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ORIGINAL REPORT

New Persistent Opioid Use Among Patients With Cancer After Curative-Intent Surgery

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ABSTRACT

Purpose

The current epidemic of prescription opioid misuse has increased scrutiny of postoperative opioid prescribing. Some 6% to 8% of opioid-naïve patients undergoing noncancer procedures develop new persistent opioid use; however, it is unknown if a similar risk applies to patients with cancer. We sought to define the risk of new persistent opioid use after curative-intent surgery, identify risk factors, and describe changes in daily opioid dose over time after surgery.

Methods

Using a national data set of insurance claims, we identified patients with cancer undergoing curative-intent surgery from 2010 to 2014. We included melanoma, breast, colorectal, lung, esophageal, and hepato-pancreato-biliary/gastric cancer. Primary outcomes were new persistent opioid use (opioid-naïve patients who continued filling opioid prescriptions 90 to 180 days after surgery) and daily opioid dose (evaluated monthly during the year after surgery). Logistic regression was used to identify risk factors for new persistent opioid use.

Results

A total of 68,463 eligible patients underwent curative-intent surgery and filled opioid prescriptions. Among opioid-naïve patients, the risk of new persistent opioid use was 10.4% (95% CI, 10.1% to 10.7%). One year after surgery, these patients continued filling prescriptions with daily doses similar to chronic opioid users ($P = .05$), equivalent to six tablets per day of 5-mg hydrocodone. Those receiving adjuvant chemotherapy had modestly higher doses ($P = .002$), but patients with no chemotherapy still had doses equivalent to five tablets per day of 5-mg hydrocodone. Across different procedures, the covariate-adjusted risk of new persistent opioid use in patients receiving adjuvant chemotherapy was 15% to 21%, compared with 7% to 11% for those with no chemotherapy.

Conclusion

New persistent opioid use is a common iatrogenic complication in patients with cancer undergoing curative-intent surgery. This problem requires changes to prescribing guidelines and patient counseling during the surveillance and survivorship phases of care.

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INTRODUCTION

Pain management is a crucial dimension of patient-centered cancer care.[1,2] However, the recent increase in prescription opioid misuse, abuse, and overdose fatalities has highlighted the dangers of these medications.[3-5] In 2015, 11.5 million adult Americans reported misusing prescription opioids, and 1.9 million met diagnostic criteria for prescription opioid abuse.[6] Patients with cancer undergoing curative-intent therapies may be particularly vulnerable to opioid misuse or dependence because of psychological distress from their diagnosis, multiple invasive procedures, pain related to adjuvant therapies, and uncoordinated prescribing from multiple providers.[1,7,8]

Although guidelines exist for prescribing opioids to patients with cancer with advanced disease,[1,7] little is known about opioid use among patients undergoing surgery for early-stage cancer. Previously opioid-naïve patients may convert to chronic opioid use, which is associated with substantial morbidity and mortality.[3,4,9,10] Recent studies have evaluated the risk of new persistent opioid use after noncancer surgery[11-13]; however, the risk of new persistent opioid use after curative-intent cancer surgery is unknown.

To understand the risk of new persistent opioid use in this population, we performed a retrospective

ASSOCIATED CONTENT

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Appendix

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cohort study of privately insured patients undergoing curative-intent cancer surgery in the United States. We sought to define the risk of new persistent opioid use after curative-intent surgery, identify patient-level risk factors for new persistent opioid use, and describe the trend of daily opioid dose over time during the year after surgery.

METHODS

Data Source

We identified eligible patients by examining insurance claims from the Truven Health Marketscan Research Databases, including the Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database.[14] These databases are obtained from employer health plans and include employees, Consolidated Omnibus Budget Reconciliation Act continuees, early retirees, Medicare-eligible retirees with employer-provided Medicare Supplemental plans, and dependents. The University of Michigan Institutional Review Board determined this study was exempt because all data were de-identified.

Study Sample

In this retrospective cohort study, we included patients age ≥ 18 years who underwent curative-intent surgery for a cancer diagnosis between January 1, 2010 and June 30, 2014 and filled an opioid prescription attributed to surgery. Figure 1 illustrates the study selection criteria. To ensure accurate assessment of preoperative and postoperative opioid use, we included only patients with continuous insurance enrollment for 1 year before and after surgery. To minimize confounding from postoperative complications, we excluded patients with hospital admissions > 30 days or a subsequent procedure within 180 days. In addition, we excluded patients discharged to home hospice care and those who died during their index hospitalization.

We selected patients undergoing the following curative-intent procedures: lumpectomy, mastectomy, wide local excision, colectomy, rectal resection, pancreatectomy, liver resection, gastric resection, esophagectomy, and lung resection. Patients were included if they had a claim with an eligible operation that was also associated with a cancer diagnosis. Procedures were identified using Current Procedural Terminology codes (Appendix Table A1, online only). Cancer diagnoses were identified using International Statistical Classification of Diseases and Related Health Problems, Ninth Revision codes (Appendix Table A2, online only).

Definitions of Opioid Prescriptions and Prescribing Patterns

Opioid prescription data were obtained from pharmacy claims and converted to oral morphine equivalents (OME) for comparison.[15] Similar to previous work,[13] we attributed an opioid prescription to surgery if it was filled between 30 days before surgery and 14 days after discharge. This window accounts for patients who developed cancer pain requiring opioids in the month before surgery and surgeons who provide patients with preoperative opioid prescriptions intended for postoperative use. For opioid prescriptions attributed to surgery, we evaluated two prescribing patterns: prescriptions filled by patients during the 30 days before surgery (preoperative opioid prescriptions) and quantity prescribed (OME) for the opioid prescription closest to the date of surgery (initial opioid prescribed).

Patients were defined as opioid-naïve if they filled no opioid prescriptions between 12 months and 31 days before surgery, a definition used in previous studies of surgical patients.[11,13] Chronic opioid users were defined as patients who filled opioid prescriptions with at least 120 days supply between 12 months and 31 days before surgery or filled at least three opioid prescriptions in the three consecutive months before surgery. This level of opioid use was selected because it is associated with an increased risk of opioid overdose mortality.[4] Intermittent opioid users were defined as those who filled opioid prescriptions less frequently than this threshold.

Outcomes

This study had two primary outcomes: new persistent opioid use, which was defined as previously opioid-naïve patients who filled an opioid prescription attributed to surgery, then filled at least one additional opioid prescription between 90 and 180 days after surgery; and daily opioid dose

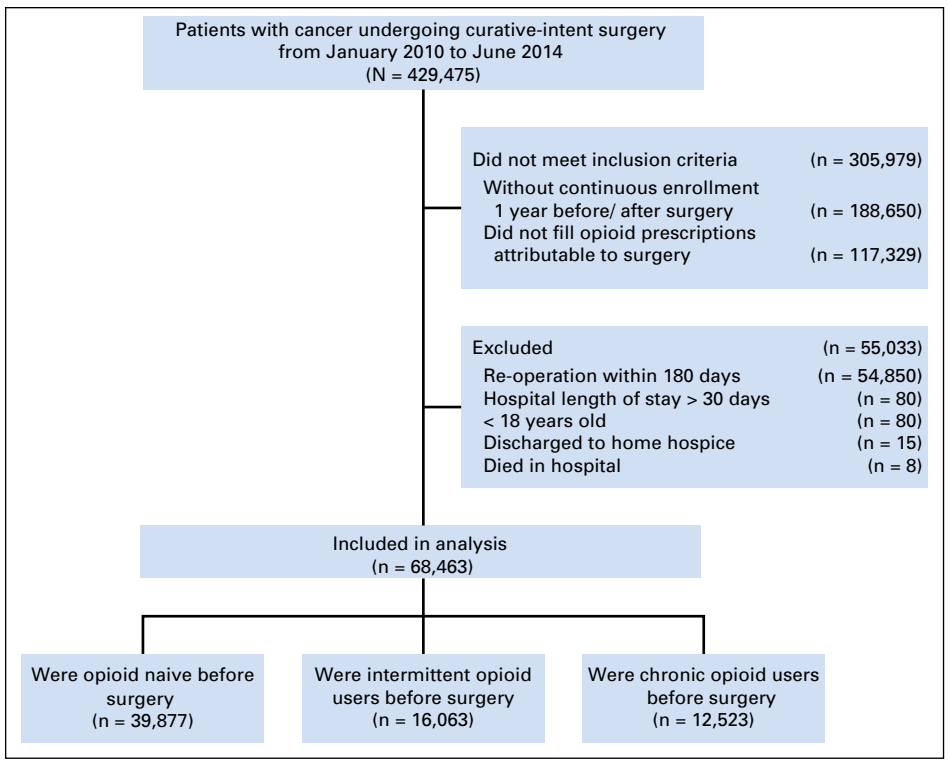

Fig 1. Study cohort and sample criteria. Patients with cancer who underwent curative-intent surgery from January 1, 2010 to June 30, 2014 were included if they met the following criteria: age ≥ 18 years, continuous insurance enrollment from 1 year before surgery to 1 year after surgery, filled an opioid prescription attributable to surgery (between 30 days before surgery and 14 days after discharge). We also specifically excluded patients with an additional operation within 180 days, hospital length of stay > 30 days, and those who died during their index admission or were discharged to home hospice.

during the year after surgery, which was calculated every 30 days by dividing the quantity prescribed (OME) by the days supplied. Like other studies of surgical patients,[11-13,16] we chose this definition of new persistent opioid use because normal surgical recovery would be expected by 90 days after surgery. This definition is more conservative than the 60-day threshold used by the International Association for the Study of Pain.[17]

Patient Covariates

We included information on age, sex, household income on the basis of metropolitan statistical area code, and insurance type. Data describing race and ethnicity are not available in the Truven Marketscan data sets. We used International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, and Current Procedural Terminology codes to identify patients who underwent neoadjuvant chemotherapy or radiation during the 12 months before surgery and patients who underwent adjuvant chemotherapy or radiation during the 180 days after surgery (Appendix Table A3, online only). Comorbidities were captured using the Elixhauser comorbidity score.[18] The Agency of Healthcare Research and Quality Clinical Classification System was used to assess for psychiatric diagnoses, including mood disorders, personality disorders, and substance use disorders. Substance use disorders included heroin use and nonmedical use of prescription opioids. This accounts for patients potentially misclassified as opioid-naïve by our definition, which is based on insurance claims for opioid prescriptions.

Statistical Analyses

Patients were stratified into four groups on the basis of perioperative opioid use: opioid-naïve patients who did not develop new persistent opioid use, opioid-naïve patients who developed new persistent opioid use, intermittent opioid users, and chronic opioid users. Opioid-naïve patients who developed new persistent use were further stratified by timing of chemotherapy. We then calculated the mean daily opioid dose for each group at 30-day intervals from 1 year before surgery to 1 year after surgery. Mixed linear models were used to adjust mean daily opioid dose for age, sex, preoperative opioid prescriptions, initial opioid prescribed, procedure type, neoadjuvant and adjuvant chemotherapy/radiation, psychiatric diagnoses, Elixhauser comorbidity score, insurance type, and median income. Daily opioid doses among patient groups were then compared using a χ^2 test.

Multivariable logistic regression was used to identify variables associated with new persistent opioid use. Because our initial regression demonstrated a significant interaction between procedure type and timing of chemotherapy, a separate regression was performed for each procedure type. Using these models, we calculated the covariate-adjusted risk of new persistent opioid use for each procedure type stratified by timing of chemotherapy.

Analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) Because of the large number of patients and statistical tests, two-sided P values $< .01$ were considered statistically significant. For our multivariable analyses, we evaluated for multicollinearity using variance inflation factors and found no significant multicollinearity in the variables included in our models. For logistic regression models, goodness of fit was evaluated using the c statistic and Hosmer-Lemeshow test.

Sensitivity Analysis

Because our initial analysis demonstrated patients receiving preoperative opioid prescriptions had a higher risk of new persistent opioid use, we performed a sensitivity analysis to evaluate the effect of these patients on the study results. Specifically, we excluded patients with preoperative opioid prescriptions from the cohort, then repeated our logistic regression models and recalculated covariate-adjusted rates of new persistent opioid use for each procedure type. These results were then compared with those including patients with preoperative opioid prescriptions.

RESULTS

During the study period, 68,463 patients underwent curative-intent surgery and were included in the analysis (Fig 1). Of these, 39,877 (58%) were opioid-naïve, 16,063 (23%) were intermittent opioid users, and 12,523 (18%) were chronic opioid users. Among previously opioid-naïve patients, 4,159 or 10% (95% CI, 10.1% to 10.7%) developed new persistent opioid use after curative-intent surgery. Table 1 lists characteristics of opioid-naïve patients stratified by whether they developed new persistent opioid use or not. Patients with new persistent opioid use were more likely to have received adjuvant chemotherapy (33% *v* 16%) and more likely to have filled preoperative opioid prescriptions (26% *v* 20%) but were initially prescribed the same quantity of opioids (200 ± 150 OME for both groups, equivalent to 40 tablets of 5-mg hydrocodone).

For comparison, we also examined patients who did not fill a surgical opioid prescription. Compared with opioid-naïve patients who filled opioid prescriptions, patients with no opioid prescriptions were more likely to have undergone wide local excision for melanoma (38% *v* 17%) and less likely to have undergone lumpectomy/mastectomy (38% *v* 56%). They also had lower rates of adjuvant chemotherapy (8% *v* 18%) and radiation (4% *v* 24%) and higher rates of neoadjuvant chemotherapy (9% *v* 5%) and radiation (16% *v* 1%). They had similar rates of substance use disorders (4% *v* 5%).

Daily Opioid Dose During the Year After Surgery

Figure 2A shows the trajectory of mean daily opioid dose with patients stratified by perioperative opioid use. Mean daily opioid dose was adjusted for patient-level factors using mixed linear models. Three months after surgery, patients with new persistent opioid use continued to fill opioid prescriptions with high daily opioid doses, equivalent to six tablets per day of 5-mg hydrocodone (25 OME). Daily opioid doses remained at this high level even 1 year after surgery. When daily opioid doses were compared among groups, new persistent opioid users had similar daily doses compared with intermittent and chronic opioid users ($P = .05$).

Figure 2B shows patients who developed new persistent opioid use stratified by timing of chemotherapy. Those who received adjuvant chemotherapy filled prescriptions with modestly higher daily doses compared with those who did not ($P = .002$). This difference, however, was the equivalent of less than one tablet per day of 5-mg hydrocodone. All groups continued filling prescriptions with high daily doses 1 year after surgery, equivalent to five to six tablets per day of 5-mg hydrocodone (25 to 30 OME).

Risk Factors for New Persistent Opioid Use

Table 2 lists results from the logistic regression models for new persistent opioid use. Adjuvant chemotherapy was the only variable significantly associated with new persistent opioid use across all procedures (odds ratios [95% CI]: breast 2.4 [2.2 to 2.7]; melanoma 2.6 [1.5 to 4.5]; colorectal 2.3 [1.9 to 2.8]; hepato-pancreato-biliary/gastric 2.2 [1.5 to 3.3]; thoracic 2.1 [1.7 to 2.7]). Adjuvant radiation was a significant risk factor for melanoma (4.7 [2.4 to 9.2]) and thoracic (2.1 [1.4 to 3.0]) procedures. In addition, patients who filled preoperative opioid prescriptions had a significantly higher risk of new persistent opioid use for breast (1.2 [1.1 to 1.3]), melanoma (1.5 [1.2 to 1.9]), colorectal

Table 1. Characteristics of Opioid-Naïve Patients

Characteristic	Naïve Patients With No Persistent Opioid Use (n = 35,718)	Naïve Patients With New Persistent Opioid Use (n = 4,159)
Age, years, mean (SD)	58.9 (12.7)	58.3 (12.4)
Female sex	27,374 (76.6)	3,255 (78.2)
Preoperative opioid prescription*	7,030 (19.7)	1,061 (25.6)
Initial opioid prescribed,† OME, median (IQR)	200 (150.0)	200 (150.0)
Procedure type		
Breast	19,928 (55.8)	2,451 (58.9)
Melanoma	6,273 (17.6)	457 (11.0)
Colorectal	5,455 (15.3)	627 (15.1)
Hepato-pancreato-biliary and gastric	1,320 (3.7)	188 (4.5)
Thoracic	2,742 (7.7)	436 (10.5)
Chemotherapy‡		
None	28,376 (79.4)	2,550 (61.3)
Neoadjuvant	1,693 (4.7)	234 (5.6)
Adjuvant	5,649 (15.8)	1,375 (33.1)
Radiation§		
None	26,901 (75.3)	3,062 (73.6)
Neoadjuvant radiation	419 (1.2)	60 (1.4)
Adjuvant radiation	8,398 (23.5)	1,037 (24.9)
Psychiatric diagnoses		
Depression	1,394 (3.9)	189 (4.5)
Anxiety	2,019 (5.7)	277 (6.7)
Substance use disorder	1,706 (4.8)	293 (7.0)
Other psychiatric condition	353 (1.0)	53 (1.3)
Elixhauser comorbidity score		
≤ 1	648 (1.8)	80 (1.9)
2-4	8,192 (22.9)	734 (17.6)
5-10	7,026 (19.7)	750 (18.0)
≥ 11	19,852 (55.6)	2,595 (62.4)
Type of insurance		
Preferred provider organization	18,590 (52.0)	2,114 (50.8)
Comprehensive	4,708 (13.2)	572 (13.8)
Health maintenance organization	5,007 (14.0)	616 (14.8)
Point of service	2,656 (7.4)	338 (8.1)
Other	2,743 (7.7)	297 (7.1)
Missing	2,014 (5.6)	222 (5.3)
Median income		
< $40,000	55 (0.2)	3 (0.1)
$40-50,000	316 (0.9)	40 (1.0)
$50-60,000	5,018 (14)	621 (14.9)
$60-70,000	12,107 (33.9)	1,477 (35.5)
≥ $70,000	12,631 (35.4)	1,329 (31.9)
Missing	5,591 (15.7)	689 (16.6)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: IQR, interquartile range; OME, oral morphine equivalent.
*Opioid-naïve patients who filled opioid prescriptions in the 30 days before surgery.
†Quantity prescribed for the opioid prescription closest to the date of surgery.
‡Three mutually exclusive groups: no chemotherapy, neoadjuvant chemotherapy, and adjuvant chemotherapy. No patients had both neoadjuvant and adjuvant chemotherapy.
§Three mutually exclusive groups: no radiation, neoadjuvant radiation, and adjuvant radiation. No patients had both neoadjuvant and adjuvant radiation.

(2.1 [1.7 to 2.7]), and thoracic (1.7 [1.3 to 2.3]) procedures. In contrast, the initial quantity of opioid prescribed was not significant for any procedures. Age, sex, neoadjuvant chemotherapy/radiation, and insurance type had no consistent association with new persistent opioid use.

Effect of Procedure and Adjuvant Chemotherapy

Figure 3 shows the adjusted risk of new persistent opioid use across different procedures with 95% CIs and patients stratified by timing of chemotherapy. For each procedure group, the risk of new persistent opioid use was adjusted for patient-level factors using logistic regression models (Table 2). Patients undergoing adjuvant chemotherapy had a significantly higher risk of new persistent opioid use for all procedures (range, 15% to 21%), but those who did not receive adjuvant chemotherapy were still at risk (7% to 11%).

Sensitivity Analysis

After excluding patients with preoperative opioid prescriptions (n = 8,091), the overall risk of new persistent opioid use was 9.7% (95% CI, 9.4% to 10.1%), which was not substantially different from the initial cohort including these patients (10.4%; 95% CI, 10.1% to 10.7%). In addition, excluding these patients did not substantially affect the results of the logistic regression models

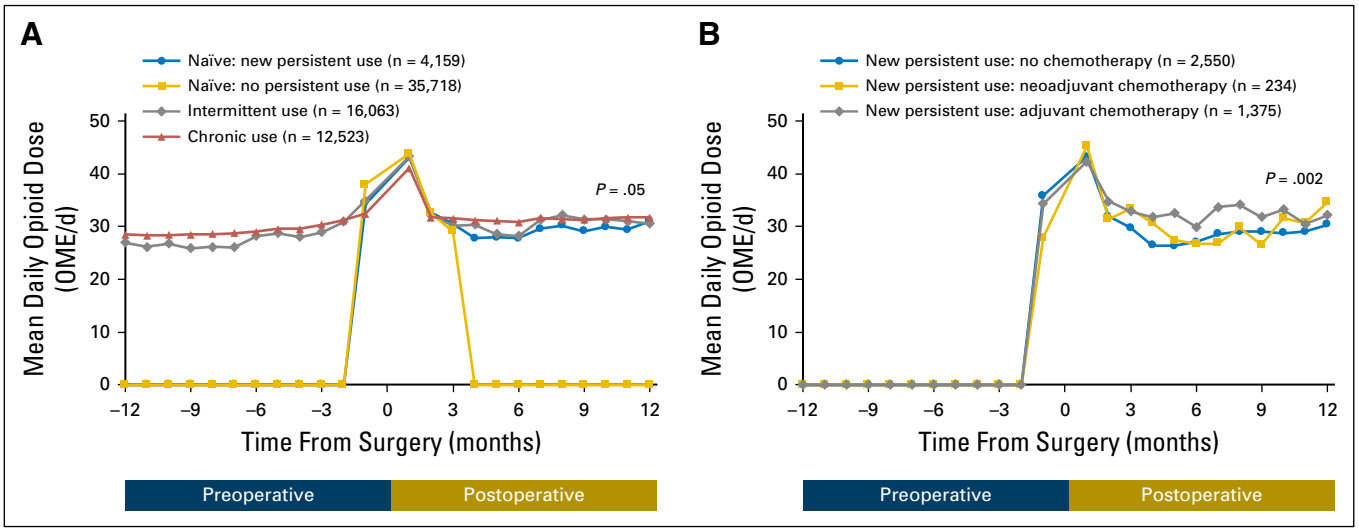

Fig 2. (A) Trajectory of daily opioid dose stratified by perioperative opioid use. Mean daily opioid dose for each group was calculated every 30 days from 1 year before surgery to 1 year after surgery, while adjusting for preoperative opioid prescriptions, initial opioid prescribed, procedure type, adjuvant and neoadjuvant therapy, and patient characteristics. One year after surgery, patients who developed new persistent opioid use continued filling opioid prescriptions with daily doses similar to intermittent and chronic opioid users ($P = .05$). (B) Trajectory of daily opioid dose stratified by timing of chemotherapy. Patients who developed new persistent opioid use and received adjuvant chemotherapy had higher daily opioid doses compared with those who received no chemotherapy ($P = .002$). All groups, however, continued filling prescriptions with high daily doses, equivalent to five to six tablets per day of 5-mg hydrocodone. OME, oral morphine equivalent.

(Appendix Table A4, online only) or the covariate-adjusted rates of new persistent opioid use (Appendix Fig A1, online only).

DISCUSSION

This study has two major findings. First, we found that 10% of opioid-naïve patients with cancer undergoing curative-intent surgery develop new persistent opioid use. These patients continue filling prescriptions with high daily doses even 1 year after surgery, equivalent to six tablets per day of 5-mg hydrocodone. This dose is similar to intermittent and chronic opioid users, suggesting that patients with new persistent opioid use may transition to chronic opioid use. Second, we found that adjuvant chemotherapy was a strong risk factor for new persistent opioid use for all procedures; however, new persistent opioid use was still common (7% to 11%) among patients with no adjuvant chemotherapy.

Similar to previous studies of surgical patients, we report the risk of new persistent opioid use among previously opioid-naïve patients.[11-13,16] However, these studies were limited in that they did not focus on, or specifically excluded, patients with cancer. Our findings show the risk of new persistent opioid use for patients with cancer undergoing curative-intent surgery was 10%, which is higher than the 6% to 8% reported for noncancer surgery.[11-13,16] Neurotoxicity from adjuvant chemotherapy may contribute to this increased risk, yet even patients who did not receive adjuvant chemotherapy had a 7% to 11% risk of new persistent opioid use. In addition, our study also describes changes in daily opioid dose after surgery, which has not been reported in previous studies of postoperative opioid use.[11-13,16] We demonstrated patients with new persistent opioid use continue filling prescriptions with daily doses similar to chronic opioid users 1 year after surgery, equivalent to six tablets per day of 5-mg hydrocodone.

Patients with cancer who undergo curative-intent surgery have several potential reasons for persistently requiring opioids. Persistent postsurgical pain is a possible contributor, affecting 13% to 50% of patients undergoing mastectomy or thoracotomy.[19,20] These patients are unlikely to achieve relief from opioids, however, and should be considered for nonopioid analgesics, behavioral therapies, or more aggressive procedural interventions.[21-23] Neurotoxicity from adjuvant chemotherapy and radiation may also play a role and causes persistent pain in 13% to 26% of patients.[20,24-27] In addition, 33% of patients develop new persistent opioid use after curative-intent chemoradiation.[28] Other medications administered with adjuvant chemotherapy, such as aromatase inhibitors and granulocyte colony-stimulating factors, can also cause pain.[29,30] The findings of this study, however, demonstrate that adjuvant chemotherapy does not account for all new persistent opioid use after curative-intent surgery. Furthermore, pain from chemotherapy-induced peripheral neuropathy is difficult to treat given the relative lack of effective pharmacologic therapies. Although opioids and gabapentin are often used to treat pain from chemotherapy-induced peripheral neuropathy, this practice is not supported by evidence,[31] and duloxetine is the only medication with demonstrated efficacy for these patients.[32] Another potential contributing factor is uncoordinated prescribing from multiple providers. Patients with cancer require multidisciplinary care, often from physicians in different health systems, and receive opioids from physicians who are accustomed to prescribing large quantities of opioids.[33,34]

New persistent opioid use after curative-intent surgery could be addressed by several strategies. First, further study is needed to develop evidence-based guidelines and reduce excessive opioid prescribing.[35] Further study is also needed to develop effective screening tools to identify patients at risk for new persistent opioid use. For example, psychosocial factors are known to drive postoperative opioid consumption,[36,37] and patients with cancer report high levels of psychosocial distress.[38-40] This could contribute to

Table 2. Logistic Regression Models for New Persistent Opioid Use

Model Variable	Breast (n = 22,379)	Melanoma (n = 6,730)	Colorectal (n = 6,082)	HPB and Gastric (n = 1,508)	Thoracic (n = 3,178)
Age, years	0.994 (0.990 to 0.999)*	1.004 (0.996 to 1.012)	0.997 (0.990 to 1.005)	0.996 (0.982 to 1.010)	0.992 (0.981 to 1.003)
Female sex	0.876 (0.364 to 2.107)	1.091 (0.895 to 1.330)	1.189 (1.003 to 1.411)	0.942 (0.686 to 1.294)	0.733 (0.593 to 0.906)*
Preoperative opioid prescription†	1.210 (1.101 to 1.330)‡	1.506 (1.198 to 1.894)‡	2.147 (1.701 to 2.709)‡	1.421 (0.943 to 2.143)	1.716 (1.275 to 2.311)‡
Initial opioid prescribed,§ OME	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)
Chemotherapy (reference: none)‖					
Neoadjuvant	1.209 (0.989 to 1.478)	0.464 (0.108 to 1.996)	1.407 (0.934 to 2.119)	1.428 (0.881 to 2.313)	1.351 (0.867 to 2.106)
Adjuvant	2.409 (2.191 to 2.648)‡	2.569 (1.457 to 4.530)*	2.265 (1.852 to 2.770)‡	2.244 (1.534 to 3.283)‡	2.117 (1.653 to 2.711)‡
Radiation (reference: none)¶					
Neoadjuvant	0.565 (0.259 to 1.232)	6.047 (1.128 to 32.413)	1.143 (0.765 to 1.706)	1.034 (0.277 to 3.863)	0.860 (0.423 to 1.748)
Adjuvant	0.893 (0.817 to 0.976)	4.713 (2.411 to 9.214)‡	1.632 (1.031 to 2.583)	0.725 (0.418 to 1.257)	2.060 (1.421 to 2.988)‡
Psychiatric diagnoses					
Depression	1.220 (0.998 to 1.491)	1.069 (0.584 to 1.956)	0.913 (0.576 to 1.447)	1.189 (0.568 to 2.490)	1.249 (0.801 to 1.947)
Anxiety	1.088 (0.919 to 1.289)	1.534 (1.005 to 2.341)	1.195 (0.832 to 1.716)	1.121 (0.549 to 2.291)	1.143 (0.758 to 1.722)
Substance use disorder	1.385 (1.129 to 1.699)*	1.401 (0.822 to 2.387)	1.430 (1.041 to 1.963)	0.707 (0.342 to 1.461)	1.316 (1.010 to 1.714)
Other psychiatric condition	1.415 (0.964 to 2.079)	1.598 (0.681 to 3.749)	1.564 (0.782 to 3.131)	0.836 (0.244 to 2.863)	0.356 (0.083 to 1.535)
Elixhauser comorbidity score	1.016 (1.011 to 1.021)‡	1.011 (0.999 to 1.024)	1.017 (1.009 to 1.025)‡	1.007 (0.994 to 1.020)	0.995 (0.985 to 1.005)
Type of insurance (reference: preferred provider organization)					
Comprehensive	1.095 (0.936 to 1.281)	0.901 (0.631 to 1.286)	1.286 (1.001 to 1.653)	1.464 (0.894 to 2.397)	1.426 (1.074 to 1.892)
Health maintenance organization	1.084 (0.959 to 1.226)	0.971 (0.719 to 1.310)	1.051 (0.810 to 1.364)	0.882 (0.528 to 1.473)	1.126 (0.792 to 1.603)
Point of service	1.184 (1.014 to 1.384)	0.939 (0.641 to 1.377)	0.965 (0.678 to 1.374)	1.719 (0.979 to 3.017)	1.166 (0.758 to 1.792)
Other	0.906 (0.766 to 1.072)	0.638 (0.419 to 0.970)	1.006 (0.703 to 1.439)	1.198 (0.681 to 2.106)	1.658 (1.069 to 2.572)
Missing	0.902 (0.744 to 1.093)	0.780 (0.531 to 1.147)	0.948 (0.595 to 1.511)	0.905 (0.341 to 2.404)	1.303 (0.764 to 2.222)
Median income (reference: $60,000-$70,000)					
< $40,000	0.353 (0.085 to 1.476)	#	#	1.825 (0.154 to 21.658)	#
$40,000-50,000	1.254 (0.807 to 1.948)	1.228 (0.522 to 2.891)	0.316 (0.076 to 1.313)	1.246 (0.262 to 5.922)	2.191 (0.790 to 6.076)
$50,000-60,000	1.060 (0.927 to 1.213)	1.064 (0.786 to 1.441)	1.029 (0.805 to 1.316)	0.624 (0.358 to 1.089)	1.007 (0.737 to 1.377)
≥ $70,000	0.871 (0.786 to 0.966)*	0.963 (0.756 to 1.227)	0.751 (0.606 to 0.931)*	0.797 (0.554 to 1.147)	0.752 (0.577 to 0.980)
Missing	1.024 (0.896 to 1.170)	1.076 (0.812 to 1.425)	1.120 (0.876 to 1.432)	0.881 (0.541 to 1.432)	1.162 (0.863 to 1.566)
c statistic	0.630	0.596	0.655	0.627	0.659
Hosmer-Lemeshow goodness-of-fit test	*P* = .951	*P* = .099	*P* = .689	*P* = .855	*P* = .597

NOTE. Data presented as odds ratio (95% CI) unless otherwise noted.
Abbreviations: HPB, hepato-pancreato-biliary; OME, oral morphine equivalent.
*$P < .01$.
†Opioid-naïve patients who filled opioid prescriptions in the 30 days before surgery
‡$P < .001$.
§Quantity prescribed for the opioid prescription closest to the date of surgery
‖Three mutually exclusive groups: no chemotherapy, neoadjuvant chemotherapy, and adjuvant chemotherapy. No patients had both neoadjuvant and adjuvant chemotherapy.
¶Three mutually exclusive groups: no radiation, neoadjuvant radiation, and adjuvant radiation. No patients had both neoadjuvant and adjuvant radiation.
#No patients in this group.

higher rates of opioid use among patients undergoing curative-intent surgery. Alcoholism and tobacco use have also been associated with increased opioid use in patients with cancer.[41]

In addition, surgeons need to play a more active role in counseling patients on postoperative pain, potential risks of opioids, and minimizing postoperative opioid use.[42] Given the high risk of new persistent opioid use in this population, physicians should consider universal precautions when prescribing opioids in this setting, including educating patients on safe use, storage, and disposal. More scrutiny is also needed on the use of opioids to treat neuropathic pain caused by adjuvant chemotherapy and persistent postsurgical pain, which is frequently unresponsive to opioids and may be better treated with nonopioid medications.[21-23] Although a recent Cochrane review found insufficient evidence to evaluate the potential harm of treating neuropathic pain with opioids,[43] the high rate of new persistent opioid use reported in our study suggests the risks of opioid use may outweigh the benefits for patients with cancer undergoing curative-intent surgery.

This study was limited by several factors. First, it only evaluated adults with continuous enrollment in employer-based insurance and did not adjust for race or ethnicity. These factors limit the generalizability of our findings. We did, however, adjust for income and insurance type in our analysis. This study also does not evaluate opioid consumption or the indications for opioid

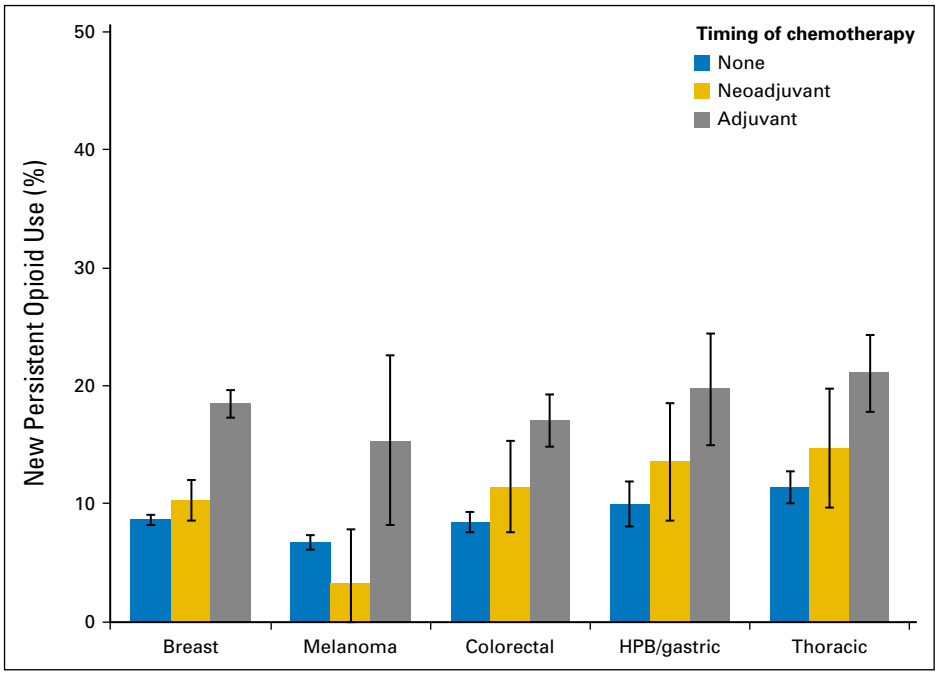

Fig 3. Risk of new persistent opioid use stratified by procedure and timing of chemotherapy. We calculated the risk of new persistent opioid use by procedure with patients stratified by timing of chemotherapy. This figure shows 95% CIs with the risk of new persistent opioid use adjusted for preoperative opioid prescriptions, initial opioid prescribed, timing of chemotherapy, and patient characteristics. Patients receiving adjuvant chemotherapy had a higher risk of new persistent opioid use (15% to 21%), but those who received no chemotherapy were still at risk (7% to 11%). HPB, hepato-pancreato-biliary.

prescriptions. It is possible patients were filling prescriptions for pain unrelated to their cancer diagnosis. Previous work, however, suggests the rate of new persistent opioid use in nonsurgical populations is only 0.4%.[13] In addition, our analysis adjusted for multiple potential contributing factors, including chemotherapy and psychiatric diagnoses.

Another limitation is the inability of claims data to capture the use of nonopioid analgesics, such as acetaminophen and ibuprofen, which are frequently filled over the counter. Nevertheless, given the high rate of new persistent opioid use reported in this study, all physicians should consider more aggressive use of nonopioid analgesics to minimize opioid use. This study also did not specifically adjust for postoperative complications. Nonetheless, we excluded patients with length of stay $>$ 30 days or reoperation within 180 days, which should provide a more conservative estimate of opioid use. Finally, the database did not include information needed to identify which physician specialties were providing opioid prescriptions. However, given the high rate of new persistent opioid use reported in this study, all physicians caring for patients with cancer after curative-intent surgery should consider more judicious prescribing of opioids.

In conclusion, we found that 10% of patients with cancer develop new persistent opioid use after curative-intent surgery. These patients continue filling opioid prescriptions 1 year after surgery, with daily opioid doses similar to chronic opioid users. This iatrogenic complication is a substantial burden on cancer survivors and requires changes to prescribing guidelines, physician education, and patient counseling during the surveillance and survivorship phases of care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

New Persistent Opioid Use Among Patients With Cancer After Curative-Intent Surgery

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Appendix

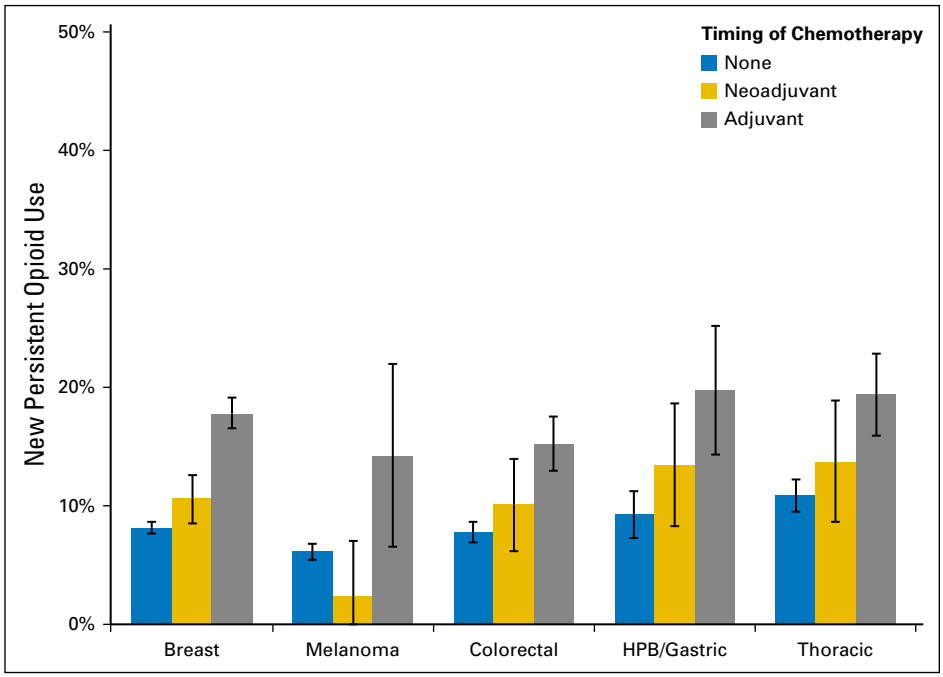

Fig A1. Risk of new persistent opioid use stratified by procedure and timing of chemotherapy (excluding patients with preoperative opioid prescriptions within 30 days before surgery). Patients who received preoperative opioid prescriptions (within 30 days before surgery) were excluded from this analysis. We calculated the risk of new persistent opioid use by procedure with patients stratified by timing of chemotherapy. This figure shows 95% CIs with the risk of new persistent opioid use adjusted for initial opioid prescribed, timing of chemotherapy, and patient characteristics. Patients receiving adjuvant chemotherapy had a higher risk of new persistent opioid use (14% to 20%), but those who received no chemotherapy were still at risk (6% to 11%).

Table A1. CPT Codes for Curative-Intent Surgery

Procedure	CPT Codes
Colectomy	44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44155, 44156, 44157, 44158, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212
Rectal resection	45110, 45111, 45112, 45113, 45114, 45116, 45119, 45123, 45126, 45160, 45171, 45172, 45395, 45397
Wide local excision	11603, 11604, 11606, 11623, 11624, 11626, 11643, 11644, 11646
Breast	19101, 19110, 19112, 19120, 19125, 19300, 19301, 19302, 19303, 19304, 19305, 19306, 19307
Pancreatectomy	48120, 48140, 48145, 48146, 48148, 48150, 48152, 48153, 48154, 48155, 48160
Liver resection	47100, 47120, 47122, 47125, 47130, 47370, 47371, 47380, 47381
Gastric resection	43605, 43610, 43611, 43620, 43621, 43622, 43631, 43632, 43633, 43634, 43659
Esophagectomy	43100, 43101, 43107, 43108, 43112, 43113, 43116, 43117, 43118, 43121, 43122, 43123, 43124
Lung resection	32440, 32442, 32445, 32480, 32482, 32484, 32486, 32488, 32503, 32504, 32505, 32663, 32666, 32669, 32670, 32671

Abbreviation: CPT, Current Procedural Terminology.

Table A2. ICD-9 Codes for Cancer Diagnoses

ICD-9 Code	Description
150	Malignant neoplasm of esophagus
151	Malignant neoplasm of stomach
152	Malignant neoplasm of small intestine including duodenum
153	Malignant neoplasm of colon
154	Malignant neoplasm of rectum rectosigmoid junction and anus
155	Malignant neoplasm of liver and intrahepatic bile ducts
156	Malignant neoplasm of gallbladder and extrahepatic bile ducts
157	Malignant neoplasm of pancreas
158	Malignant neoplasm of retroperitoneum and peritoneum
159	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
162	Malignant neoplasm of trachea, bronchus, and lung
172	Malignant melanoma of skin
173	Other malignant neoplasm of skin
174	Malignant neoplasm of female breast
175	Malignant neoplasm of male breast
197	Secondary malignant neoplasm of respiratory and digestive systems
209	Neuroendocrine tumors

Abbreviation: ICD-9, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision.

Table A3. CPT and ICD-9 Codes for Chemotherapy and Radiation Therapy

Treatment	ICD-9 Codes	CPT Codes
Chemotherapy	9925, 0010	96401-96549
Radiation treatment	9220, 9221, 9222, 9223, 9224, 9225, 9226, 9227, 9229, 9230, 9231, 9232, 9233, 9239	77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 0073T

Abbreviations: CPT, Current Procedural Terminology; ICD-9, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision.

Table A4. Logistic Regression Models (Excluding Patients With Preoperative Opioid Prescriptions Within 30 Days Before Surgery)

Model Variable	Breast (n = 16,645)	Melanoma (n = 5,482)	Colorectal (n = 5,510)	HPB and Gastric (n = 1,297)	Thoracic (n = 2,852)
Age, years	0.996 (0.991 to 1.000)	1.006 (0.997 to 1.015)	0.997 (0.989 to 1.006)	0.997 (0.981 to 1.013)	0.992 (0.980 to 1.004)
Female sex	0.904 (0.347 to 2.350)	1.038 (0.825 to 1.306)	1.152 (0.956 to 1.387)	0.973 (0.685 to 1.383)	0.726 (0.577 to 0.914)*
Preoperative opioid prescription†	‡	‡	‡	‡	‡
Initial opioid prescribed,§ OME	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)
Chemotherapy (reference: none)‖					
Neoadjuvant	1.332 (1.060 to 1.673)	0.371 (0.050 to 2.736)	1.331 (0.843 to 2.101)	1.528 (0.918 to 2.544)	1.312 (0.813 to 2.117)
Adjuvant	2.453 (2.191 to 2.746)¶	2.576 (1.342 to 4.946)*	2.147 (1.722 to 2.678)¶	2.436 (1.588 to 3.736)¶	2.004 (1.527 to 2.632)¶
Radiation (reference: none)#					
Neoadjuvant	0.596 (0.236 to 1.506)	5.225 (0.529 to 51.618)	1.136 (0.738 to 1.748)	1.083 (0.275 to 4.260)	0.962 (0.455 to 2.034)
Adjuvant	0.904 (0.814 to 1.005)	5.391 (2.500 to 11.628)¶	1.492 (0.869 to 2.563)	0.569 (0.288 to 1.124)	2.106 (1.391 to 3.187)¶
Psychiatric diagnoses					
Depression	1.084 (0.846 to 1.389)	0.987 (0.492 to 1.979)	0.923 (0.544 to 1.566)	1.348 (0.615 to 2.954)	1.151 (0.697 to 1.899)
Anxiety	1.145 (0.936 to 1.401)	1.245 (0.743 to 2.085)	1.168 (0.778 to 1.754)	1.256 (0.582 to 2.708)	1.149 (0.737 to 1.791)
Substance use disorder	1.383 (1.092 to 1.752)*	1.472 (0.798 to 2.716)	1.254 (0.866 to 1.816)	0.932 (0.447 to 1.943)	1.226 (0.916 to 1.640)
Other psychiatric condition	1.066 (0.638 to 1.779)	1.531 (0.543 to 4.316)	1.317 (0.613 to 2.830)	0.695 (0.159 to 3.034)	0.316 (0.042 to 2.380)
Elixhauser comorbidity score	1.016 (1.010 to 1.022)¶	1.018 (1.003 to 1.033)	1.019 (1.011 to 1.028)¶	1.004 (0.989 to 1.018)	0.995 (0.984 to 1.006)
Type of insurance (reference: preferred provider organization)					
Comprehensive	1.135 (0.948 to 1.361)	0.762 (0.500 to 1.163)	1.169 (0.887 to 1.539)	1.423 (0.822 to 2.463)	1.428 (1.057 to 1.930)
Health maintenance organization	1.095 (0.945 to 1.269)	0.988 (0.701 to 1.392)	1.132 (0.853 to 1.501)	0.948 (0.542 to 1.657)	1.164 (0.789 to 1.717)
Point of service	1.216 (1.014 to 1.459)	0.741 (0.461 to 1.190)	0.912 (0.618 to 1.346)	1.479 (0.773 to 2.831)	1.116 (0.683 to 1.823)
Other	0.940 (0.770 to 1.147)	0.626 (0.392 to 1.000)	1.074 (0.731 to 1.578)	1.215 (0.653 to 2.260)	1.677 (1.042 to 2.699)
Missing	1.129 (0.887 to 1.436)	0.922 (0.567 to 1.500)	0.917 (0.551 to 1.524)	0.944 (0.316 to 2.819)	1.578 (0.894 to 2.785)
Median income (reference: $60,000-70,000)					
< $40,000	0.266 (0.036 to 1.966)	‡	‡	3.754 (0.205 to 68.837)	‡
$40,000-50,000	1.028 (0.585 to 1.806)	1.419 (0.555 to 3.627)	0.189 (0.026 to 1.383)	1.270 (0.260 to 6.197)	1.302 (0.336 to 5.044)
$50,000-60,000	1.116 (0.952 to 1.309)	0.989 (0.697 to 1.402)	1.119 (0.859 to 1.458)	0.621 (0.332 to 1.163)	1.164 (0.836 to 1.621)
≥ $70,000	0.917 (0.812 to 1.036)	0.922 (0.701 to 1.214)	0.717 (0.565 to 0.908)‡	0.705 (0.471 to 1.055)	0.737 (0.551 to 0.986)
Missing	1.130 (0.965 to 1.325)	1.043 (0.758 to 1.437)	1.128 (0.863 to 1.474)	0.822 (0.482 to 1.401)	1.266 (0.918 to 1.745)
c statistic	0.931	0.591	0.632	0.621	0.647
Hosmer-Lemeshow goodness-of-fit test	*P* = .628	*P* = .077	*P* = .167	*P* = .984	*P* = .086

NOTE. Data presented as odds ratio (95% CI) unless otherwise noted.
Abbreviations: HPB, hepato-pancreato-biliary; OME, oral morphine equivalent.
*$P < .01$.
†Opioid-naïve patients who filled opioid prescriptions in the 30 days before surgery.
‡No patients in this group.
§Quantity prescribed for the opioid prescription closest to the date of surgery.
‖Patients were categorized into three mutually exclusive groups: no chemotherapy, neoadjuvant chemotherapy, and adjuvant chemotherapy. No patients in this cohort had both neoadjuvant and adjuvant chemotherapy.
¶$P < .001$.
#Patients were categorized into three mutually exclusive groups: no radiation, neoadjuvant radiation, and adjuvant radiation. No patients in this cohort had both neoadjuvant and adjuvant radiation.