Risk of Persistent Opioid Use following Major Surgery in Matched Samples of Patients with and without Cancer

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ABSTRACT

Background: The opioid crisis has reached epidemic proportions, yet risk of persistent opioid use following curative intent surgery for cancer and factors influencing this risk are not well understood.

Methods: We used electronic health record data from 3,901 adult patients who received a prescription for an opioid analgesic related to hysterectomy or large bowel surgery from January 1, 2013, through June 30, 2018. Patients with and without a cancer diagnosis were matched on the basis of demographic, clinical, and procedural variables and compared for persistent opioid use.

Results: Cancer diagnosis was associated with greater risk for persistent opioid use after hysterectomy [18.9% vs. 9.6%; adjusted OR (aOR), 2.26; 95% confidence interval (CI), 1.38–3.69; $P = 0.001$], but not after large bowel surgery (28.3% vs. 24.1%; aOR 1.25; 95% CI, 0.97–1.59; $P = 0.09$). In the cancer hysterectomy cohort, persistent opioid use was associated with cancer stage (increased rates among those with stage III cancer compared with stage I) and use of neoadjuvant or adjuvant chemotherapy; however, these factors were not associated with persistent opioid use in the large bowel cohort.

Conclusions: Patients with cancer may have an increased risk of persistent opioid use following hysterectomy.

Impact: Risks and benefits of opioid analgesia for surgical pain among patients with cancer undergoing hysterectomy should be carefully considered.

Introduction

Prescription opioid abuse has become a major public health crisis (1, 2). More than 70% of patients undergoing surgery in the United States obtain opioid prescriptions (3), but the majority (67%–92%) report receiving more opioids than needed to manage postoperative pain (4). Patients with cancer exposed to opioids for curative intent surgery may be especially vulnerable to persistent opioid use due to high levels of anxiety and depression (5), comorbid medical conditions (6), and concomitant medications (7, 8).

Guidelines for prescribing opioids have largely exempted the cancer population from consideration under the precept that cancer pain should be treated differently than noncancer pain due to the unique nature of the disease and its treatment (9–11). Opioid misuse among patients with cancer may be underappreciated, even though 1 in 5 patients with cancer are at risk of abusing opioids (12). Recent studies suggest that 10%–18% of previously opioid-naïve patients with cancer who received an opioid prescription following curative intent surgery continue to use opioids after the postoperative healing period is complete (13–17), which is a risk factor for developing chronic postsurgical pain (18); among patients with prior opioid exposure, this proportion is 30%–50% (15, 17).

To our knowledge, no study has directly compared rates of persistent opioid use after similar major surgeries in patients with cancer compared with those without. Furthermore, no studies have examined whether the risk associated with cancer may differ for patients undergoing different surgeries. An improved understanding of the factors associated with progression to persistent opioid use in oncology would help identify patients at greatest risk who might benefit from alternative approaches to pain management.

To address this knowledge gap, we conducted a retrospective, observational study utilizing data from the University of Pennsylvania Health System (UPHS; Philadelphia, PA) electronic health record (EHR) to examine differences in the risk of persistent opioid use between patients with and without cancer following exposure to prescription opioids after hysterectomy or after large bowel (colorectal) surgery. We chose these surgeries because they are prevalent and exemplars of similar surgical procedures performed for both cancer and noncancer indications. This enabled an analytic approach designed to assess the association of cancer versus noncancer diagnoses with persistent opioid use after surgery. We further examined

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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patient-level, provider-level, procedural, geographic, and clinical/disease-related factors which might be associated with the likelihood of transition to new persistent opioid use following surgery among patients with cancer and those without.

Materials and Methods

Data sources

The UPHS Epic Clarity EHR comprises longitudinal inpatient, outpatient, physician, and pharmacy data for patients treated at five hospitals in Pennsylvania. The data includes information on patient characteristics (such as demographics and clinical history) and medical care use (such as visit records, diagnosis, and procedure codes) linked to physician National Provider Identifier. These data were augmented with UPHS Tumor Registry data, which contains tumor records [such as primary site, histopathologic type, and tumor stage, as well as a custom International Classification of Diseases (ICD) Oncology 3-to-ICD 9/10 diagnosis code mapping table]. We also linked the EHR with the 2017 American Community Survey by patient zip code to obtain census tract median household income. The study was conducted in accordance with the Declaration of Helsinki, approved by the University of Pennsylvania Institutional Review Board (Philadelphia, PA), and granted a waiver of informed consent.

Study population

We included adults aged 18 years or older who underwent elective hysterectomy or large bowel surgery between January 1, 2013 and June 30, 2018 (180 days prior to records retrieval), received a surgery-related opioid prescription, and could be reliably assigned to a cohort (see cohort definitions below). These types of surgery were chosen because they involve similar procedures for patients with cancer and noncancer diagnoses, affording an opportunity to isolate the effects of cancer. Current procedural terminology codes were used to identify eligible surgeries and categorize patients into surgical cohorts (Supplementary Table S1). Surgery-related prescriptions were prescriptions for opioids issued from 30 days before to 14 days after the date of the index surgery on the basis of definitions used in prior studies of persistent opioid use following surgery (13, 19). Patients were excluded if they were discharged to hospice care or in-patient rehabilitation, remained admitted to the hospital for >30 days, or died in the hospital following the surgery. **Figure 1** details the study definition.

Defining cancer and noncancer groups

We categorized patients into cancer or noncancer groups based on whether the surgery was related to a cancer diagnosis or not. The cancer group included patients who received curative intent hysterectomy for cervical, uterine, or ovarian cancer, or received curative intent large bowel surgery (including colectomy, rectal excision, and/or proctectomy) for colorectal cancer. The noncancer group included patients who were not diagnosed with cancer and who received hysterectomy or large bowel surgery for benign conditions. Group classifications were based on ICD-9/10 diagnosis codes associated with the surgery (Supplementary Table S2), and verified with the Tumor Registry. We excluded patients with stage IV cancer, stage III ovarian cancer (such patients may receive debulking surgery rather than curative intent), missing/unknown stage, or whose surgery could not be matched to a diagnosis code of interest or the Tumor Registry (**Fig. 1**).

Covariates

We used the EHR linked to census data to define patient-level, procedural, provider-level, and geographic covariates. Patient-level covariates included demographics (age, sex, and self-reported race) and clinical history [prior opioid exposure, comorbidities, concomitant medications, and body mass index (BMI) at the time of surgery]. For patients with cancer, stage and treatment data (including neoadjuvant and adjuvant radiotherapy or systemic chemotherapy) were extracted from the Tumor Registry.

Patients were classified as chronic, intermittent, or naïve opioid users. Chronic opioid users had at least one opioid prescription with a 120-day supply between 31 and 365 days prior to surgery or at least three opioid prescriptions in the 3 consecutive months prior to surgery; intermittent users had at least one opioid prescription between 31 and 365 days prior to surgery, but did not meet criteria for chronic use; and opioid-naïve patients had no opioid prescriptions from 31 to 365 days prior to surgery (13).

Comorbidity burden was determined on the basis of the Elixhauser comorbidity index (20, 21), modified to omit cancer-related comorbidities to minimize confounding (Supplementary Table S3). Concomitant medications previously associated with risk of persistent opioid use were identified (refs. 14, 22–25; Supplementary Table S4). Procedural variables included measures of surgical complexity [minimally invasive vs. open; partial -ectomy vs. complete or multiple organ removal (complete/extensive); operating room time; and estimated blood loss]. We included a facility-level variable that captured the hospital in which the surgery took place (operating room location). Census tract median household income was included as an ecologic variable to reflect socioeconomic status.

Primary outcome assessment

The primary outcome was persistent opioid use following surgery, defined as at least one opioid prescription issued 60–180 days post-surgery. This time frame was chosen based on the International Association for the Study of Pain definition of persistent postoperative pain and the expectation that standard procedures for the surgeries included in this study would not require opioid treatment for more than 60 days (26).

Statistical analyses

Our primary analysis used a propensity score matching approach for cancer and noncancer cases implemented separately by surgical cohort with a nearest neighbor matching algorithm (27). Propensity scores represent the probability that patients are undergoing surgery for cancer versus noncancer indications on the basis of the observed covariates, and can be used to reduce bias due to systematic differences in distributions of potential confounders between groups at baseline (28, 29). To create propensity scores, we used logistic regression with cancer diagnosis as the primary outcome and age, race, BMI, opioid history, Elixhauser comorbidity index, concomitant medications, surgical complexity, surgical extent, operating room time, estimated blood loss, operating room location, and household income as predictors. Matching was performed using a nearest neighbor matching algorithm with a 1:1 match ratio and proper caliper values (27, 30). We calculated the adjusted odds ratio (aOR) of persistent opioid use between cancer and noncancer groups and conducted matched χ^2 test (i.e., Cochran–Mantel–Haenszel test) in the matched samples (31, 32). To validate, we also calculated aOR by multivariate logistic regression in the matched samples. Analyses were done using the R package, MatchIt (33). All statistical tests were performed at the 0.05 level of significance.

In the secondary analyses, we investigated heterogeneity in associations between cancer and persistent opioid use by surgical cohort on the basis of prespecified hypotheses on stratifying variables.

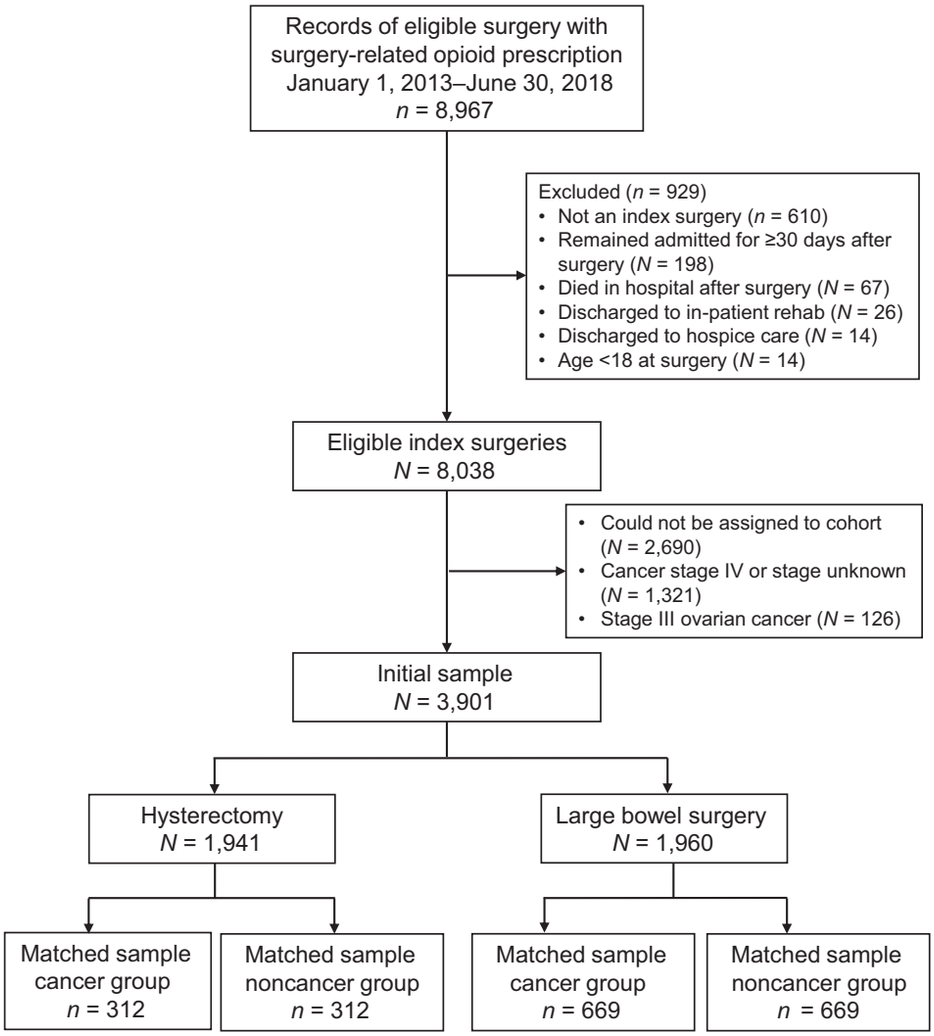

Figure 1.
Study flow diagram.

Specifically, we hypothesized that the likelihood of persistent opioid use would be more pronounced among patients with cancer compared with those without cancer for those with age 65 or older (16, 17, 24, 34), male gender (16, 23), prior opioid use (13, 22, 35), and history of depression (23). Gender differences were examined only in the large bowel surgery cohort. We further examined the effects of cancer stage, surgery extent, and use of neoadjuvant or adjuvant treatments in each cancer surgery cohort by a logistic regression.

Although we retrieved all prescriptions issued within UPHS (Philadelphia, PA), it is possible that patients may have obtained opioid prescriptions from an outside provider within the follow-up window; these patients would not have been counted as persistent opioid users in our analysis. To assess the potential impact of unobserved opioid use, we conducted sensitivity analyses to evaluate the robustness of our primary result to outcome misclassification (36). Prior research has shown persistent opioid use following surgery in 5%–30% of patients with and without cancer (13, 15, 16, 19, 37). Therefore, we randomly selected 10%, 20%, and 30% of patients in the matched samples with no identified persistent opioid use and reversed their outcomes (36). The OR for persistent opioid use in the cancer versus noncancer group was then calculated on the basis of the reassigned outcomes. This procedure was repeated 100 times and the average ORs and confidence intervals (CI) were calculated (36).

Results

Descriptive characteristics in matched samples

After propensity score matching, two matched samples were obtained by surgical cohort: 624 hysterectomy patients (312 each with and without cancer) and 1,338 large bowel surgery patients (669 each with and without cancer). Descriptive characteristics for the matched samples are summarized in **Table 1**. Patients in the hysterectomy cohort were younger (mean age, 56.7 years; SD, 12.3), had a higher BMI (mean, 30.4; SD, 8.2), and were less likely to be White (68.9%) than the large bowel surgery cohort (mean age:

Table 1. Baseline characteristics by group in the matched samples.

	Surgery type					
	Hysterectomy			Large bowel surgery		
Group	Cancer ($n = 312$)	Noncancer ($n = 312$)	*P*	Cancer ($n = 669$)	Noncancer ($n = 669$)	*P*
Age, mean (SD)	56.7 (12.5)	56.6 (12.1)	0.904	61.1 (14.3)	59.7 (13.6)	**0.009**
Sex, *n* (%) female	312 (100)	312 (100)	NA	335 (50.1)	278 (41.6)	**0.002**
Race, *n* (%)						
White	219 (70.2)	211 (67.6)		540 (80.7)	534 (79.8)	
Nonwhite	93 (29.8)	101 (32.4)	0.484	129 (19.3)	135 (20.2)	0.728
BMI, mean (SD)	30.3 (8.4)	30.5 (7.9)	0.674	28.4 (6.3)	28.6 (6.3)	0.713
Opioid history, *n* (%)						
Naïve	230 (73.7)	223 (71.5)		499 (74.6)	490 (73.2)	
Intermittent	64 (20.5)	75 (24.0)	0.483	128 (19.1)	133 (19.9)	0.828
Chronic	18 (5.8)	4 (4.5)		42 (6.3)	46 (6.9)	
Elixhauser comorbidity score[a], mean (SD)	0.5 (4.1)	0.2 (4.0)	0.341	2.0 (5.7)	2.0 (5.4)	0.876
Concomitant meds, *n* (%)						
Benzodiazepines	24 (7.7)	11 (3.5)	**0.043**	48 (7.2)	62 (9.3)	0.189
Nonopioid analgesics	20 (6.4)	35 (11.2)	0.050	70 (10.5)	57 (8.5)	0.263
NSAID	20 (6.4)	12 (3.6)	0.216	59 (8.8)	35 (5.2)	**0.016**
SSRI	11 (3.5)	4 (1.7)	0.121	27 (4.0)	24 (3.6)	0.779
SNRI	5 (1.6)	7 (0.6)	0.773	9 (1.3)	2 (0.3)	0.070
NBA/SH	2 (0.6)	2 (0.8)	1.000	6 (0.9)	9 (1.3)	0.606
Operating room time (hours), mean (SD)	4.5 (1.8)	4.5 (1.4)	0.886	4.6 (2.1)	4.6 (1.7)	0.731
Estimated blood loss (100 mL), mean (SD)	3.3 (4.8)	3.1 (4.8)	0.624	2.0 (2.7)	1.9 (2.6)	0.294
Surgical extent, *n* (%)						
Partial	19 (6.1)	14 (4.5)	0.472	605 (90.4)	592 (88.5)	0.255
Complete/extensive	293 (93.9)	298 (95.5)		64 (9.6)	77 (11.5)	
Operating room location, *n* (%)						
Operating room 1	154 (49.4)	142 (45.5)		417 (62.3)	425 (63.5)	
Operating room 2	137 (43.9)	148 (47.4)		196 (29.3)	181 (27.1)	
Operating room 3	0 (0.0)	9 (2.9)	**0.017**	18 (2.7)	40 (6.0)	**0.003**
Operating room 4	17 (5.4)	9 (2.9)		38 (6.7)	23 (3.7)	
Other	4 (1.3)	4 (1.3)		0 (0.0)	0 (0.0)	
Other treatment, *n* (%)						
Neoadjuvant RT	3 (1.0)	NA		117 (17.5)	NA	
Adjuvant RT	87 (27.9)	NA	NA	28 (4.2)	NA	NA
Neoadjuvant SYS	14 (4.5)	NA		56 (8.4)	NA	
Adjuvant SYS	161 (51.6)	NA		192 (28.7)	NA	
Zip code median annual household income ($1,000), mean (SD)	76.0 (28.8)	74.7 (30.9)	0.597	75.7 (28.3)	76.1 (29.9)	0.819

Note: *P* values in bold indicate statistically significant results ($P < 0.05$).

Abbreviations: NBA/SH, non-benzodiazepine anxiolytics/sedative hypnotics; NSAID, nonsteroidal anti-inflammatory drug; RT, radiotherapy; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; SYS, systemic chemotherapy.

[a]Elixhauser comorbidity score excludes cancer-related items to avoid confounding by cohort.

60.4 years, SD: 14.0; mean BMI: 28.5, SD: 6.3; and percent white: 80.3%; all $P < 0.001$). There were no significant differences in prior opioid usage between the two surgical cohorts (percent opioid naïve, 72.6% and 73.9%, respectively; $P = 0.57$).

The majority of characteristics and covariates were balanced in cancer and noncancer groups after the matching; age and sex were not balanced in the large bowel surgery cohort, and operating room location and concomitant medications were not balanced in either cohort due to the small sample sizes within some of these subgroups (**Table 1**).

Primary outcome

In the matched samples, 89 patients who received hysterectomy and 350 patients who received large bowel surgery showed persistent opioid use. Cancer was associated with greater odds of persistent opioid use after hysterectomy (18.9% vs. 9.6%; aOR, 2.26; 95% CI, 1.38–3.69; $P = 0.001$). However, the association with cancer was not significant for patients who received large bowel surgery (28.3% vs. 24.1%; aOR, 1.25; 95% CI, 0.97–1.59; $P = 0.09$). The adjusted differences in risk of persistent opioid use for patients with and without cancer were significantly different between the hysterectomy and large bowel cohorts (difference of ORs, 1.01; 95% CI, 0.07–2.46; $P = 0.03$). Multivariate logistic regression (Supplementary Table S5) in the matched samples provided results similar to our main findings.

Subgroup analysis

In the secondary analyses of heterogeneity, we found consistent associations with cancer in subgroups in the hysterectomy cohort, and consistent lack of associations with cancer in subgroups in the large bowel cohort (**Fig. 2**). There were no significant interaction effects between cancer and age or history of depression in either cohort, and no interaction between cancer and gender in the large bowel surgery group ($P > 0.05$). In the analysis within cancer groups, patients in the hysterectomy cohort were more likely to show persistent opioid use

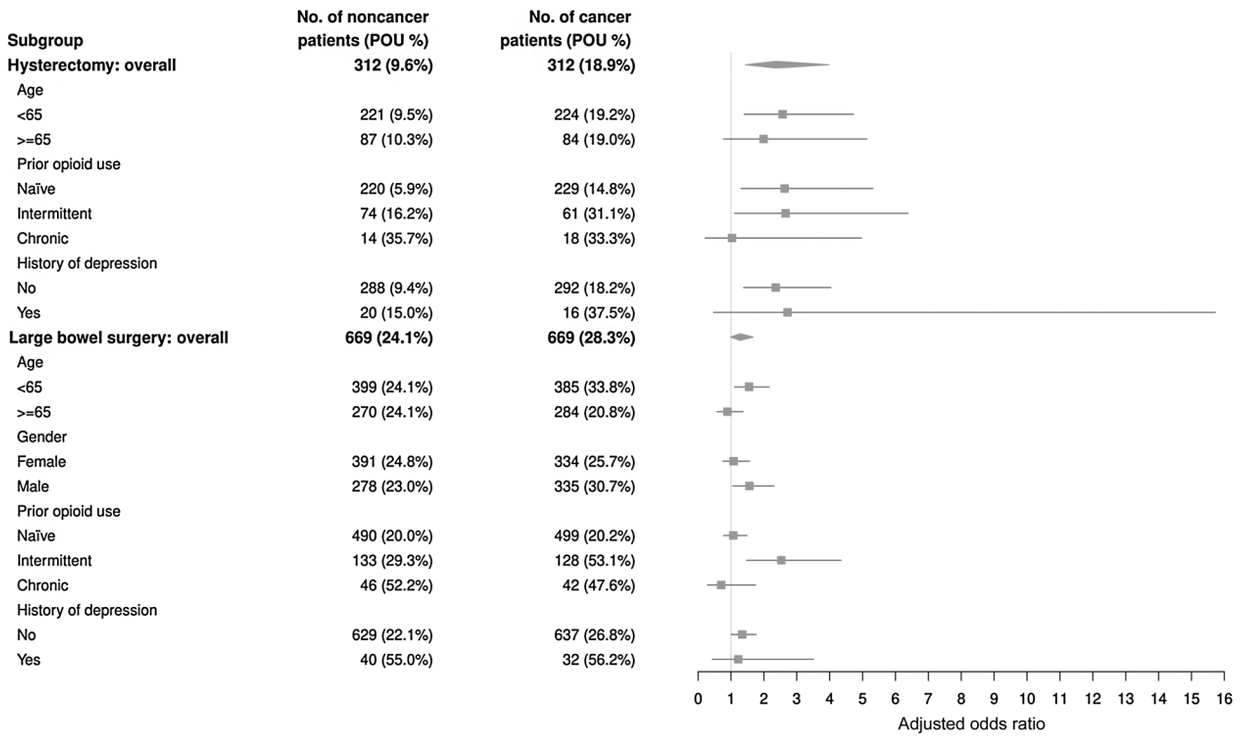

Figure 2.

Forest plot of subgroup analyses in matched samples. Number of patients and percentage of persistent opioid use (POU) in each subgroup with forest plot of estimated aOR for the heterogeneity analysis. There was a significant difference in the effect of cancer between the hysterectomy and large bowel surgery groups (difference of odds ratios, 1.01; 95% CI, 0.07–2.46; $P = 0.03$), but no significant interactions between cancer and any of the subgroups.

if they had stage III cancer (compared with stage I, aOR 2.83; 95% CI, 1.32–6.08; $P = 0.008$) or if they received systemic chemotherapy (neoadjuvant systemic chemotherapy aOR, 4.82; 95% CI, 1.13–20.6; $P = 0.034$ and adjuvant systemic chemotherapy aOR, 3.14; 95% CI, 1.44–6.85; $P = 0.004$; Supplementary Table S6). However, these factors were not associated with persistent opioid use in the large bowel surgery cohort ($P > 0.05$). Patients with cancer in the large bowel surgery cohort were more likely to show persistent opioid use if they received more extensive surgery (aOR, 1.85; 95% CI, 1.02–3.37; $P = 0.044$), consistent with a main effect of surgical extent in the large bowel surgery cohort in the matched sample ($P < 0.001$; Supplementary Table S5).

Table 2. Results of sensitivity analysis in the hysterectomy cohort.

Outcome misclassification rate	aOR	95% CI
10%	1.69	(1.15–2.50)
20%	1.44	(1.02–2.03)
30%	1.36	(0.98–1.88)

Note: Average aORs for persistent opioid use in the cancer group in the hysterectomy cohort calculated for the estimated misclassification rates, obtained by randomly reassigning 10%, 20%, and 30% of individuals without persistent opioid use to the opposite outcome. This process was repeated 100 times for each misclassification rate, and the resulting odds ratios were averaged. These results show a significant increase in risk of persistent opioid use in the cancer group, for up to almost 30% misclassification rate in the hysterectomy cohort.

Sensitivity analyses

In sensitivity analyses for the hysterectomy cohort, random reassignment of 10%, 20%, or 30% of patients to the persistent opioid use outcome did not significantly or meaningfully change the results. The average estimated aOR for persistent opioid use in the cancer group compared with the noncancer group was greater than 1.0 for each of the estimated misclassification rates (**Table 2**). This analysis suggests that the estimated aORs in the propensity matched samples are largely robust to the potential misclassification of the outcome.

Discussion

In the first study to directly compare opioid use between matched samples of patients undergoing surgery for cancer and noncancer indications, patients who received hysterectomy for cancer were approximately 2.3-fold more likely to develop persistent opioid use compared with those who received the same surgery for noncancer indications. There was no significant association with cancer in the large bowel surgery cohort. We found no significant difference in the association with cancer based on age, gender, or history of depression in either cohort. In subgroup analyses within the cancer groups, patients receiving hysterectomy were more likely to show persistent opioid use if they had advanced (stage III) cancer or if they received adjuvant or neoadjuvant systemic chemotherapy; large bowel surgery patients were more likely to show persistent opioid use if they received more extensive surgery, consistent with the main effect of surgical extent in the large bowel surgery cohort. Collectively, these findings highlight the need for careful consideration of the risks of prescribing

opioid to patients with cancer who are undergoing curative intent hysterectomy, and for additional research examining particular risk factors for these vulnerable groups.

Our findings are consistent with and extend prior studies demonstrating the risks of persistent prescription opioid use following exposure to opioids for surgical pain. In the hysterectomy cohort, we found that approximately 10% of patients without cancer and approximately 19% of patients with cancer showed persistent opioid use after surgery. Studies of patients without cancer undergoing surgery found that 3%–10% of patients were still using opioids 3–6 months later (19, 24, 25, 38); in patients with cancer, this rate has been shown to be 10%–30% (13–15). Because we used propensity score matching to balance sociodemographic, clinical, and procedural factors between patients with and without cancer in each surgery cohort, it is unlikely that the interaction between cancer and surgery cohort reflects differences in rates of these factors between the cohorts. Additional research is necessary to examine the factors that contribute to differences in risk of persistent opioid use between patients with different cancers undergoing different types of surgery.

Several possible reasons have been proposed to explain why patients with cancer might experience greater risk from prescription opioid exposure following surgery compared with patients without cancer. It has been suggested that anxiety and depression may contribute to risk of persistent opioid use among patients with cancer (5). Although a clinical diagnosis of depression was not more common in patients with cancer in our sample and did not modify the association between cancer group and persistent opioid use, it is possible that a cancer diagnosis may increase subjective symptoms of anxiety and depression in the absence of clinical diagnosis. Patients diagnosed with cancer may also experience chronic pain resulting from adjuvant treatment, such as neuropathy, visceral pain, and musculoskeletal pain, and clinical trials often report pain as an independent side-effect of adjuvant treatments (39, 40); in our sample, adjuvant and neoadjuvant chemotherapy were associated with greater risk of persistent opioid use in patients with cancer in the hysterectomy cohort, but not in the large bowel surgery cohort. It is possible that different types of cancer and resulting treatment are associated with different degrees of psychologic impact or pain which are not routinely captured in the EHR. Patients with cancer require analgesics during and after cancer treatment (41); however, there is limited evidence for the efficacy of opioids for treating cancer pain (42). Physicians who are treating patients with cancer who develop chronic pain following surgery and/or adjuvant treatment should consider alternative analgesics after the acute recovery phase is completed.

We also examined potential interactions between cancer diagnosis and other risk factors for persistent opioid use, and found that the associations were largely consistent across the subgroups examined. Prior studies have shown increased risk of persistent opioid use following surgery among patients with cancer with a history of opioid use, consistent with the main effect of opioid history in our sample (13, 17). Younger age, male gender, and history of depression have previously been associated with elevated risk of persistent opioid use in patients undergoing surgery (13, 16, 17, 23, 24), but our findings suggest that these factors generally do not modify the associations between cancer and opioid use.

Our study has strengths and limitations. Strengths include the large sample size and use of propensity score matching to directly compare patients with and without cancer who received two different types of surgery. A limitation is that we were only able to track opioid prescriptions issued within our health system; although the Pennsylvania state prescription drug monitoring program was implemented in 2016, it is not currently structured to allow for research use (43). It is possible that some patients might have obtained opioid prescriptions from another provider outside of UPHS (Philadelphia, PA) either prior to surgery or within the follow-up window, and these patients would not have been counted as prior opioid users or persistent opioid users in our analysis. However, our sensitivity analysis shows consistent results estimated with up to almost 30% misclassification rate, suggesting that our findings are robust to misclassification. Other prescriptions, including benzodiazepine prescriptions, may be underrepresented if patients obtained these prescriptions from other providers. Second, our analysis of comorbid risk factors relied on medical history entered into the EHR, which did not consistently capture important risk factors (such as tobacco use). Future studies examining prescription opioid outcomes in patients with cancer using a prospective design to fully capture known risk factors would be beneficial. In addition, because type of surgery received and diagnosis are confounded, we cannot say whether the association of a cancer diagnosis with persistent opioid use in cancer in patients receiving hysterectomy versus large bowel surgery is due to different impacts of cancer type or the surgery itself. Although we expect that patients undergoing curative intent surgery would not experience cancer progression in the 6 months following surgery, it is possible that some patients may have had cancer progression, which may in turn have influenced persistent opioid use. Additional research is needed to examine the relationship between cancer progression and long-term opioid use. Future studies might further probe the mechanisms that contribute to persistent opioid use among patients with cancer.

Our findings of greater risk of persistent prescription opioid use following hysterectomy in patients with cancer contribute to the growing body of literature demonstrating the need for evidence-based guidelines for prescription opioid treatment in patients with cancer undergoing curative intent surgery (13, 14). Historically, cancer pain has been treated differently than noncancer pain, and current opioid prescribing guidelines explicitly exclude patients with cancer (10, 44, 45). Improvements in cancer care mean more patients are surviving longer than ever before (46); therefore, the risks associated with prescription opioid pain management for patients with cancer must be carefully considered in terms of the impact on survivors. These risks must be balanced against the need for adequate pain control in light of studies showing that pain management often falls short of cancer patients' needs (9). Additional research is necessary to examine mechanisms contributing to different risk factors among patients with cancer, and to evaluate optimal opioid prescribing strategies for reducing risks and managing surgical pain in patients with cancer.

Disclosure of Potential Conflicts of Interest

E.M. Ko reports grants from Tesaro (associated research support to institution for clinical trial protocol 4010-01-001) outside the submitted work. J.E. Bekelman reports personal fees from Centers for Medicare and Medicaid Services, Optum, CVS Health, UnitedHealthcare, and National Comprehensive Cancer Network and grants from UnitedHealth Group, North Carolina Blue Cross Blue Shield, Embedded Healthcare, and Pfizer outside the submitted work. C. Lerman reports grants from NIH (R35 CA197461) during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

M. Falcone: Visualization, methodology, writing–original draft, project administration, writing–review and editing. **C. Luo:** Formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **Y. Chen:** Formal analysis, methodology, writing–original draft, writing–review and editing.

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