Retrospective Study

Association Between Smoking Status and Opioid Dose in Prescriptions Written for Breast Cancer-related Pain

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Background: Cancer-related pain has historically been undertreated. Prescription opioids have been shown to be an integral part of the treatment of cancer pain. Despite the significant amount of scientific evidence that smoking is associated with variation in pain expression and opioid misuse in both cancer and non-cancer populations, little is known about the association between smoking status and opioid utilization in cancer populations.

Objectives: To assess the association between smoking status and high-risk opioid-prescribing behaviors of oncologists prescribing opioids in the outpatient setting to patients with breast cancer-related pain.

Study Design: A retrospective cross-sectional study of opioid prescriptions written by oncologists for breast cancer-related pain was conducted using the Patient Cohort Explorer (PCE) database at the University of Mississippi Medical Center (UMMC) from March 15, 2015 to March 15, 2017.

Setting: Tertiary academic medical center.

Methods: De-identified data from UMMC PCE were utilized for this study. Patient-level information, such as age, gender, race, insurance status, and smoking status, were also selected for each prescription. Prescription-level data, such as name of opioid, dose, frequency, route, and primary diagnosis, were also obtained. Prescriptions were included if they are written in the outpatient setting, for breast cancer-related pain, and for women 18 years or older. Prescriptions were excluded if they were written by a specialist other than a medical oncologist or if the information necessary to calculate morphine milligram equivalence (MME) was missing.

Results: The sample consisted of 577 opioid prescriptions that were written in the outpatient setting to women ages 18 years and older for breast cancer-related pain. The majority of the sample were ages 46 to 64 years (60.5%), Nonwhite (75.2%), publicly insured (66.2%), and with nonmetastatic disease (86.1%). Almost one-fifth (19.6%) of the prescriptions were written to current smokers, 21.3% to former smokers, and 58.1% to nonsmokers. Nonsmoking status predicted an increased odds of receiving a prescription ≥ 50 MME (odds ratio [OR] = 1.98, 95% confidence interval [CI]: 1.08-3.60, $P = 0.030$) and ≥ 90 MME (OR = 6.29, 95% CI: 1.38-28.58, $P = 0.017$) compared to current smokers. Nonsmoking status also predicted an increased odds of receiving a prescription ≥ 90 MME (OR = 4.29, 95% CI: 1.43-12.92, $P = 0.009$) compared to former smokers.

Limitations: This cross-sectional sample was drawn from a single institution and only included the breast cancer population and may not be generalizable to other populations or institutions. Second, our sample was drawn from secondary data not collected for the purposes of our study. This limits the inclusion of other variables that may impact the opioid-prescribing behaviors of oncologists, potentially resulting in bias.

Conclusions: During a time of heightened awareness of opioid-related harm, as well as implementation of national opioid-prescribing guidelines, current smoking may potentially be impacting how oncologists evaluate the need for opioids to treat breast cancer-related pain.

Further studies that examine the relationship between smoking status, perceived need for opioids, and evaluative need for opioids in cancer populations are warranted.

Key words: Cancer pain, opioids, smoking, breast cancer, opioid-prescribing guidelines, health policy, oncology, end of life

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Approximately 30% to 50% of patients with cancer and 70% of those with advanced cancer will experience moderate to severe pain (1,2). Patients with breast cancer metastasis are likely to have bone involvement, more extensive surgery, and psychological distress secondary to having an incurable disease (3-6). High-impact chronic pain, which is pain that results in at least one major activity restriction, has been reported to be disproportionately higher in cancer patients with low education levels, low socioeconomic status, and current smokers (7,8). In general, the intensity of the pain is greater in more advanced stages and can vary from acute and chronic from biopsies, surgeries, radiation, and chemotherapy (2,7,9). Moreover, psychological distress makes controlling cancer pain even more challenging as patients with more advanced disease have a greater likelihood of reporting anxiety, depression, inadequate pain control, and decreased quality of life (6,9-11).

Prescription opioids have been shown to be an integral part of the treatment of cancer pain. An estimated 95% of cancer patients report going from moderate-severe pain to mild pain within 2 weeks of starting opioids. Although there have been some improvements in the treatment of cancer-related pain over time with the implementation of multidisciplinary approaches to pain treatment, cancer-related pain has historically been undertreated and the undertreatment may be getting worse (12-15).

Epidemiological studies (16-19) have shown that smokers tend to have a greater frequency of chronic pain, more pain locations, more intense pain, and greater functional impairment. In addition, it has been reported that nicotine dependence is associated with increased odds of being prescribed high-dose opioids and greater opioid use (20,21). Interestingly, epidemiological studies (22,23) have shown that pain may potentiate smoking behavior as a coping mechanism, yet still result in increased pain intensity and disability. Moreover, the relationship between pain and tobacco dependence is modified by gender, such that increased pain has been shown to be associated with increased smoking in women but not men (23). Similar to pain studies in the non-cancer population, current smoking despite a cancer diagnosis has been shown to be associated with increased pain, increased interference from pain, and higher pain expression (24-26).

Poorly controlled pain may be a potent motivator for smoking. Despite the significant amount of scientific evidence that smoking is associated with variation in pain expression and opioid misuse in both cancer and non-cancer populations, little is known about the association between smoking status and opioid utilization in cancer populations. Given the heightened awareness of opioid-related harm in the oncology community and national opioid-prescribing guidelines, current smoking status potentially may be influencing how oncologists evaluate the need for high-dose opioids in cancer populations. Our study assessed the relationship between smoking status and high-risk opioid-prescribing by oncologists in the breast cancer population.

Methods

Study Design and Sample

A cross-sectional retrospective database analysis was conducted using opioid prescriptions written by oncologists for breast cancer-related pain over a 2-year study period (March 15, 2015 to March 15, 2017). De-identified data from the University of Mississippi Medical Center (UMMC) Patient Cohort Explorer (PCE) was used for this study (27). This study was approved by the UMMC Institutional Review Board.

UMMC is Mississippi's only academic medical center. This medical center provides care for about 2,000 new cancer patients annually and follows more than 5,800 survivors. Patient-level information, such as age, gender, race, insurance status, and smoking status were selected for each prescription. Prescription-level data, such as name of opioid, dose, frequency, route, and primary diagnosis, were also obtained. Prescriptions were included if they were written in the outpatient setting, for breast cancer-related pain, and for women 18 years or older. Prescriptions were excluded if they were written by a specialist other than a medical oncologist or if the information necessary to calculate milligram morphine equivalents (MME) was missing.

Study Variables

The outcome variables of interest for this study were the proportion of prescriptions written for ≥ 50 MME (moderate risk) and the proportion of prescriptions written for ≥ 90 MME (high risk). MMEs were calculated using the Centers for Disease Control and Prevention opioid conversion chart (28) with an exception for tramadol, which required using the Centers for Medicare and Medicaid Services opioid conversion chart (29). If MME was ≥ 50, the prescription was grouped in the moderate risk category, and if MME was ≥ 90, the prescription was grouped in the high-risk category. Smoking status was the predictor variable of interest. Smoking status was categorized as smoker, former smoker, or nonsmoker. Sociodemographic and clinical characteristics included age, race, insurance status, and stage of disease. Stage of disease was categorized as metastatic disease or not metastatic disease based on the primary diagnosis assigned to the prescription. If the primary diagnosis on the prescription included metastatic or stage 4, it was categorized as metastatic. All other diagnoses were categorized as not metastatic. Age was categorized into 3 groups: 26 to 45 years (i.e., young), 46 to 64 years (i.e., middle age), and ≥ 65 years or older (i.e., elderly) (30). Race was categorized as White or Nonwhite (i.e., Black, Hispanic, Mississippi branch Choctaw, multiracial). Insurance status was categorized as Medicaid, Medicare, Private, or Self-pay (Table 1).

Statistical Analysis

Frequencies and percentages were calculated for all variables of interest. Multivariate logistic regression was used to predict the association between smoking status and each of the outcome variables (i.e., proportion of prescriptions ≥ 50 MME [moderate risk] and proportions of prescriptions ≥ 90 MME [high risk]) while controlling for age, race, insurance status, and stage of disease. Missing data were handled with listwise deletion, meaning that any prescription missing data on one or more variables was removed from the logistic regression models. An a priori alpha level of 0.05 was used to evaluate the statistical significance for all analyses. STATA® 16 (StataCorp LLC, College Station, TX) was used to conduct all analyses.

Results

After applying inclusion and exclusion criteria, 577 patients were included in the sample for this study. Figure 1 shows the sample selection flow diagram.

Table 1. *Sample population demographic and clinical characteristics.*

VARIABLE (n = 577)	n	Percentage
AGE		
26 to 45 years	83	14.4
46 to 64 years	349	60.5
≥ 65 years	145	25.1
RACE/ETHNICITY		
White	143	24.8
Nonwhite†	434	75.2
INSURANCE		
Private	102	17.7
Medicare	241	41.8
Medicaid	141	24.4
Self-pay	89	15.4
Missing	4	0.7
SEVERITY		
Metastatic	80	13.9
Not Metastatic	497	86.1
SMOKING		
Smoker	113	19.6
Former Smoker	123	21.3
Nonsmoker	335	58.1
Missing	6	1.0

†Nonwhite includes: African American (98.2%), Multiracial, Mississippi Band Choctaw, Hispanic, and Other.

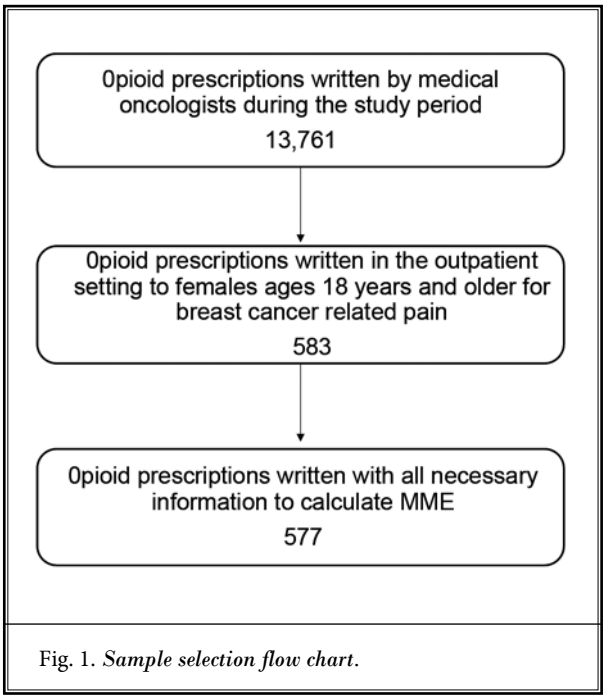

Fig. 1. *Sample selection flow chart.*

The majority of the sample were ages 46 to 64 years (60.5%), Nonwhite (75.2%), publicly insured (66.2%), nonsmokers (58.1%), and with nonmetastatic disease (86.1%). Table 1 reports the baseline demographic and clinical characteristics of the sample.

The majority of the prescriptions were written for short-acting opioids (SAOs) and < 50 MME. In the overall sample, 74.8% were written for < 50 MME, 17.0% were written in the ≥ 50 but < 90 MME range, and 7.5% of the prescriptions were written for ≥ 90 MME. Approximately 84% of the prescriptions were SAOs and 16% long-acting opioids. Table 2 reports the prevalence of different MME levels and opioid types in the sample.

The odds of a prescription being written with an MME ≥ 50 by a UMMC oncologist for breast cancer-related pain did vary significantly based on smoking status when adjusting for other variables. Nonsmoking status predicted an increased odds of receiving a prescription for ≥ 50 MME relative to smokers (odds ratio [OR] 1.98, 95% confidence interval [CI]: 1.08-3.60, P = 0.030). Table 3 reports the results of the logistic regression model assessing the association between smoking and prescriptions ≥ 50 MME after adjusting for age, race, insurance, and severity of disease.

The odds of a prescription MME ≥ 90 being written by an oncologist for breast cancer-related pain did vary significantly based on smoking status when adjusting for other variables. Nonsmoking status predicted an increased odds of receiving a prescription for ≥ 90 MME relative to smokers (OR 6.29, 95% CI: 1.38-28.58, P = 0.017) and relative to former smokers (OR = 4.29, 95% CI: 1.43-12.92, P = 0.009). Table 4 reports the results of the logistic regression model assessing the association between smoking and prescriptions ≥ 90 MME after adjusting for age, race, insurance, and severity of disease.

Table 2. *Frequency distributions of MME level and opioid type.*

VARIABLE (n = 577)	n	Percentage
MME ≥ 50		
≥ 50 MME	83	14.4
< 50 MME	349	60.5
MME ≥ 90		
≥ 90 MME	53	9.2
< 90 MME	524	90.8
OPIOID TYPE		
SAO	482	83.5
LAO {AU: Deleted "*" and "†"/See abbreviations list below}	95	16.5

Abbreviations: MME = morphine milligram equivalence; SAO = short-acting opioid; LAO = long-acting opioid.

Discussion

In our study, we found that one in five of the prescriptions written by an oncologist for breast cancer-related pain were to patients currently smoking, which is approximately the same as a similar study by Novy et al (31) that assessed the association between smoking, pain, symptoms burden, and risk of opioid misuse in cancer populations. The high prevalence of smoking in patients receiving opioid prescriptions for breast cancer-related pain suggests that smoking has real potential to impact the pain experience in the breast cancer population.

For our main finding, we found higher doses of opioid prescriptions written to nonsmokers when compared to both smokers and former smokers. Nonsmokers were 1.98 times more likely than smokers to receive prescriptions for > 50 MME. In the highest-risk outcome, nonsmokers were 6.29 times more likely than smokers to receive prescriptions > 90 MME and 4.29 times more likely than former smokers to receive prescriptions > 90 MME (Tables 3 and 4).

Interestingly, our findings are not consistent with prior studies that have assessed the association between opioid dose and smoking status. For instance, current smoking has been independently associated with a 27 mg/d greater MME than nonsmokers in a non-cancer population (20). In the cancer population, no difference in opioid dose was found based on smoking status in patients with advanced cancer despite smokers having higher pain expression, Cut down/Annoyed/Guilty/Eye-opener positivity, and illicit drug use (26). Furthermore, it has been shown that smokers and nonsmokers used similar amounts of opioids in a sample containing many types of cancer (31).

Our findings in the breast cancer population may be different because the sample of patients from this study is drawn from a time period focused on opioid-related harm and national guidelines for safe opioid prescribing (28). Clinical guidelines have been shown to be effective in changing clinical practice (32). Moreover, the American Society of Clinical Oncology Educational Book encourages oncologists prescribing opioids for cancer-related pain to stratify current smokers as moderate risk for opioid misuse (33).

Such stratification of risk requires judgment by prescribers, which is synonymous in the theoretical framework of the Andersen Behavioral Model with

Table 3. *Association between smoking and prescriptions written for ≥ 50 MME by UMMC oncologists for breast cancer-related pain.*

VARIABLE (n = 567)	ADJUSTED OR	95% CI	*P* value
SMOKING			
Smoker	Reference	Reference	Reference
Former Smoker	1.40	0.72-2.67	0.333
Nonsmoker	1.98	1.08-3.60	0.030†
AGE			
26 to 45 years	0.82	0.36-1.89	0.648
46 to 64 years	1.64	0.90-3.00	0.109
≥ 65 years	Reference	Reference	Reference
RACE/ETHNICITY			
White	Reference	Reference	Reference
Nonwhite‡	1.06	0.64-1.75	0.820
INSURANCE			
Private	Reference	Reference	Reference
Medicaid	1.34	0.74-2.41	0.341
Medicare	0.40	0.22-0.72	0.002†
Self-pay	0.53	0.27-1.08	0.081
SEVERITY			
Non Metastatic	Reference	Reference	Reference
Metastatic	1.42	0.81-2.48	0.217

†*P* value ≤ 0.05.
‡Nonwhite includes: African American (98.2%), Multiracial, Mississippi Band Choctaw, Hispanic, and Other.
Abbreviations: MME = morphine milligram equivalence; UMMC = University of Mississippi Medical Center; OR = odds ratio; CI = confidence interval.

Table 4. *Association between smoking status and prescriptions written for ≥ 90 MME by UMMC oncologists for breast cancer-related pain.*

VARIABLE (n = 567)	ADJUSTED OR	95% CI	*P* value
SMOKING			
Smoker	Reference	Reference	Reference
Former Smoker	1.47	0.25-8.58	0.672
Nonsmoker	6.29	1.38-28.58	0.017†
AGE			
26 to 45 years	2.77	0.47-9.13	0.335
46 to 64 years	4.44	1.42-13.80	0.010†
≥ 65 years	Reference	Reference	Reference
RACE/ETHNICITY			
White	Reference	Reference	Reference
Nonwhite‡	1.65	0.64-4.26	0.299
INSURANCE			
Private	Reference	Reference	Reference
Medicaid	0.18	0.06-0.52	0.002†
Medicare	0.30	0.14-0.64	0.002†
Self-pay	0.27	0.09-0.78	0.016†
SEVERITY			
Non Metastatic	Reference	Reference	Reference
Metastatic	0.94	0.41-2.17	0.886

†*P* value ≤ 0.05.
‡ Nonwhite includes: African American (98.2%), Multiracial, Mississippi Band Choctaw, Hispanic, and Other.

evaluative need (34,35). The Andersen Behavioral Model provides a framework to analyze access to health care services (34,35). It posits that how clinicians judge the need for a health care service (i.e., evaluative need) can be impacted by social conditions, policy, and clinical guidelines (34,35). Thus, how oncologists assess evaluative need may predict who will receive a prescription for opioids, when they will receive it, and how much opioid they will receive.

The findings of this study have both clinical and economic implications as it relates to cancer pain. Opioids are recommended for the treatment of cancer-related pain and poorly controlled cancer pain results in significant decreases in patient satisfaction and value (36). If current smokers tend to have a higher burden of pain but decreased access to opioids, the patients' perceived need for opioids and the prescribers' evaluative need for opioids may be diverging. Indeed, this potential dichotomy needs further investigation, as current smoking may be exacerbating the problem of poorly controlled cancer pain leading to increased motivation to continue smoking (23), which can be associated with an increase in all-cause mortality in breast cancer patients (37).

Physicians have reported barriers to treating chronic pain in smokers with non-cancer pain and patients have reported that distress and pain increase the urge to smoke (38). Moreover, smoking cessation after a cancer diagnosis has been shown to be associated with decreased severity of cancer pain (39). Our findings highlight the need for further studies that examine the relationship between smoking status, perceived need for opioids, and evaluative need for opioids in cancer populations. Qualitative investigations that assess the relationship between smoking, cancer-related pain, and opioid utilization patterns will be useful in steering quantitative investigations toward improvement in the quality of pain management for cancer popula-

tions. Furthermore, such investigations would provide insight on how to properly construct targeted smoking cessation interventions for patients with cancer-related pain.

The results of this study should be interpreted with limitations in mind. First, our cross-sectional sample was drawn from a single institution and only included the breast cancer population and may not be generalizable to other populations or institutions. Second, our sample was drawn from secondary data not collected for the purposes of our study. This limits the inclusion of other variables that may impact the opioid-prescribing behaviors of oncologists, potentially resulting in bias. For instance, alcohol status, inappropriate findings on prescription drug monitoring systems, and inappropriate findings on urine drug screens could potentially be confounding the association between smoking status and risky opioid prescribing. However, the impact of such variables would still most likely suggest that oncologists have a heightened awareness of opioid-related harm. In other words, smoking status may be a marker for other factors that suggest higher risk, such as substance abuse, anxiety, and chemical and chemical coping (17,19,24). If possible, other factors, such as aberrant behavior found on the prescription drug monitoring program and/or urine drug screens that portend to the risk of opioid-related harm should also be included in future studies to broaden the conclusions that can be drawn about the relationship between smoking status and opioid utilization patterns in cancer populations. Lastly, our study did not control for prescriptions that may have been written by other physicians, such as pain management specialists, as the result of a referral from an oncologist.

Conclusions

Prior studies assessing the relationship between smoking and opioid dose in cancer populations have found no difference based on smoking status. However, this cross-sectional study shows that nonsmoking status is associated with an increased odds of a prescription being written by an oncologist for ≥ 50 MME and ≥ 90 MME for breast cancer-related pain relative to current smokers. During a time of heightened awareness of opioid-related harm, as well as implementation of national prescribing guidelines, current smoking may be impacting how oncologists evaluate the need for opioids. Future studies that assess variation in opioid-prescribing patterns based on smoking status in patients with cancer-related pain are warranted.

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