
	Opioid tolerant	40 (5.8%)	21 (21.4%)	19 (3.2%)	
Number of prescribers	0–1	525 (75.6%)	36 (36.8%)	489 (82%)	< 0.0001
	2+	169 (24.4%)	62 (63.3%)	107 (18%)	
Daily morphine equivalent dose pre-diagnosis	Mean (STD)	11.3 (24.5)	27.3 (39.5)	8.7 (19.8)	< 0.0001
Daily morphine equivalent dose post-diagnosis	Mean (STD)	28.7 (47.2)	65.1 (65)	22.7 (40.7)	< 0.0001

behaviors, increased mortality, endocrinopathies, infections and immunosuppression, falls and fracture risk, and cognitive dysfunction [39]. Given the potential harm to patients and emerging evidence of the potential for opioid misuse in cancer populations [18], it is important to evaluate an individual patient's opioid use at regular intervals to determine the need for ongoing opioids.

Similarly, clinicians should be aware of risk factors associated with chronic opioid use in oncology populations. We found that irrespective of stage, type of cancer, or type of treatment, patients with moderate to severe pain were more likely to become chronic opioid users. As demonstrated in prior studies, poor management of initial pain can lead to chronic pain [19] which may ultimately lead patients to become chronic opioid users. Thus, pain management strategies should include a thorough assessment of cancer pain at diagnosis, early intervention for moderate to severe pain, and repeated assessments of pain and medications being used to manage the symptom.

The number of opioid prescribers is also an important factor when trying to mitigate chronic opioid use. We found that as the number of prescribers increased, so did the risk for chronic opioid use. While this correlation has not been previously evaluated in cancer populations, it has been consistently described in non-cancer populations [40–42]. The practice of having one responsible physician for pain management and opioid prescribing has been endorsed by recent clinical practice guidelines [3]. It is also highlighted in these guidelines that a thorough patient assessment prior to starting opioids should be carried out to determine comorbid non-cancer chronic pain syndromes and the individual patient's history of opioid use. Given we demonstrated that patients who were opioid tolerant at diagnosis were at greater odds of becoming chronic opioid users, obtaining the patient's opioid use history prior to prescribing would also be an important aspect to consider.

We did not find that anxiety and depression were associated with chronic opioid use. This is contrary to previous studies demonstrating a strong association between psychiatric comorbidity and chronic opioid use in cancer and non-cancer populations [8, 43, 44]. The null association in our cohort may be explained by the following. We included patient-reported symptoms of anxiety and depression as gathered by the ESASr. This is considered a screening instrument for anxiety and depression and not a clinical diagnosis of either of these conditions. In addition, the nature of anxiety and depression in cancer populations may be different than the anxiety and depression frequently found to be comorbid in non-cancer populations.

Strengths and limitations

This study included patient-reported outcomes and robust opioid data representative of a large Canadian province. Our administrative health databases are one of the few in Canada to have information at a provincial level on opioid prescriptions. In addition, our administrative health datasets have been well validated and described in previous cancer and non-cancer populations. Our sample size was relatively large for patient-

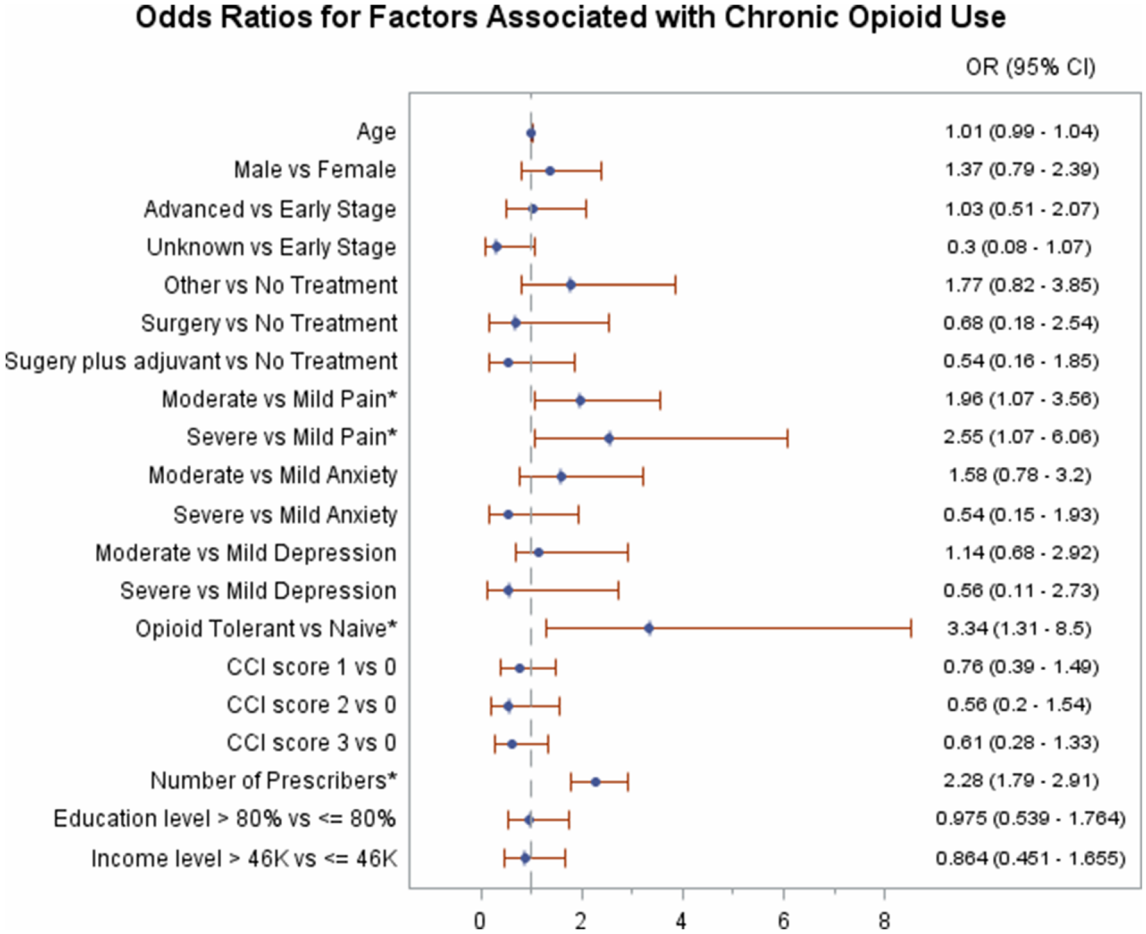

Fig. 2 Odds ratios and 95% confidence intervals for factors associated with chronic opioid use $n = 694$. Asterisk (*) denotes statistically significant $p < 0.05$

reported outcome data and patients completed their questionnaires prospectively. Finally, we were able to account for a number of important variables in our analysis, including stage and type of cancer, type of treatment, opioid use pre-diagnosis, and socioeconomic status.

The findings of the study should be interpreted with several limitations in mind. We did not have data on the reasons for opioid use pre-diagnosis, meaning that some patients may have had comorbid chronic pain syndromes that contributed to their chronic opioid use post-diagnosis. We did not have information on the timing of opioid use pre-diagnosis. We also did not have any information on the specialty type of the prescribers (e.g., specialists, general practitioners, surgeons etc.). The ± 60-day window for completion of the symptom survey means that the index date (start of timing of opioid use) could include those patients without a definitive diagnosis and those patients who had already started treatment. We choose this window for two reasons. Our cohort included rural patients who may have a delay between being diagnosis and their first appointment at a cancer center (when the PRO survey is collected). In addition, some patients have an appointment at the cancer center (and complete a PROs survey) prior to a definitive diagnosis. On average, the time between filling out the survey and the definitive diagnosis date was 26 days. Further, we did not have treatment completion data so some of the patients could have been undergoing cancer treatment during the time that their opioid use was measured. Another limitation is generalizability. We included only patients who completed the symptom survey; however, it should be noted that there was a 95% survey completion rate. We had no information on health literacy level. In addition, we did not have information on factors such as behavioral pattern of chronic opioid users, the use of other substances, or other pain management medications such as NSAIDs, antidepressants, or anticonvulsants. Finally, there are current limitations in evidence regarding the appropriateness or inappropriateness of continued opioid use throughout the cancer trajectory. To clearly define a population, we used standard definitions of chronic opioid use, however, it should be highlighted that this may be an appropriate use of opioids in many cancer populations.

Conclusions

Considering the current scrutiny around opioid prescribing in oncology populations, this study provides important information for clinicians. Pain management strategies including the use of opioids will continue to be a necessary part of clinical practice, given the incidence of pain with cancer. In light of the growing evidence for potential harms from opioids, providers should adopt an approach to prescribing opioids that considers the patient's opioid history pre-diagnosis, adapts prescribing to the individual patient, and ensures only one prescriber is providing opioid prescriptions. In addition, the inclusion of pain management specialists (palliative care, pain anesthesia, physical rehabilitation) throughout the illness trajectory should be considered an important strategy for comprehensive pain management and supportive care.

Future research should focus on longitudinal symptom burden and opioid use to clarify if chronic opioid use is related to chronic pain or opioid misuse. More information is needed on the type of pain (e.g., nociceptive, neuropathic, acute, or chronic) experienced throughout the cancer trajectory so that non-opioid strategies could be considered. In addition, future studies should aim to include other important variables such as concomitant non-opioid medications that are being used to control pain, the type of chronic pain experienced by patients, and additional factors that may influence opioid use (e.g., lifestyles, health-related behaviors). Finally, efforts to develop specific mitigation strategies, including clinical care pathways and multidisciplinary chronic pain clinics, are highly warranted.

Compliance with ethical standards

This study received approval from the Health Research Ethics Board of Alberta (HREBA.CC-17-0238).

Conflict of interest The authors declare that they have no conflict of interest.

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