Patterns and Trends in Receipt of Opioids Among Patients Receiving Treatment for Cancer in a Large Health System

Lindsay M. Sabik, PhD1; Kirsten Y. Eom, MPH1; Zhaojun Sun, PhD1; Jessica S. Merlin, MD, PhD, MBA2,3; Hailey W. Bulls, PhD, MA2,3; Patience Moyo, PhD4; Jennifer A. Pruskowski, PharmD5; G.J. van Londen, MD, MS6,7; Margaret Rosenzweig, PhD, CRNP-C, AOCNP5; and Yael Schenker, MD, MAS, FAAHPM2,3

ABSTRACT

Background: Given limited evidence on opioid prescribing among patients receiving treatment for cancer during the ongoing opioid epidemic, our objective was to assess predictors of and trends in opioid receipt during cancer treatment, including how patterns differ by type of cancer. Methods: Using cancer registry data, we identified patients with a first lifetime primary diagnosis of breast, colorectal, or lung cancer from 2013 to 2017 who underwent treatment within a large cancer center network. Cancer registry data were linked to electronic health record information on opioid prescriptions. We examined predictors of and trends in receipt of any opioid prescription within 12 months of diagnosis. Results: The percentage of patients receiving opioids varied by cancer type: breast cancer, 35% (1,996/5,649); colorectal, 37% (776/2,083); lung, 47% (1,259/2,654). In multivariable analysis, opioid use in the year before cancer diagnosis was the factor most strongly associated with opioid prescription. Conclusions: Our findings suggest that prescription of opioids to patients with cancer varies by cancer type and other factors. In particular, patients are more likely to receive opioids after cancer diagnosis if they were previously exposed before diagnosis, suggesting that pain among patients with cancer may commonly include non-cancer-related pain. Heterogeneity and complexity among patients with cancer must be accounted for in developing policies and guidelines aimed at addressing pain management while minimizing the risk of opioid misuse.

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ORIGINAL RESEARCH

Background

Pain is one of the most common and potentially debilitating symptoms among patients diagnosed with cancer. Unmitigated pain can impact patients’ activities of daily living, motivation, overall quality of life, and survival. Among individuals undergoing cancer treatment, more than half report pain, making pain management an essential element in cancer care. Opioids are included in clinical guidelines as a critical component in the management of pain associated with cancer and are often thought of as a cornerstone of treatment for cancer-related pain. Over recent years, increased attention has been given to opioid risks in the treatment of “noncancer” pain in light of the opioid epidemic, and there has been an increase in policies and guidelines aimed at curbing opioid overuse or misuse.

Most of these policies and guidelines exclude patients with cancer or cancer-related pain; the CDC guideline for prescribing opioids for chronic pain explicitly excludes “patients undergoing active cancer treatment.” Yet, there have been concerns about how regulatory changes may have spillover effects impacting patients with cancer. There is increasing recognition of the need to maintain balance between appropriate opioid access and the potential for harm due to risk of opioid misuse, including opioid-related admissions and deaths, among patients with cancer. Despite these concerns, there has been little assessment of recent prescribing of opioids across a broad population of patients undergoing treatment for cancer in the United States.

Our objective was to assess predictors of and trends in opioid receipt during cancer treatment, including how patterns differ by cancer type. Using administrative data from one of the largest integrated community networks of cancer care providers in a region of high opioid-related deaths in the United States, we examined receipt of opioids among patients receiving active cancer treatment.
across different primary cancer sites and disease stages. Increased regulation of opioid prescribing (including potential spillovers of policies that do not directly apply to cancer pain) and awareness of risks associated with opioid misuse motivated our hypothesis that prescription of opioids for patients with cancer undergoing treatment would have declined over recent years. Understanding broad patterns of opioid prescribing for patients with cancer receiving treatment can inform future research and efforts to improve prescribing practices to ensure pain management needs are met while risks are minimized and managed.

Methods

Data Sources

We worked with honest brokers to link data across different sources and settings within UPMC Health System, a network of academic, community, and specialty hospitals and outpatient sites,\(^5\) including the UPMC Hillman Cancer Center (HCC) network of sites across the region centered on Western and Central Pennsylvania.\(^6\) More than 90% of HCC patients live in 25 rural and 4 urban counties in Western Pennsylvania.\(^6\) The HCC catchment area has a total population of >4 million, evenly distributed between rural and urban counties. Approximately 90.5% of the population is White; Black individuals, the largest minority population, account for only 6.4% of the total catchment area population and reside predominately in the urban counties, whereas Hispanic individuals make up <2% of the catchment area population. The region has experienced high rates of drug overdose deaths throughout the ongoing opioid epidemic.\(^33\)

The UPMC Network Cancer Registry identified patients with a first lifetime primary diagnosis of breast, colorectal, or lung cancer from 2013 to 2017 treated at 1 of 13 facilities within the network, spanning both urban and rural locations. We focused on breast, colorectal, and lung cancers because they represent 3 of the most commonly diagnosed cancers in the United States, accounting for >36% of new cancer cases in 2020,\(^34\) and most newly diagnosed patients with these cancers undergo treatment. The registry provided patient demographics (age, sex, race/ethnicity) and cancer-related information (cancer type, stage at diagnosis, date of diagnosis, treatments received, date of treatment). Encounter records and outpatient prescription data from electronic health record (EHR) systems for 2012 through 2018 were merged with patient data from the cancer registry. The time period for EHR data was selected to allow 12-month look-back and follow-up periods before and after the date of cancer diagnosis. Of patients identified in the registry, 94.9% were matched to EHRs and included in the analysis. This study was reviewed and determined exempt by the University of Pittsburgh Institutional Review Board.

Study Population

The study population consisted of patients with a first lifetime primary diagnosis of breast, colorectal, or lung cancer between 2013 and 2017 who received cancer treatment within 12 months of diagnosis (supplemental eFigure 1, available with this article at JNCCN.org). We defined treatment as receipt of surgery, radiation, chemotherapy, immunotherapy, or hormone therapy, or any combination of these. We excluded patients who died within 6 months of diagnosis in order to exclude those near the end of life who may have received opioids for multiple palliative reasons, and patients who did not receive any treatment in the aforementioned categories. Because we aimed to include patients receiving all or most care within the UPMC Health System and considered prescriptions by UPMC providers before cancer diagnosis, we excluded patients with no visits to UPMC facilities between 1 and 24 months before cancer diagnosis (with the exception of those diagnosed in 2013, for whom we had only a single year of data before diagnosis and thus required a visit between the beginning of 2012 and 1 month before diagnosis).

Key Variables

The primary outcome measure was whether a patient in the study population received any opioid prescription within 12 months after the date of diagnosis. Based on previous literature, we included age, sex, race/ethnicity, stage, treatment, and previous opioid receipt in all models as covariates to control for relevant clinical and demographic factors identified ex ante.\(^24,35–39\) Patient age was defined as a categorical variable (<50, 50–64, 65–80, >80 years). Race/Ethnicity indicated whether a patient was non-Hispanic White or minority and was included, given previously documented differences in opioid prescribing by race.\(^40\) Because <2% of the sample fell into a racial/ethnic category other than non-Hispanic White or non-Hispanic Black, we grouped non-White patients into a single group composed primarily, but not exclusively, of Black patients, which allowed us to retain patients from smaller racial/ethnic groups. Stage at diagnosis was defined based on 4 combined categories of SEER summary stage\(^41\): in situ/localized, regional, distant/metastatic, and unstaged/unknown. Treatment was categorized as surgery alone, surgery plus other therapy, or nonsurgical. We defined prediagnosis opioid receipt based on opioid prescriptions from UPMC providers between 31 and 365 days before the cancer diagnosis date. Finally, we included indicator variables for year of diagnosis to assess trends in opioid prescribing over time.
Opioid Receipt Among Patients With Cancer

Statistical Analysis
We assessed unadjusted differences between the populations that did and did not receive an outpatient opioid prescription within 12 months after cancer diagnosis using chi-square tests. We then estimated multivariable logistic regression models to assess the association of patient characteristics, previous opioid receipt, treatment category, and year of diagnosis with receipt of an opioid prescription in the year after cancer diagnosis. Finally, based on the regression coefficients, we examined adjusted trends in receipt of any opioid prescription for each cancer type. We generated the predicted probability of receiving an opioid prescription within 1 year of diagnosis for a standardized patient: female, non-Hispanic White, aged 50 to 64, diagnosed with in situ/localized cancer, and received surgery plus radiation and/or systemic therapy, with no previous opioid prescription by a UPMC provider before diagnosis.

Results
The unadjusted percentage of patients receiving opioids in the year after cancer diagnosis varied by cancer type, with 35.3% of all patients with breast cancer (1,996/5,649), 37.3% of patients with colorectal cancer (776/2,083), and 47.4% of patients with lung cancer (1,259/2,654) in our sample receiving an opioid prescription (Table 1). Across all cancer types, patients prescribed opioids tended to be younger. Among those with breast or colorectal cancer, the proportion of non-White patients was higher among those prescribed versus not prescribed opioids (13.9% vs 8.7% for breast cancer; 12.6% vs 9.5% for colorectal cancer), whereas no significant difference in race/ethnicity was seen among patients with lung cancer by opioid prescribing. Opioid use was more likely among those with more advanced disease for breast (4.2% vs 2.1%) and colorectal cancer (22.0% vs 12.8%) compared with no opioid use. In contrast, the stage distribution did not differ significantly in the lung cancer cohort.

Figure 1 presents odds ratios from multivariable logistic regression models assessing factors associated with receipt of any outpatient opioid prescription within 12 months of diagnosis for each of the 3 cancer types examined. Models also included indicators for year of diagnosis (estimates not shown). Across all 3 cancer types, opioid use in the year before cancer diagnosis was the strongest factor associated with receipt of opioids in the year after cancer diagnosis; patients with opioid prescriptions in the year before diagnosis were 3 to 5 times more likely to receive opioids after diagnosis, depending on the type of cancer, with 4.90 (95% CI, 4.10–5.86), 5.09 (95% CI, 3.88–6.69), and 3.31 (95% CI, 2.68–4.10) higher odds for those with breast, colorectal, and lung cancer, respectively. Other factors that showed a consistent association with opioid receipt across cancer types were age and cancer stage at diagnosis, because younger patients and those with more advanced disease were consistently more likely to receive opioids. Receipt of surgery was associated with increased likelihood of opioid receipt for patients with lung cancer; patients with surgery alone or surgery and other therapies had 1.74 (95% CI, 1.39–2.20) and 1.96 (95% CI, 1.55–2.50) higher odds, respectively, than those with no surgery.

Finally, we examined trends in the predicted probability of receiving opioids over our study period (Figure 2). We did not observe evidence of a consistent decline in opioid prescribing after cancer diagnosis, contrary to our hypothesis. Adjusting for age, race/ethnicity, stage, and sex, trends in receipt of an opioid prescription varied by cancer type. Among patients with lung cancer, the likelihood of receiving an opioid prescription declined slightly over the study period. In contrast, for patients with breast cancer, the likelihood of receiving an opioid prescription increased from 2013 to 2017. For patients with colorectal cancer, the adjusted proportion who received an outpatient opioid prescription was similar in 2013 and 2017, with no statistically significant differences across study years.

Discussion
This study examined predictors of and trends in receipt of opioid prescriptions in a large population of patients newly diagnosed with and undergoing treatment for 3 of the highest incidence cancers, including adult patients of all ages across all stages of disease. More than one-third of patients studied received an outpatient opioid prescription within the health system within 12 months of cancer diagnosis. The strongest predictor of receiving an opioid prescription in the year after cancer diagnosis was the receipt of an opioid prescription in the year before cancer diagnosis. Overall, we did not see evidence of a consistent decline over time in whether patients received any opioid prescription, as hypothesized, and trends differed across the 3 cancer types examined.

Findings from recent studies examining opioid use among patients undergoing treatment for cancer are mixed. Most previous studies from the US context examining opioid prescriptions among patients with cancer have examined patients covered by a single insurance type, often limited to patients undergoing surgery and/or those without previous opioid use. In contrast, we drew on data for all patients with 3 prevalent cancers who underwent treatment for their cancer in a large regional health system operating in an area of the country with high rates of opioid overdoses and deaths during our study period. In response to the opioid epidemic, state and federal agencies and clinical organizations have implemented a range of policies, strategies, and guidelines to guide opioid prescribing and prevent opioid-related harms, including misuse and overdoses, and typically make blanket exclusions of patients with cancer.
However, there are concerns about inadvertent negative consequences for this population, and our results highlight that patients with cancer are a heterogeneous group. Furthermore, for any type of cancer, patients may embark on cancer treatment with a history of opioid use, suggesting that they have other conditions that contribute to use, and potentially misuse, of opioids.

Given increased regulation of opioid prescribing, attention to the risks of opioid use, and reports of barriers to accessing opioids among patients with cancer, we hypothesized that the likelihood of a patient with cancer undergoing treatment to be prescribed opioids would decline over our study period. We did not observe evidence of consistent declines, although it is important to note that this analysis does not account for changes in prescription details (such as dose, quantity, or specific drugs prescribed).

Although we observed a decline in receipt of any opioids among patients with lung cancer, among whom receipt of opioids was highest at baseline, the likelihood of receiving an opioid prescription increased for patients with breast cancer. Over the period we studied, the total number of opioid prescriptions nationally declined steadily; thus, the patterns we observed for breast and colorectal cancer contrast with this overall trend, which may be appropriate, given the exclusion of cancer-related pain from broader guidelines and policies. We do not know the optimal level of

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Table 1. Patient Characteristics Within 12 Months After Cancer Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer</th>
<th>Colorectal Cancer</th>
<th>Lung Cancer</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>No Opioid</td>
<td>Any Opioid</td>
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<tr>
<td>Total, n</td>
<td>10,386</td>
<td>5,649</td>
<td>3,654</td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>&lt;50 y</td>
<td>14.0</td>
<td>19.8</td>
<td>15.8</td>
</tr>
<tr>
<td>50–64 y</td>
<td>36.3</td>
<td>38.2</td>
<td>37.9</td>
</tr>
<tr>
<td>65–80 y</td>
<td>40.0</td>
<td>34.9</td>
<td>38.2</td>
</tr>
<tr>
<td>≥81 y</td>
<td>9.8</td>
<td>7.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>78.5</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Male</td>
<td>21.5</td>
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<td></td>
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<tr>
<td>Race/Ethnicity</td>
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<td>***</td>
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<tr>
<td>Non-Hispanic White</td>
<td>89.4</td>
<td>89.5</td>
<td>91.3</td>
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<tr>
<td>Non-White</td>
<td>10.6</td>
<td>10.5</td>
<td>8.7</td>
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<tr>
<td>Stage at diagnosis</td>
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<td>***</td>
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<tr>
<td>In situ/localized</td>
<td>57.8</td>
<td>75.9</td>
<td>78.7</td>
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<tr>
<td>Regional</td>
<td>26.5</td>
<td>19.1</td>
<td>17.2</td>
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<tr>
<td>Distant/ Metastatic</td>
<td>13.2</td>
<td>2.8</td>
<td>2.1</td>
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<tr>
<td>Unstaged/ Unknown</td>
<td>2.5</td>
<td>2.2</td>
<td>2.0</td>
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<tr>
<td>Treatments received within 12 mo of diagnosis</td>
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<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>22.4</td>
<td>9.4</td>
<td>9.0</td>
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<tr>
<td>Surgery and others</td>
<td>59.6</td>
<td>86.4</td>
<td>87.2</td>
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<tr>
<td>Nonsurgical</td>
<td>18.0</td>
<td>4.2</td>
<td>3.8</td>
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<tr>
<td>Prescribed opioids in year before diagnosis</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>14.3</td>
<td>11.8</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*Because <2% of the sample fell into a racial/ethnic category other than non-Hispanic White or non-Hispanic Black, we grouped non-White patients into a single group composed primarily (but not exclusively) of Black patients.

Regional stage includes regional by direct extension, regional lymph nodes only involved, regional by both direct extension and to lymph nodes, and regional not otherwise specified.

*P<.05; **P<.01; ***P<.001 for chi-square test comparing those with any outpatient opioid prescription within 12 months after cancer diagnosis date with those with no opioid prescription after cancer diagnosis.
### Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>OR (95% CI)</th>
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<tr>
<td>50–64 y vs &lt;50 y</td>
<td>0.58 (0.50–0.68)</td>
</tr>
<tr>
<td>65–80 y vs &lt;50 y</td>
<td>0.39 (0.34–0.46)</td>
</tr>
<tr>
<td>&gt;80 y vs &lt;50 y</td>
<td>0.31 (0.24–0.41)</td>
</tr>
<tr>
<td>Other vs non-Hispanic White</td>
<td>1.57 (1.32–1.89)</td>
</tr>
<tr>
<td>Distant/Metastatic vs in situ/localized at diagnosis</td>
<td>2.46 (1.61–3.76)</td>
</tr>
<tr>
<td>Regional vs in situ/localized at diagnosis</td>
<td>1.54 (1.33–1.79)</td>
</tr>
<tr>
<td>Unstaged/Unknown vs in situ/localized at diagnosis</td>
<td>1.48 (1.01–2.19)</td>
</tr>
<tr>
<td>Any opioid prescriptions vs none in a year prior to diagnosis</td>
<td>4.90 (4.10–5.86)</td>
</tr>
<tr>
<td>Surgery + other treatment vs nonsurgical</td>
<td>1.11 (0.77–1.61)</td>
</tr>
<tr>
<td>Surgery alone vs nonsurgical</td>
<td>1.36 (0.95–2.05)</td>
</tr>
</tbody>
</table>

### Figure 1

**Breast Cancer**

- 50–64 y vs <50 y: OR 0.58 (95% CI 0.50–0.68)
- 65–80 y vs <50 y: OR 0.39 (95% CI 0.34–0.46)
- >80 y vs <50 y: OR 0.31 (95% CI 0.24–0.41)

**Colorectal Cancer**

- 50–64 y vs <50 y: OR 0.70 (95% CI 0.51–0.97)
- 65–80 y vs <50 y: OR 0.45 (95% CI 0.33–0.62)
- >80 y vs <50 y: OR 0.28 (95% CI 0.19–0.42)

**Lung Cancer**

- 50–64 y vs <50 y: OR 0.68 (95% CI 0.45–1.04)
- 65–80 y vs <50 y: OR 0.49 (95% CI 0.33–0.75)
- >80 y vs <50 y: OR 0.33 (95% CI 0.21–0.54)

**Figure 1.** Odds ratios (95% CIs) from multivariable logistic regression assessing factors associated with receipt of any outpatient opioid prescription within 12 months of diagnosis for (A) breast, (B) colorectal, and (C) lung cancer.

Multivariable logistic regression models adjusted for age, sex, race/ethnicity, stage at diagnosis, treatments received, receipt of an opioid prescription in the year before diagnosis, and individual year indicators (estimates on year indicators not shown).

Abbreviation: OR, odds ratio.
opioid prescribing for this population of patients with cancer, so we cannot assess whether changes we observed over time are appropriate within the evolving landscape of guidelines and policies to promote safe and effective opioid use.

Similar to other studies, we found higher rates of opioid use among patients with lung cancer than among those with breast or colorectal cancer. The diverging trends we see over time between patients with lung and breast cancer in our sample could reflect an increasing recognition of the different risk factors for opioid misuse, although an in-depth examination of the specific factors (including different types of surgery and other detailed treatment factors) that determine the use of opioids for each patient with cancer was outside the scope of the data used for this study.

For all 3 cancer types, approximately two-thirds of those with opioid use in the year before their diagnosis were prescribed opioids in the year after diagnosis, and in multivariable models, prior opioid use was the strongest predictor of use after diagnosis. This finding aligns with previous studies from other settings. Our finding that a sizable minority of patients were prescribed opioids in the year before cancer diagnosis highlights that patients with cancer may also be undergoing treatment for other types of pain. Cancer and chronic pain are conditions with complex sets of sociodemographic, behavioral, and clinical risk factors that overlap and may concurrently predispose some patient groups to both conditions.

Understanding this complex interplay between underlying risk factors, noncancer pain, and cancer incidence is an important area for future research.

Other factors consistently associated with receipt of opioids for all 3 cancers included stage at diagnosis and age. Our finding that distant stage was associated with higher likelihood of receiving opioids is consistent with evidence that pain prevalence and severity are high among patients with metastatic disease. Similar to other studies, we found that older patients are less likely to be prescribed opioids, despite the fact that age is not significantly associated with pain prevalence. We also found that having surgery as part of the first course of treatment was associated with increased likelihood of receiving an opioid prescription for lung cancer, but not for breast or colorectal cancer. Recent efforts have sought to curb potential overprescribing of opioids at the time of surgery, although longer-term impacts on pain can differ by cancer and surgery type. The literature suggests that pain prevalence during anticancer treatment is approximately 55% across multiple cancer types and that breast, colorectal, and lung cancers are associated with higher pain prevalence than some other common cancers, although there are gaps in our understanding of how pain prevalence and severity differ across subgroups of patients with cancer. Understanding how well opioid prescribing patterns match patterns of self-reported pain and pain severity among patients undergoing cancer treatment is an important area of future research.

This study had limitations. First, the data came from a single health system and may not capture opioid prescriptions outside the system. To partially address this concern, we limited the sample to patients seen within the system before their cancer diagnosis to focus on a group likely to receive all or most of their care within the same health system. Second, data were compiled from multiple data sources (registry and multiple EHR systems), which did not consistently track information such as dose or quantity required to calculate details of longer-term opioid prescribing patterns or morphine milligram equivalents. Thus, we focus on any opioid prescribing (as opposed to high dose or other prescribing patterns examined in other research) to prioritize inclusion of a broad population of patients with cancer using data consistently available for all patients in the study sample. Third, we did not have information on prescription indication or other clinical conditions that may drive opioid prescribing in the cancer population we studied, and we did not have data available on patient-reported pain levels. Finally, our sample did not include a sufficient number of patients of races other than White and Black to allow a more nuanced analysis of differences by race and ethnicity that may be driven by the systemic marginalization of some populations.

Conclusions
Data on opioid prescribing patterns can inform policies and guidelines aimed at addressing pain management needs while minimizing the risk of opioid misuse. Our
findings highlight that patients with cancer are a heterogeneous group and that many begin cancer treatment with previous exposure to opioids. Additional research is needed to further understand trends in opioid prescribing for patients with cancer in greater detail, including changes over time and differences across groups in dose, quantity, and specific opioids prescribed. More detailed evidence on opioid prescribing and use among patients with cancer can inform nuanced and patient-centered policy and clinical practice changes to promote safe and effective use of opioids in this population, acknowledging the heterogeneity of clinical experiences and needs among the large group of newly diagnosed patients with cancer and cancer survivors in the United States.

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Supplemental online content for:

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**eFigure 1:** Study Population Selection Criteria
Patients diagnosed with first lifetime primary breast, colorectal, or lung cancer between 2013 and 2017 at included UPMC facilities (N=16,912)

Patients diagnosed with first lifetime primary breast, colorectal, or lung cancer between 2013 and 2017 under active treatment at the selected UPMC facilities (n=10,387)

Excluded (n=6,525):
- Inconsistent information across patient records (n=439)*
- Male patients with breast cancer (n=49)
- Died within 6 mo of diagnosis (n=2,027)
- Did not receive surgery, radiation, chemotherapy, immunotherapy, and/or hormone therapy within 12 mo of diagnosis (n=347)
- Did not have an encounter with a UPMC provider between 1 and 24 mo prior to diagnosis (n=3,663)b

Breast cancer (n=5,650)
Colorectal cancer (n=2,083)
Lung cancer (n=2,654)

**eFigure 1.** Study population selection criteria.

*aIncludes patients with inconsistent sequence numbers, diagnosis dates, primary sites, and stages at diagnosis (n=434) and patients with incomplete birth dates and diagnosis months (n=5).

bFor those diagnosed in 2013, prior visits were assessed on data available between January 2012 and the date of diagnosis (between 12 and 23 mo of data before diagnosis).