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Association between long-term NSAID use and opioid abuse among patients with breast cancer

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ABSTRACT

Background: Improving survival rates among patients with breast cancer has been associated with an increase in the prevalence of co-morbidities like cancer-related pain. Opioids are an important component in the management of pain among these patients. However, the progression from judicious use to abuse defeats the aim of pain control. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first step in cancer-related pain management. Due to their anti-inflammatory, anti-neoplastic and neuroprotective properties, NSAIDs have been shown to reduce the risk of progression of certain cancers including breast cancers. In this study, we assessed whether an association exists between long-term NSAID use and opioid abuse among breast cancer survivors. We also explored the relationship between long-term NSAID use and inpatient mortality and length of stay (LOS).

Methods: Using ICD-9-CM codes, we identified and selected women aged 18 years and older with breast cancer from the National Inpatient Sample. Our primary predictor was a history of long-term NSAID use. Multivariable regression models were employed in assessing the association between long-term NSAID use and opioid abuse, inpatient mortality and LOS.

Results: Among 170,644 women with breast cancer, 7,838 (4.6%) reported a history of long-term NSAID use. Patients with a history of long-term NSAID use had lower odds of opioid abuse (adjusted odds ratio (aOR) 0.53; 95% CI [0.32–0.88]), lower in-hospital mortality (aOR 0.52; 95% CI [0.45–0.60]) and shorter LOS (7.12 vs. 8.11 days).

Discussion: Further studies are needed to understand the underlying mechanism of the association between long-term NSAID use and opioid abuse.

Background

Although the incidence of breast cancer continues to increase, the mortality rate among patients with breast cancer has steadily declined over the past 30 years due to improved disease detection and treatment options [1]. The 2018 estimate for new cases of breast cancer was 266,120 with an 89.7% overall five-year survival rate between 2008 and 2014 [2]. Better survival indices increase the likelihood that survivors will report cancer-related pain as a complication of surgical treatment [3,4], chemotherapy [5], radiotherapy [4] or advanced disease, potentially leading to a growing population requiring pain management [6].

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About 54% of the estimated 3418,124 breast cancer patients in the United States experience cancer-related pain [2,7]. The widely adopted WHO 1996 guidelines for cancer pain management recommends a stepwise approach for analgesic pharmacotherapy [8] and is reported to provide pain relief to 70–90% of patients [9]. The guidelines recommend as a first step, the use of non-opioids such as NSAIDs with or without an adjuvant (e.g. corticosteroids, psychotropics) for mild pain. Adjuvant drugs serve to enhance the analgesic effect of standard treatment, treat medication side effects or comorbid conditions. In the event of persistent pain or increased severity, the WHO recommends the addition of an opioid analgesic [8]. Despite the potent pain-relieving effect of opioids, the progression from appropriate use to dependence and abuse presents serious risks with overall poor outcomes. Opioid abuse is not a new occurrence but in the past decade, has become a worsening public health problem [10].

Current evidence regarding the long-term benefits of NSAIDs to treat pain in cancer patients, though limited, show benefits [11]. Chronic use of NSAIDs has been shown to improve survival in cancer patients through its anti-inflammatory properties [12–14]. NSAIDs, in addition to their analgesic effects, have been shown to have anti-neoplastic properties by inhibiting tumor growth, [15] and reducing the risk of developing certain cancers [16] including breast cancer [17]. They are frequently used in the management of various types of cancer pain, either alone or in combination with opioids [18]. Additionally, NSAID use has been shown to reduce the requirements for opioids with up to 50% decrease in the need for morphine administration noted [19–21]. Given the multiple benefits of NSAIDs highlighted above, we sought to determine whether a relationship exists between long-term NSAID use and opioid abuse among women with breast cancer. Additionally, we evaluated the impact of long-term NSAID use on secondary outcomes, specifically inpatient mortality and LOS.

Methods

Data source and study population

We conducted a retrospective study using secondary de-identified data from the 2007 to 2014 National Inpatient Sample (NIS). The NIS is a database component of the Healthcare Cost and Utilization Project (HCUP) administered by the Agency for Healthcare Research and Quality (AHRQ). The NIS database is the largest publicly available all-payer inpatient healthcare database in the US and consists of discharge records from NIS participating hospitals, representing over 7 million unweighted and 35 million weighted annual inpatient hospital stays [22,23]. As the NIS is a public use database, our study did not require an IRB approval.

We included all female patients with a primary diagnosis of breast cancer admitted and discharged from US hospitals between January 1st, 2007 and December 31st, 2014 represented in the NIS. Males and patients younger than 18 years were excluded ($n = 170,644$) (Supplemental Fig. 1). Inpatient stays were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes [24] (Supplemental Table 1). Previous studies have employed the same ICD-9-CM codes used in selecting this population sub-group [25–28].

Measures

Our primary outcome was opioid abuse status. Opioid abuse was defined using ICD-9 codes for dependent opioid use (304.0) and non-dependent opioid use (305.5). The primary predictor of interest was long-term NSAID use. Inpatient mortality and LOS were secondary outcomes. We extracted records on demographics (patient and hospital level) including race/ethnicity (white, black, Hispanic, other), primary payer (Medicare, Medicaid, private insurance, self-pay, other), income quartile of patient's zip code, and hospital region (northeast, midwest/northcentral, south, west). Other covariates selected were patient baseline characteristics (nonopioid substance abuse, non-cancer related pain, past surgical history, psychosocial stress, anxiety, history or long-term use of steroids, chemotherapy or immunotherapy, Charlson/Deyo comorbidity index).

The demographic variables and secondary outcomes were available and defined in the NIS. Opioid abuse, long-term NSAID use, as well as baseline characteristics, were identified and defined using ICD-9-CM diagnosis codes (Supplemental Table 1).

Statistical analysis

Appropriate discharge weights provided by the NIS for estimate adjustments were used in our analysis to ensure accuracy and to provide nationally representative adjustments. We adopted HCUP recommendations in our analysis to account for the complex NIS design.

We conducted descriptive analyses for our study variables. We computed means and standard deviations with 95% CI for age, LOS and Charlson/Deyo comorbidity score by long-term NSAID use status.

For our categorical variables, using Rao Scott design adjusted chi-square statistics, we stratified our study characteristics by long-term NSAID status. Study variables across the levels of long-term NSAID use were reported as percentages with associated p-values. We assessed the effect of long-term NSAID use on our outcomes by computing crude and adjusted odds and mean ratios from univariable and multivariable regression analyses [29]. We constructed three multivariable regression models representing three outcomes: opioid abuse, inpatient mortality, and length of stay. Opioid abuse and inpatient mortality were analyzed using PROC SURVEY LOGISTIC under a generalized logit function. We employed PROC GENMOD with log link function in the regression analysis of LOS. A negative binomial distribution was specified to account for overdispersion in the count variable, LOS.

All analyses were performed using SAS v9.4 [Statistical Analysis System, Version 9.4, SAS Institute Inc, Cary, NC] with statistical significance set at 95% CI and p-value at <0.05, two-tailed.

Results

Distribution of study characteristics by long-term NSAID use

The mean age of patients of the sample was 62.1 years (SD $\pm$ 14.36) with an average LOS of 4.36 days (SD $\pm$ 5.47). The proportion of patients with long-term NSAID use was 4.6% ($n = 7838$). Among patients with long-term NSAID use, 2% had cancer-related pain; about 30% and 0.2% used and abused opioids, respectively. Slightly more than two-thirds of those with long-term NSAID use were white; nearly 70% were on Medicare, and 12% had a past surgical history. Using median household income quartiles for the patients' ZIP code as a proxy for socioeconomic status, we observed a similar distribution of income across the four categories. Few patients had symptoms of depression and anxiety. Table 1 shows the distribution of study characteristics by long-term NSAID use.

Association between long-term NSAID use and opioid abuse

Table 2A shows the results of the multivariable logistic regression model comparing long term NSAID use and opioid abuse. We found 46% lower odds of opioid abuse among patients with a history of long-term use of NSAIDs compared to patients without a history of long-term use (aOR 0.53; 95% CI [0.32–0.88]). The association between long-term NSAID use and opioid abuse was significant with a 3-fold increased odds of opioid abuse among breast cancer patients with cancer-related pain compared to those without cancer-related pain (aOR 2.96; 95% CI [2.34–3.74]).

The odds of opioid abuse were found to be lower with increasing age (aOR 0.96; 95% CI [0.95–0.96]) and among patients residing in ZIP

Table 1
Study characteristics by Long-term NSAID Use.

Study characteristics	No Long-term NSAID Use, % (n = 162,806) 95.41%	Long-term NSAID Use, % (n = 7,838) 4.59%	p-value
Age(years)*	**61.71 (0.09)**	**70.36 (0.15)**	
Length of Stay(days)*	**4.39 (0.02)**	**3.98 (0.05)**	
Charlson-Deyo Score*	**9.39 (0.01)**	**9.33 (0.03)**	
Race/ Ethnicity¶			<.0001
White	69.31	76.15	
Black	16.33	14.1	
Hispanic	8.4	5	
Other	5.97	4.76	
Insurance type			<.0001
Medicare	44.73	68.64	
Medicaid	12.69	6.34	
Private Insurance	38.39	22.59	
Self-pay/ Uninsured	1.73	0.9	
Others	2.46	1.53	
Median Household Income for ZIP code			<.0001
Less than $39,000	25.47	26.57	
$39,000-$47,999	23.4	25.8	
$48,000-$62,999	24.89	25.07	
Above $63,000	26.24	22.55	
Hospital Region			<.0001
Northeast	22.66	16.65	
Midwest/Northcentral	19.01	25.57	
South	38.66	37.1	
West	19.67	20.68	
Opioid Abuse			0.0053
No	99.61	99.82	
Yes	0.39	0.18	
Died			<.0001
No	95.97	97.82	
Yes	4.03	2.18	
Opioid Use			<.0001
No	91.19	72.74	
Yes	8.81	27.25	
Cancer Related Pain			<.0001
No	96.08	97.78	
Yes	3.92	2.22	
Long-term Use of Steroids, Chemotherapy or Immunotherapy			0.0002
No	94	92.87	
Yes	6	7.13	
Depression			<.0001
No	90.14	87.89	
Yes	9.86	12.11	
Anxiety			<.0001
No	90.28	88.55	
Yes	9.72	11.45	
Psychosocial stress			0.0991
No	99.59	99.72	
Yes	0.41	0.28	
Past Surgical History			<.0001
No	95.25	88.34	
Yes	4.75	11.66	
Non-Cancer Related Pain			<.0001
No	97.32	96.11	
Yes	2.68	3.89	
Other Substance Abuse			<.0001
No Substance Abuse	80.41	69.77	
Non-dependent Other substance Abuse	11.44	20.83	
Dependent Other substance Abuse	8.16	9.4	

* Mean (Standard Error of Mean in parenthesis)
¶ Categorical variables reported as percentage

codes with the highest income quartile compared to the lowest income quartile (aOR 0.76; 95%CI [0.6–0.97]).

We observed higher odds of opioid abuse among patients with dependent non-opioid substance abuse (aOR 5.78; 95% CI [4.85–6.9]) compared to patients without dependent substance abuse. Similarly, odds of abuse were higher among subjects with non-dependent non-opioid substance abuse (aOR 2.33; 95% CI [1.9–2.87]) compared to subjects without a history of non-dependent non-opioid substance abuse. In addition, significantly higher odds were found among patients with depression, anxiety disorder, and psychosocial stress. The odds of opioid abuse were not statistically different between the levels of past surgical history.

Table 2A
Crude and Adjusted Odds Ratios for Opioid Abuse among hospitalized patients with Breast cancer.

Effect	cOR[a]	aOR[b]	(aOR 95%	CI)	aOR pvalue
Long-term Current NSAID Use	0.46	**0.53**	0.32	0.88	0.0148
Age	0.96	**0.96**	0.95	0.96	<.0001
Charlson/Deyo Comorbidity Index	1.04	**1.01**	0.99	1.03	<.0001
Cancer Related Pain	4.39	**2.96**	2.34	3.74	<.0001
Depression	2.1	**1.39**	1.13	1.7	0.0016
Long-term Current Use of Steroids, Chemotherapy or Immunotherapy	1.54	**1.12**	0.86	1.47	0.3961
Non-Cancer Related Pain	6.78	**4.28**	3.44	5.31	<.0001
Anxiety	2.52	**1.45**	1.2	1.75	0.0002
Psychosocial	13.51	**5.16**	3.55	7.5	<.0001
Socioeconomic Status					
Zip income $39,000-$47,999 vs Less than $39,000	0.8	**0.96**	0.78	1.17	0.6658
Zip income $48,000-$62,999 vs Less than $39,000	0.8	**1.01**	0.82	1.23	0.9584
Zip income Above $63,000 vs Less than $39,000	0.51	**0.76**	0.6	0.97	0.0247
Hospital Region					
Midwest/Northcentral vs Northeast	0.91	**0.64**	0.49	0.83	0.0008
South vs Northeast	0.82	**0.61**	0.48	0.77	<.0001
West vs Northeast	1.6	**1.45**	1.15	1.83	0.0016
Race/Ethnicity					
Hispanic vs Black	0.61	**0.56**	0.4	0.78	0.0006
Other race vs Black	0.4	**0.5**	0.32	0.78	0.0019
White vs Black	0.56	**0.69**	0.57	0.84	0.0002
Insurance type					
Medicaid vs Private Insurance	5.07	**2.65**	2.11	3.32	<.0001
Medicare vs Private Insurance	1.35	**2.38**	1.86	3.05	<.0001
Other/Free vs Private Insurance	1.53	**1.37**	0.8	2.33	0.2501
Self-pay vs Private Insurance	3.11	**2.27**	1.49	3.48	0.0002
Other Substance abuse					
Dependent Other Substance Abuse vs No Substance Abuse	9.15	**5.78**	4.85	6.9	<.0001
Non-dependent Other Substance Abuse vs No Substance Abuse	2.5	**2.33**	1.9	2.87	<.0001
Past Surgical History	0.66	**0.82**	0.56	1.22	0.3296

[a] cOR Crude Odds Ratio
[b] aOR Adjusted Odds Ratio

Association between long-term NSAID use and inpatient mortality

Although the odds of in-hospital mortality were 51% higher among breast cancer patients with cancer-related pain (aOR 1.51; 95% CI [1.39–1.65]), we also found in-hospital mortality to be 48% lower (aOR 0.52; 95% CI [0.45–0.60]) among those with history of long-term use of NSAIDs Table 2B.

No significant association with inpatient mortality was found among patients with a diagnosis of opioid abuse, anxiety disorder, and psychosocial stress; however, the odds of mortality were increased for depression.

Table 2B
Crude and Adjusted Odds Ratios for Inpatient mortality among Hospitalized patients with Breast cancer.

Effect	cOR[a]	aOR[b]	(aOR 95% CI)		aOR p value
Age	1.02	**1.03**	1.02	1.03	<.0001
Charlson/Deyo Comorbidity Index	1.3	**1.3**	1.27	1.31	<.0001
Opioid Abuse	0.83	**0.91**	0.6	1.37	0.6336
Long-term Current NSAID Use	0.53	**0.52**	0.45	0.6	<.0001
History or Long-term Current Use of Steroids, Chemotherapy or Immunotherapy	0.95	**0.93**	0.84	1.02	0.134
Cancer Related Pain	0.43	**1.51**	1.39	1.65	<.0001
Non-Cancer Related Pain	0.97	**0.92**	0.8	1.06	0.2299
Depression	0.7	**0.72**	0.66	0.78	<.0001
Anxiety	0.85	**0.97**	0.9	1.06	0.4927
Psychosocial	0.54	**0.74**	0.465	1.179	0.2052
Socioeconomic Status					
zip income $39,000-$47,999 vs Less than $39,000	0.93	**1**	0.93	1.06	0.9084
zip income $48,000-$62,999 vs Less than $39,000	0.82	**0.9**	0.85	0.97	0.0064
zip income Above $63,000 vs Less than $39,000	0.78	**0.91**	0.84	0.98	0.0089
Hospital Region					
Midwest/Northcentral vs Northeast	1.01	**0.95**	0.865	1.04	0.2328
South vs Northeast	1.15	**1.06**	0.98	1.16	0.1495
West vs Northeast	1.03	**1.02**	0.93	1.12	0.6371
Race					
Hispanic vs Black	0.8	**0.86**	0.78	0.95	0.0032
Other race vs Black	0.77	**0.89**	0.8	1	0.0435
White vs Black	0.74	**0.86**	0.81	0.92	<.0001
Insurance type					
Medicaid vs Private Insurance	1.25	**1.07**	0.99	1.17	0.0845
Medicare vs Private Insurance	1.25	**0.67**	0.62	0.72	<.0001
Other/Free vs Private Insurance	2.22	**1.87**	1.62	2.15	<.0001
Self-pay vs Private Insurance	2.17	**1.75**	1.45	2.12	<.0001
Other substance Abuse					
Dependent Other Substance Abuse vs No Substance Abuse	0.64	**0.66**	0.6	0.73	<.0001
Non-dependent Other Substance Abuse vs No Substance Abuse	0.72	**0.71**	0.66	0.77	<.0001
Past Surgical History	0.9	**0.76**	0.68	0.84	<.0001

[a] cOR Crude Odds Ratio
[b] aOR Adjusted Odds Ratio

Association between long-term NSAID use and LOS

Patients with a history of long-term NSAID use had significantly shorter average hospital LOS compared to those with no history of long-term NSAID use: 7.12 days (95% CI [6.62–7.66]) vs 8.11 days (95% CI [7.55–8.7]) corresponding to a 12% reduction in average LOS (aMR 0.88; 95% CI [0.86–0.90]).

Conversely, patients with cancer-related pain had a 31% increase in average LOS (aMR 1.31; 95% CI [1.27–1.35]) spending 8.69 days (95% CI [8.06–9.36]) on the average compared to 6.65 days (95% CI [6.20–7.13]) spent by patients with no cancer-related pain diagnosis.

The average LOS among patients with opioid abuse was 8.21 days (95% CI [7.45–9.03]) and 7.03 days (95% CI [6.60–7.49]) among those with no history of opioid abuse. The average LOS among patients with opioid abuse was 17% higher relative to patients with no reported opioid abuse (aMR 1.17;95% CI [1.08–1.26]) Table 2C.

Discussion

Our study highlights the benefits of long-term NSAID use with respect to opioid abuse and adds to the limited number of studies exploring this relationship among hospitalized patients with breast cancer. Our findings suggest that long-term NSAID use is protective against opioid abuse. Even after adjusting for several covariates, this association remained significant. In addition, we found similar associations between long-term NSAID use and hospitalization outcomes such as inpatient mortality and LOS.

Table 2C
Mean, crude and adjusted mean ratios for length of stay among hospitalized patients with breast cancer.

Effect	Mean (days)	cMR	aMR	(95% CI)	*P* value
Long-term current NSAID use	7.12			6.62-7.66	<0.0001
No Long-term current NSAID use	8.11			7.55-8.7	<0.0001
Long-term current NSAID use vs no long-term current NSAID use		0.88	0.88	0.86-0.9	<0.0001
Opioid abuse	8.21			7.45-9.03	<0.0001
No opioid abuse	7.03			6.6-7.49	<0.0001
Opioid abuse vs no opioid abuse		1.28	1.17	1.08-1.26	0.0001
Cancer related pain	8.69			8.06-9.36	<0.0001
No cancer related pain	6.65			6.2-7.13	<0.0001
Cancer related pain vs no cancer related pain		1.53	1.31	1.27-1.35	<0.0001

cMR Crude Mean Ratio.
aMR Adjusted Mean Ratio.

The anti-neoplastic [30] and neuroprotective effects [31,32] of NSAIDs as described in previous studies, may provide a biologically plausible and mechanistic explanation of the observed protective effect of NSAID use on opioid abuse risk. However, additional processes currently un-identified may be involved, warranting further studies to better understand this association as well as optimal dosing and duration in this population.

Compared to patients who were not on long-term NSAID use, those with a history of long-term NSAID use had lower inpatient mortality. This is not surprising as studies have documented improved cardiovascular risk factors among patients who were placed on long-term NSAIDs such as aspirin, and prognostic indices and survival in cancers including breast cancer, colorectal cancer and lung cancer [12,14,33,34]. A possible explanation could be linked to the fact that since pain suppresses immunity, and immunity is vital for protecting against cancer, pain relief would lead to improved survival [35,36]. Another possible explanation is that NSAIDs have antineoplastic properties through their inhibition of cyclooxygenase-2 enzyme (COX-2); there is evidence of an inverse relationship between COX-2 expression and tumor metastases [37].

We found that long-term NSAID use was associated with a shorter LOS. Our findings are consistent with other studies, which suggest that cancer-related pain (usually associated with advanced metastatic disease especially to the bone) increases the likelihood of patient referral for specialist treatments such as radiotherapy [35,38].

This study has several important limitations which directly relate to the data available in the NIS database. First, the NIS database employs ICD-9 codes, which makes it impossible to determine the source of the opioid abuse, in addition to the potential for misreporting of opioid use resulting from the variations in code accuracy across hospitals and state. Second, we cannot rule out residual confounding from unmeasured covariates such as characteristics of the breast tumor, duration of opioid use and type of opioid. However, we carried out a robust methodological analysis and adjusted for comorbidity indices, previous chemotherapy and radiotherapy, the presence of cancer and non-cancer related pain. In addition, using breast cancer-specific hospitalization, our findings may not be generalizable to patients with other forms of cancer pain. Despite these limitations, the strength of the study lies in the inclusion of a large number of hospitalizations from a large sociodemographic pool, addressing pertinent issues in pain management and

opioid abuse in an important subpopulation of cancer patients.

In conclusion, our assessment of the impact of long-term NSAID use on select health outcome indices among women with breast cancer showed that long-term NSAID use was associated with lower opioid abuse, lower inpatient mortality and reduced hospital LOS. In addition to addressing existing knowledge gaps, this study also lends to the limited body of evidence on the role of NSAIDs in the management of cancer pain. We hope this study will contribute to management guidelines as well as policies aimed at addressing the epidemic of opioid abuse in the US.

Declarations of interest

The authors declare no conflict of interest.

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Supplementary materials

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