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ORIGINAL PAPER

Changes in use of opioid therapy after colon cancer diagnosis: a population-based study

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Abstract

Purpose To describe patterns of opioid use in cancer survivors.

Methods In a cohort study of colon cancer patients diagnosed during 1995–2014 and enrolled at two Kaiser Permanente regions, we constructed quarterly measures of opioid use from 1 year before cancer diagnosis through 5 years after diagnosis to examine changes in use. Measures included any use, incident use, regular use (use ≥ 45 days in a 91-day quarter), and average daily dose (converted to morphine milligram equivalent, MME). We also assessed temporal trends of opioid use.

Results Of 2,039 colon cancer patients, 11–15% received opioids in the four pre-diagnosis quarters, 68% in the first quarter after diagnosis, and 15–17% in each subsequent 19 quarters. Regular opioid use increased from 3 to 5% pre-diagnosis to 5–7% post diagnosis. Average dose increased from 15 to 17 MME/day pre-diagnosis to 14–22 MME/day post diagnosis (excluding the quarter in which cancer was diagnosed). Among post-diagnosis opioid users, 73–95% were on a low dose (< 20 MME/day). Over years, regular use of opioids increased in survivorship with no change in dosage.

Conclusion Opioid use slightly increased following a colon cancer diagnosis, but high-dose use was rare. Research is needed to differentiate under- versus over-treatment of cancer pain.

Keywords Opioid therapy · Colon cancer · Survivorship · Cancer pain

Introduction

Pain management is a key component of cancer care [1]. During active treatment, approximately 60% of cancer patients suffer from pain [2]. The tumor and various cancer treatments, including surgery, chemotherapy, radiation therapy, and hormonal therapy, can result in long-lasting pain [3]. During survivorship, one in three patients reported chronic pain and 16% reported pain that interfered with their daily life [2, 4]. For cancer patients with moderate to severe pain, opioid therapy is a typical first-line treatment [1]. However, empirical data are lacking on the incidence and prevalence of opioid therapy, type of opioid, and dosage among cancer survivors. Several recent studies have focused on time immediately following cancer diagnosis and treatment [5–7]. These analyses suggested that most patients undergoing cancer surgery received opioids, and between 10 and 19% of previously opioid naïve patients who filled opioids during cancer surgery had another prescription of opioids in 90–180 days postoperatively, a period during which opioid

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is typically not required in general surgical patients. However, data describing opioid use as cancer patients transition to survivorship or experience secondary cancer events are scant. In a Danish cancer population, any use of opioids increased from about 12% at diagnosis to 38% during 5-year follow-up among those who survived, and from 38% at diagnosis to 68% at death among those who died within 5 years [8]. In a Canadian cohort of cancer survivors who were at least 5 years post cancer diagnosis, the rate of opioid prescribing was 2.6 fills per person-year, 20% higher than otherwise similar individuals without cancer [9]. To our knowledge, no data on patterns of opioid use focusing on the first 5 years of cancer survivorship have been published for U.S. populations.

In the general U.S. population, there was a sharp increase in any opioid use, long-term opioid therapy use, and high-dose opioid use from the mid-to-late 1990s to early 2010 [10–12]. Gauging the status of opioid therapy use in cancer patients is important as there are concerns about undertreatment of cancer pain; however, long-term opioid use is associated with abuse, addiction, fatal and non-fatal overdose, and cardiovascular events [13–15]. With a growing population of 1.3 million colorectal cancer survivors in the United States [16], addressing this gap is timely and important. Using data from a population-based cohort study, we sought to characterize trends and patterns of opioid therapy use in colon cancer survivors.

Materials and methods

We used data from a population-based cohort study conducted at two integrated health care systems: Kaiser Permanente Washington (KPWA) and Kaiser Permanente Colorado (KPCO). Details about the study protocol have been previously published [17]. We briefly describe the study population, data sources, and measures of opioid exposure. The KPWA institutional review board, to which KPCO ceded, approved this study with a waiver of consent for patient health record data.

Study setting and population

KPWA and KPCO maintain a virtual data warehouse (VDW) [18], a decentralized data model with common variables and definitions from electronic health records and other health plan databases. We used the VDW's Tumor table to identify incident cancer cases. The Tumor table is populated from the Seattle-Puget Sound Surveillance Epidemiology and End Results (SEER) program's registry at KPWA and the health plan's internal cancer registry at KPCO.

We identified 3,326 patients aged 18 years or older when diagnosed with incident stage I–IIIA colon cancer from 1995 through 2014. Details of eligibility criteria were published previously [17]. Briefly, to ensure data availability, we excluded patients who were not continuously enrolled for at least 12 months before cancer and 3 months after the incident colon cancer ($n=393$), or had an incomplete medical record ($n=288$). We then examined electronic health record data in the VDW and conducted manual medical chart review to exclude patients who might not be "cancer free" within 90 days after the end of treatment (people with a diagnosis of a prior or concurrent colorectal or metastatic non-colorectal tumors, a diagnosis of additional primary tumors or having recurrence of the incident colon cancer within 90 days after the end of treatment, no surgery, having positive surgical margins or indeterminate imaging results, or death within 90 days after the end of treatment; $n=606$). The final cohort for this analysis was 2,039. They were referred to as colon cancer survivors in this study.

Data sources

We collected data on participants using the VDW and medical chart abstraction from 1 year before cancer diagnosis through the earliest of death, disenrollment from the health plan, or date of medical record abstraction. The VDW includes data on health plan enrollment, diagnoses and procedures (International Classification of Diseases [ICD] and Current Procedural Terminology [CPT] codes), outpatient prescription medication dispensings, and death. Opioid prescription dispensings from 1 year before cancer diagnosis through the end of follow-up were ascertained from the VDW Pharmacy table, which has information on days of supply, strength, and generic names of each outpatient prescription dispensed. Run-out dates were calculated as the medication dispensing date plus days supply associated with each dispensing. The pharmacy table includes all medications dispensed at Kaiser Permanente's outpatient pharmacies and claims from contracting pharmacies. Second cancer events included second primary cancers and recurrence in the colon or at other sites. We ascertained second primary cancers from cancer registries at both sites, while cancer recurrence was ascertained by medical chart abstraction solely (KPWA) or in combination with VDW cancer registry data (KPCO). All-cause death was extracted from the VDW Death table, which incorporates information sourced from cancer registries, state vital records departments, and the health plan. Patient demographics (i.e., sex, race, and ethnicity) were obtained from the VDW. Charlson comorbidity score [19] at colon cancer diagnosis was calculated based on the presence of relevant diagnosis and procedure codes in the year before cancer diagnosis. Height and weight at diagnosis and cancer treatments were extracted from the VDW and supplemented by medical record review.

Analysis

To evaluate changes in opioid use before and after cancer diagnosis, we studied opioid prescription dispensings within fixed quarters of 91 days, anchored at colon cancer diagnosis. The quarter of cancer diagnosis, Quarter 0, was from the day of diagnosis through the 90th day after diagnosis. We then divided 364 days prior to cancer diagnosis into four pre-diagnosis quarters such that Quarter-1 includes 91 days immediately before cancer diagnosis. Following the quarter of cancer diagnosis, we examined 19 subsequent quarters, from the 91th day through the 1,819th day post diagnosis (approximately 5 years after diagnosis). Patients with fewer than 5 years of follow-up (earliest of death or disenrollment from the health plan) were censored after their last complete quarter of follow-up.

Within each quarter, we assessed any opioid use, prevalent use, incident use, and regular use. Any opioid use was defined as having one or more dispensings of prescription opioids in the quarter of interest. For patients with any opioid use, we further divided them into incident use and prevalent use (mutually exclusive). Incident use was defined as an opioid dispensing with no prior opioid dispensing in the past two quarters. Patients who had any opioid use during a quarter without meeting the criteria for incident use were defined as prevalent users. In each quarter, we calculated the proportion of patients who had any use, prevalent use, and incident use of opioids among colon cancer patients who survived the whole quarter. We constructed opioid continuous use episode(s) by rolling successive opioid dispensings that were within 2 days between the run-out date of one dispensing and the dispense date of the next dispensing. Regular use of opioid therapy was defined as use for at least 45 days in a fixed quarter.

For each quarter, we also estimated average daily dose among patients dispensed an opioid in that quarter. We first calculated morphine milligram equivalent (MME) for each dispensing by multiplying medication strength, amount dispensed, and a drug-specific conversion factor used previously [20]. Next, to calculate individual average daily dose, we summed the MMEs of all prescription opioids dispensed in a quarter and then divided it by 91 days. Last, we averaged the daily dose across patients who were dispensed an opioid in the quarter to calculate average daily dose at the cohort level. Based on guidelines and previous studies, we defined high dose as an average daily dose of at least 90 MME/day, medium dose as 20–90 MME/day, and low dose as under 20 MME/day [21, 22]. For each quarter, we reported average daily dose and proportions of patients on different levels of dosage among patients dispensed an opioid in each quarter. We also assessed the predominant type of opioid prescribed in the 5 years following colon cancer diagnosis according to total number of dispensings and total days supply.

To assess changes in use of opioid therapy from 1994 to 2014, we examined frequencies of any use, incident use, regular use, proportion of low- or high-dose users, and dosage in quarters before and after colon cancer diagnosis by year of cancer diagnosis (1995–1999, 2000–2004, 2005–2009, and 2010–2014).

For patients experiencing a second cancer event within 5 years, we assessed opioid use in the quarters before and after a second cancer event (the day that a second cancer event occurred was included in the quarter after). For those who died within 5 years, we assessed opioid use in two quarters before death. These quarters were constructed as 91-day intervals relative to these events; for instance, a quarter before a second cancer event was 91 days before the event.

Means and proportions were calculated for descriptive analyses. We compared characteristics stratified by any use of opioids in the 5 years following cancer diagnosis and computed p values from χ^2 tests for binary outcomes and t test for continuous outcomes. To assess temporal changes in opioid use, Poisson models were performed for any use, incident use, regular use, and high- or low- daily dose of opioid use, whereas linear models were used for average daily dose. We used generalized estimating equations (GEE) with a robust error variance that accounted for correlation among measures of the same subject across quarters to estimate proportions or means and associated 95% confidence intervals (CI) for these measures in each the four time periods [23, 24]. We stratified analysis according to quarters relative to cancer diagnosis and estimated separate GEE models in four quarters before cancer diagnosis, cancer diagnosis quarter (Quarter 0), and 19 quarters after cancer diagnosis. For measures in post-diagnosis periods, we did not include cases diagnosed in 2010–2014 because many of them did not have the opportunity to be observed for 5 years following diagnosis as of the time of our study data collection in 2014. We also assessed linear trends of these measures across time periods by fitting separate models with time periods as a continuous variable. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

A total of 2,039 colon cancer patients were included in our study. The median follow-up period was 5.0 years (interquartile range 3.1–5.0). Of all patients, 1,746 (86%) were dispensed at least one opioid in the 5 years following diagnosis. Compared to patients with no opioid dispensings during follow-up, those dispensed an opioid were somewhat younger and more likely to have smoked, to be obese, to have higher stage tumors, to have received chemotherapy, and to have a shorter follow-up time (Table 1). Nearly all patients received partial colectomy. There were no

Table 1 Patient characteristics by opioid use after colon cancer diagnosis

Characteristics	All	Any opioid use in the 5 years following colon cancer diagnosis		*p* value
		No	Yes	
	n = 2039	*n* = 293	*n* = 1746	
	n (%)	*n* (%)	*n* (%)	
Year of colon cancer diagnosis				
1995–1999	410 (20.1)	62 (21.2)	348 (19.9)	0.408
2000–2004	569 (27.9)	71 (24.2)	498 (28.5)	
2005–2009	579 (28.4)	83 (28.3)	496 (28.4)	
2010–2014	481 (23.6)	77 (26.3)	404 (23.1)	
Age at diagnosis (years)				
< 50	94 (4.6)	7 (2.4)	87 (5)	< 0.05
50–59	294 (14.4)	28 (9.6)	266 (15.2)	
60–69	530 (26)	79 (27.0)	451 (25.8)	
70–79	677 (33.2)	97 (33.1)	580 (33.2)	
80 +	444 (21.8)	82 (28.0)	362 (20.7)	
Sex				
Female	1,066 (52.3)	157 (53.6)	909 (52.1)	0.629
Male	973 (47.7)	136 (46.4)	837 (47.9)	
Hispanic ethnicity				
Not Hispanic	1,742 (85.4)	248 (84.6)	1,494 (85.6)	0.316
Hispanic	93 (4.6)	10 (3.4)	83 (4.8)	
Unknown	204 (10.0)	35 (11.9)	169 (9.7)	
Race				
White	1,582 (77.6)	218 (74.4)	1,364 (78.1)	0.565
Black	70 (3.4)	11 (3.8)	59 (3.4)	
Asian	66 (3.2)	12 (4.1)	54 (3.1)	
American Indian/Alaska Native	9 (0.4)	0 (0)	9 (0.5)	
Hawaiian/Pacific Islander	5 (0.2)	1 (0.3)	4 (0.2)	
Multiple race	19 (0.9)	2 (0.7)	17 (1.0)	
Other/unknown	288 (14.1)	49 (16.7)	239 (13.7)	
Smoking before diagnosis[a]				
Never	916 (45.2)	154 (52.9)	762 (43.9)	< 0.05
Ever	1,112 (54.8)	137 (47.1)	975 (56.1)	
Unknown	11	2	9	
Charlson score in the year before colon cancer diagnosis				
0	1,085 (56.4)	162 (57.9)	923 (56.2)	0.802
1	429 (22.3)	62 (22.1)	367 (22.3)	
2	184 (9.6)	28 (10.0)	156 (9.5)	
3 +	225 (11.7)	28 (10.0)	197 (12.0)	
Missing	116	13	103	
BMI at diagnosis (kg/m^2)[a]				
< 25	651 (33.5)	96 (34.9)	555 (33.3)	< 0.05
25– < 30	702 (36.2)	117 (42.5)	585 (35.1)	
30 +	588 (30.3)	62 (22.5)	526 (31.6)	
Unknown	98	18	80	
Stage at diagnosis				
I	911 (44.7)	145 (49.5)	766 (43.9)	< 0.05
II	1,052 (51.6)	143 (48.8)	909 (52.1)	
III	76 (3.7)	5 (1.7)	71 (4.1)	

Table 1 (continued)

Characteristics	All	Any opioid use in the 5 years following colon cancer diagnosis		*p* value
		No	Yes	
	n = 2039	*n* = 293	*n* = 1746	
	n (%)	*n* (%)	*n* (%)	
Cancer[a] surgery				
Total colectomy	5 (0.2)	0 (0.0)	5 (0.3)	< 0.05
Partial colectomy	2,020 (99.2)	288 (98.3)	1,732 (99.4)	
Surgery, unspecified	11 (0.5)	5 (1.7)	6 (0.4)	
Unknown	3	0	3	
Cancer treatment[b]				
Chemotherapy	277 (13.6)	24 (8.2)	253 (14.5)	< 0.05
Radiation	30 (1.5)	3 (1)	27 (1.5)	0.492
Years of follow-up (median, interquartile range)	5.0 (3.1–5.0)	4.9 (2.5–5.0)	5.0 (3.3–5.0)	< 0.05

BMI body mass index

[a]Persons with unknown values were not included for percentage calculation

[b]Not mutually exclusive

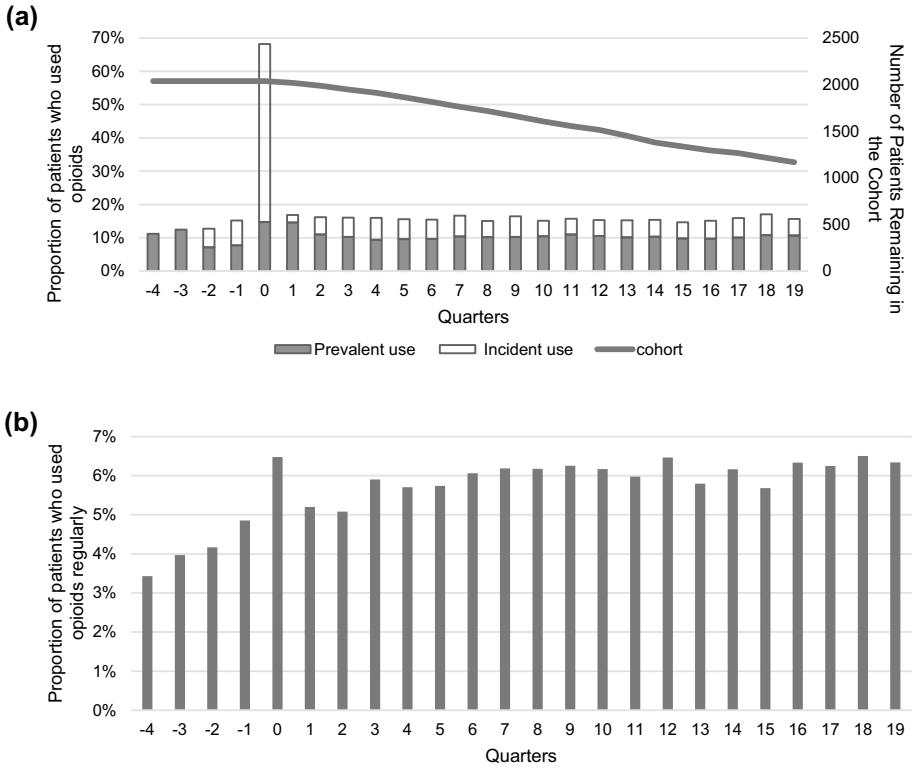

Fig. 1 Quarterly proportion of colon cancer patients who had **a** any use (including incident use), and **b** regular use of opioid therapy. Quarter 0 was the quarter when colon cancer was diagnosed. Incident use was defined as having an opioid fill after a 6-month or longer period without a prior fill. It was not assessed for the first 2 quarters of the year before diagnosis because information on prior use was not collected. Regular opioid use was defined as use for 45 days or longer within a quarter

major differences by sex, race, or ethnicity. In the 5 years following colon cancer diagnosis, the most common opioids dispensed were hydrocodone, oxycodone, and codeine (Supplement Table 1). Among patients with at least one opioid dispensing in this period, 77% received hydrocodone and 53% received oxycodone, each type dispensed

about five times per individual among those who received these drugs.

Figure 1 shows the proportions of prevalent users, incident users, and any users (including both prevalent and incident users) in the cohort in four quarters before diagnosis, the quarter of diagnosis, and 19 subsequent quarters. In the year before colon cancer diagnosis, the proportion of patients who dispensed any opioid steadily increased from 11% in Quarter-4 to 15% in Quarter-1. In Quarter 0 which spans 91 days starting from the day of incident cancer diagnosis, 68% of patients used an opioid, and the majority were incident users. In the following 19 quarters, between 15 and 17% patients had any use and 2–7% had incident use in each quarter (Fig. 1a). Patients who used opioid therapy regularly (≥ 45 days in a 91-day quarter) increased slightly from 3 to 5% in pre-diagnosis quarters to 5–7% in the 5 years after diagnosis (Fig. 1b).

Among patients who used opioids in each quarter, the average dose ranged from 15 to 17 MME/day in four pre-diagnosis quarters, dropped to 6 MME/day in Quarter 0 (as low-dose users surged), and fluctuated between 14 and 22 MME/day in the remaining quarters during the 5 years post diagnosis (Fig. 2a). As shown in Fig. 2b, in each quarter, 73–95% of patients who received an opioid were low-dose users and 2–6% were high-dose users.

During the 5-year follow-up, 313 patients had a second cancer event (including 154 recurrences, 27 second primary colon cancers, and 132 other cancers), and 339 patients died (Table 2). The 313 second cancer events occurred on average 2 years after the incident colon cancer (median: 24.2 months, interquartile range 13.6–36.6 months). Comparing opioid use in the quarter before a second cancer event to the quarter after the event, there was an increase in any use (from 25 to 52%), incident use (from 11 to 31%), and regular use (from 7 to 9%) of opioid therapy. Across these two quarters around a second cancer event, average dose dropped from 21 MME/day to 14 MME/day and 81–85% patients with any opioid use were low-dose users. Among 339 patients who died within 5 years of colon cancer diagnosis, similar increases in various aspects of opioids were observed in quarters before death, yet about 64% of those who used opioids before death were on a low dose with an average dose of 29 MME/day.

From 1994 to 2014, an increase in some aspects of opioid use was observed over time (Fig. 3). Proportions of patients with any opioid use significantly increased from 9% (95% CI 7–12%) in 1995–1999 to 16% (95% CI 13–18%) in 2010–2014 in quarters before cancer diagnosis (p value for trend < 0.05), fluctuated around 66–68% with no significant change over time in the quarter of cancer diagnosis, and significantly increased from 13% (95% CI 11–15%)

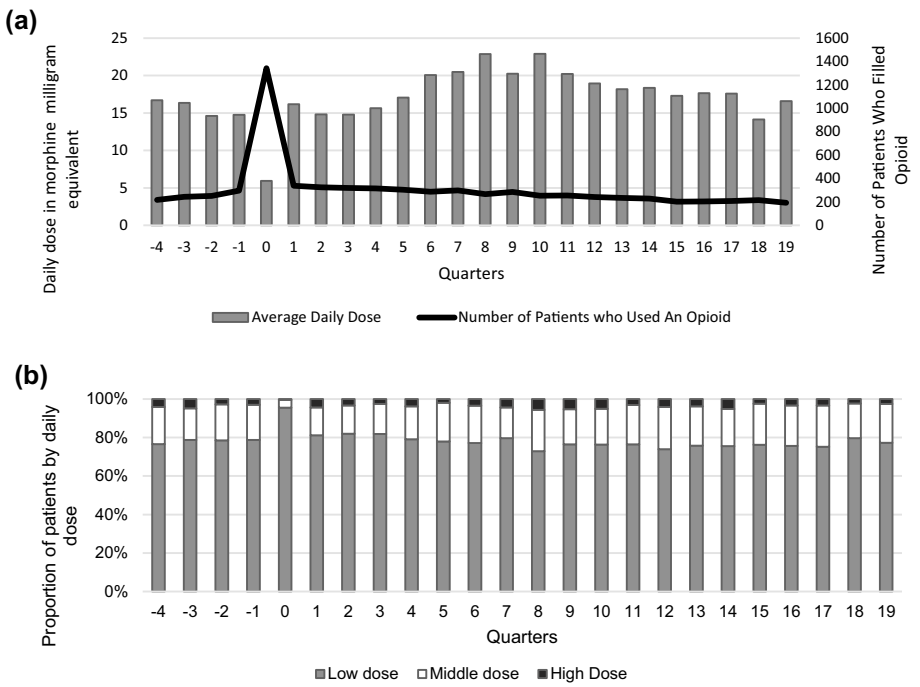

Fig. 2 Quarterly **a** average daily dose of opioid therapy in morphine milligram equivalent (MME) and **b** proportion of colon cancer patients by daily dose among those with any opioid use. High dose was defined as an average daily dose ≥ 90 MME, low dose as an average daily dose < 20 MME and middle dose as an average daily dose between 20 to < 90 MME. Quarter 0 was the quarter when cancer was diagnosed

Table 2 Use of opioids around the time of second cancer events and death

	Patients with second cancer events[a]				Patients who died			
	The quarter before the event		The quarter including and after the event		Second to last quarter before death		Last quarter before death	
	n	%	*n*	%	*n*	%	*n*	%
Total	313	100.0	246[b]	100.0	326[b]	100.0	339	100.0
Any use	77	24.6	127	51.6	129	39.6	167	49.3
Incident use	35	11.2	77	31.3	33	10.1	63	18.6
Regular use	21	6.7	21	8.5	65	19.9	69	20.4
Average daily dose among users (MME/day)	21		14		29		29	
High-dose use (≥90 MME/day)[c]	3	3.9	3	2.4	12	9.3	14	8.3
Low-dose use (<20 MME/day)[c]	62	80.5	108	85.0	82	63.6	106	63.5

Any opioid use was defined as having one or more dispensings of opioid in any quarter. Incident opioid use was defined as an opioid dispensing with no prior opioid dispensing in the previous two quarters. Regular use of opioid therapy was defined as use for 45 days or longer in a quarter

MME Morphine milligram equivalents

[a]Second cancer events include cancer recurrence and second primary cancers

[b]Patients who did not survive for 91 days or longer after a second cancer event were not included in the analysis for the quarter after events. Similarly, patients who did not survive for 182 days or longer from cancer diagnosis until death were not included in the analysis for the second to last quarter

[c]Proportion of high- or low-dose users were calculated among those who had any use

in 1995–1999 to 17% (95% CI 15–19%) in 2005–2009 in quarters after cancer diagnosis (p value for trend < 0.05). No significant temporal change in incident use was observed. Proportions of patients who used opioids regularly significantly increased over years in all phases of cancer diagnosis: from 1% (95% CI 1–2%) in 1995–1999 to 4% (95% CI 3–6%) in 2010–2014 in quarters before cancer diagnosis, from 3% (95% CI 2–5%) in 1995–1999 to 7% (95% CI 5–10%) in 2010–2014 in the quarter of cancer diagnosis, and from 4% (95% CI 3–6%) in 1995–1999 to 7% (95% CI 6–9%) in 2005–2009 in quarters after cancer diagnosis (all p values for trend < 0.05). With respect to dosage, no significant temporal trends were observed in proportions of opioid users on high or low dose, and a slight but significant increase in average daily dose among opioid users was observed only during cancer diagnosis quarter (from 5 MME/day, 95% CI 4–6, in 1995–1999 to 7 MME/day, 95% CI 5–9, in 2010–2014; p value for trend < 0.05) but not in quarters before or after diagnosis (Supplement Fig. 1).

Discussion

In this U.S. cohort of colon cancer patients, we report trends and patterns of opioid use from a year before cancer diagnosis through 5 years after cancer diagnosis. Except for the time immediately following incident cancer diagnosis, when most patients were undergoing treatment, we observed a slight increase in any use, incident use, or regular use of opioids comparing the time before diagnosis versus after diagnosis. In each quarter during this period, about 15–17% of patients were dispensed an opioid and 5–7% used opioid regularly. Despite a higher proportion of patients who had any use of opioids in the quarter immediately following cancer diagnosis, most of them were on a low dose, which is reflected by the drop in average daily dose in this quarter. Among patients who ever used opioids after colon cancer diagnosis, the majority were on a low daily dose. Over time, significant increases in any opioid use and regular opioid use were observed before a colon cancer diagnosis from 1994 to 2014 and throughout the 5-year follow-up from 1994 to 2010, with no major changes in daily dose.

Our finding that any use of opioids slightly increased from 11 to 15% in the year before cancer to 15–17% in survivorship periods after active treatment is largely comparable with findings from a previous analysis based on national insurance claims which reported that only 10% of previous opioid naïve patients continued to use opioids in 90–180 days postoperatively [6]. Both studies suggest that majority of cancer patients did not use opioids persistently. However, direct comparison between our study and this previous study is difficult because of different populations (we followed stage I–IIIa colon cancer patients from the incident cancer diagnosis through the first 5 years after diagnosis, whereas the previous study included patients with a prevalent cancer diagnosis of various types and stages who

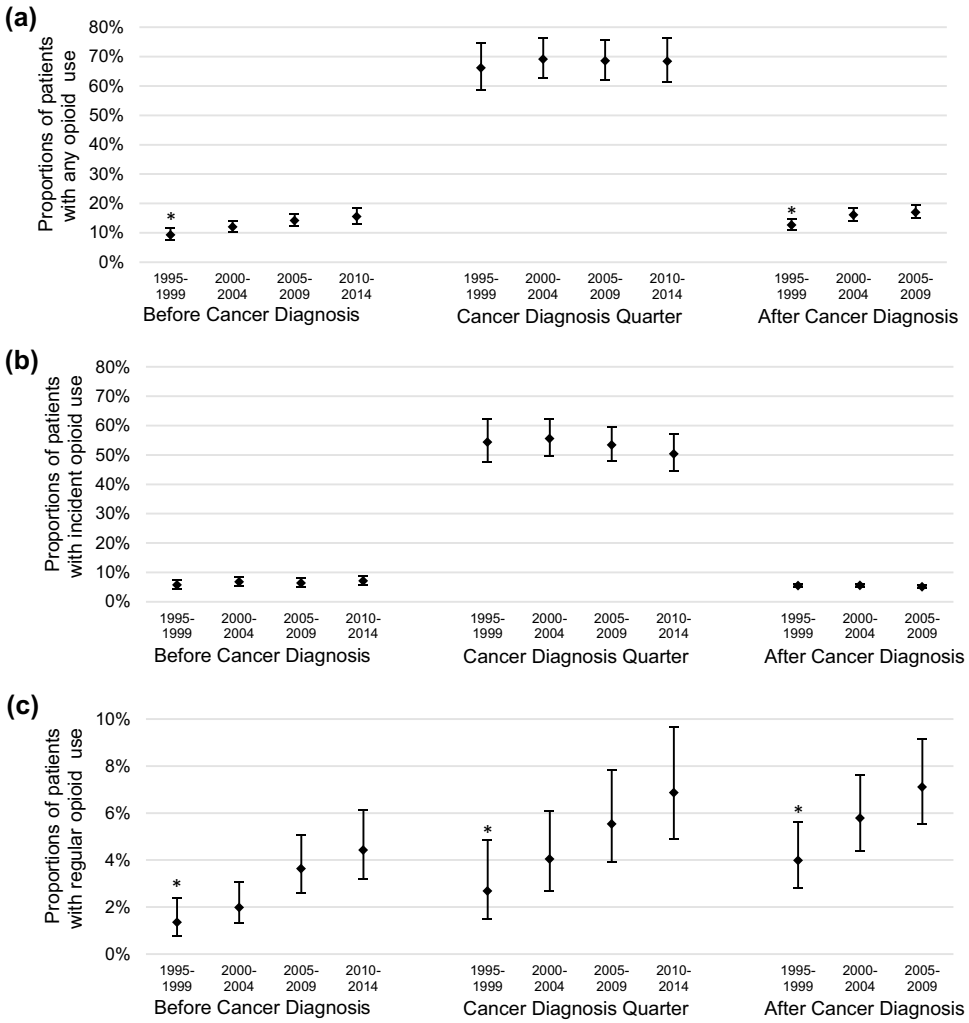

Fig. 3 Average proportions and associated 95% confidence intervals of colon cancer patients who had **a** any use, **b** incident use, and **c** regular use of opioid therapy by cancer diagnosis years. Values in before cancer diagnosis period were averages across 4 quarters prior to the incident colon cancer diagnosis (only 2 quarters prior to cancer diagnosis were included for calculating incident use as incident use was defined as having an opioid fill after a 6-month or longer period without a prior fill and was not assessed in the first 2 quarters in the year prior to cancer diagnosis). Cancer diagnosis quarter was a 91-day window following colon cancer diagnosis (including diagnosis day). Values of after cancer diagnosis period were averages across 19 quarters following cancer diagnosis and patients were censored after their last complete quarter. Regular opioid use was defined as use for 45 days or longer within a quarter. Cases diagnosed in 2010–2014 were not included in calculating opioid use after cancer diagnosis due to inadequate follow-up. Confidence intervals were estimated using GEE models to account for correlations within subjects across quarters. * denotes p values of a linear trend < 0.05

underwent a cancer surgery with curative intent) and different methodologies (we included both patients who were naïve users and who had used opioids prior to cancer diagnosis). Further, our findings on changes of opioid use throughout the 5-year survivorship, over calendar time and in time before and after secondary cancer events are unique and add to existing data which mostly focused on opioid use immediately following cancer surgery [5–7]. As opioid use in the first 5 years after cancer diagnosis was found a strong predictor of opioid use in longer-term survivorship [25], additional research on indications and predictors of opioid use in the first 5 years after cancer diagnosis is warranted.

To situate our findings in a larger context, 1–2% of all U.S. adults use opioids regularly with an average daily dose of 22 MME among regular users [22, 26]. Regular use of opioid therapy was higher in our cohort of colon cancer patients (5–7%), which is expected given the higher prevalence of pain reported in cancer populations [2, 4]. Of note, in the four quarters prior to cancer diagnosis, the prevalence of regular use (3–5%) in our cohort was already higher than the national average. One possible explanation is that some patients experienced pain proceeding the diagnosis of colon cancer. It can also be due to older age of patients included in our cohort, as studies have found the prevalence of long-term opioid use

increases with age [27]. We observed an increase in any use and regular use of opioids from 1994 to 2014, in quarters both before cancer diagnosis and after diagnosis, which may reflect increases in opioid use in the general population [10].

In patients who experienced death or a subsequent cancer, we observed some increases in use of opioids. For instance, in those who died, 49% received an opioid dispensing in the quarter before death. This is comparable to findings from a recent study in Washington state where 41% of cancer patients diagnosed in 2007–2015 used opioids within last 30 days of their life [28]. Of note, most patients in our study were still on a low daily dose around the time of these subsequent cancer events, and the average daily dose was 29 MME in the last quarter of life among those who died. This is consistent with other studies reporting similar low dose of opioid use in patients dying from cancer or non-cancer causes at the end of their life [29, 30].

Currently, the U.S. Centers for Disease and Control and Prevention's guideline for prescribing opioids for chronic pain does not apply to cancer patients [21], and the American Society of Clinical Oncology (ASCO) guideline for management of chronic pain in adult cancer survivors recommends "a trial of opioids" when other pain management strategies fail [1]. It can be challenging to achieve a delicate balance between adequate treatment for cancer pain and not causing harm from overuse and high-dose use of opioid. One national survey of medical oncologists reported physicians' reluctance to prescribe opioids and patients' reluctance to take opioids, along with poor pain assessment as barriers to pain management in cancer patients [31]. In some sense, our results together with a previous study reporting only 10% persistent use provided some reassurance that despite a sharp increase in use of opioids immediately following colon cancer diagnosis, for a majority of patients, this increase did not persist over time.

Our study has several strengths. We had a large population-based cohort of cancer patients with extensive and comprehensive data on all health care utilization including pharmacy dispensing data to objectively characterize use of opioids. Incident and second cancer event data were ascertained through tumor registries and we conducted manual medical record review to ascertain cancer recurrence, allowing us to examine changes in opioid use when cancer progresses. Of note, we did not remove patients from our overall analysis after they had a second cancer event within 5 years because these events reflect patients' experiences in cancer survivorship and censoring them after the event would not materially change the results given the small size of this group.

Limitations of our study should be considered. We did not have information on pain control, so we cannot say whether patients were adequately treated or whether opioids were over-prescribed. We did not have information on actual ingestion of these medications. Lastly, our study included patients enrolled in two pre-paid capitated health plans in two Western regions of the United States, potentially limiting generalizability of our findings to patients receiving care in other types of systems and regions.

In our study, we observed only slight increases in any use, incident use, and regular use of opioids comparing use before and after cancer diagnosis. Any use and regular use of opioids increased over time in cancer patients. Of note, dosage received by cancer patients was similar to that given to patients in the general population who use opioids regularly. These findings may reflect a success in not over-prescribing opioids or a failure in achieving adequate pain treatment in cancer patients. Future studies should include pain assessments to differentiate between these scenarios. As we are responding to a national opioid crisis in the general population and become more aware of risks associated with long-term opioid therapy to manage non-cancer chronic pain, we hope future research will also investigate trends and outcomes of opioid use among cancer survivors across different types of cancer and diverse health care delivery settings.

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Compliance with ethical standards

Conflict of interest Onchee Yu reports receiving funding from a research grant awarded to the Kaiser Permanente Washington Health Research Institute from Bayer. Monica Fujii reports receiving funding from a research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward. Denise Boudreau reports receiving funding from research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward. Gaia Pocobelli reports receiving funding from a research grant awarded to the Kaiser Permanente Washington Health Research Institute from Jazz Pharmaceuticals. Rebecca Hubbard reports receiving a research grant to University of Pennsylvania from Humana.

Research involving in human and animal participants For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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