Original Article

The Association of Prescription Opioid Use With Incident Cancer: A Surveillance, Epidemiology, and End Results-Medicare Population-Based Case-Control Study

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BACKGROUND: Cancer is the second leading cause of death globally, and researchers seek to identify modifiable risk factors Over the past several decades, there has been ongoing debate whether opioids are associated with cancer development, metastasis, or recurrence. Basic science, clinical, and observational studies have produced conflicting results. The authors examined the association between prescription opioids and incident cancers using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. A complex relation was observed between prescription opioids and incident cancer, and cancer site may be an important determinant. **METHODS:** By using linked SEER cancer registry and Medicare claims from 2008 through 2013, a case-control study was conducted examining the relation between cancer onset and prior opioid exposure. Logistic regression was used to account for differences between cases and controls for 10 cancer sites. **RESULTS:** Of the population studied (n = 348,319), 34% were prescribed opioids, 79.5% were white, 36.9% were dually eligible (for both Medicare and Medicaid), 13% lived in a rural area, 52.7% had ≥1 comorbidity, and 16% had a smoking-related diagnosis. Patients exposed to opioids had a lower odds ratio (OR) associated with breast cancer (adjusted OR, 0.96; 95% CI, 0.92-0.99) and colon cancer (adjusted OR, 0.90; 95% CI, 0.86-0.93) compared with controls. Higher ORs for kidney cancer, leukemia, liver cancer, lung cancer, and lymphoma, ranging from lung cancer (OR, 1.04; 95% CI, 1.01-1.07) to liver cancer (OR, 1.19; 95% CI, 1.08-1.31), were present in the exposed population. **CONCLUSIONS:** The current results suggest that an association exists between prescription opioids and incident cancer and that cancer site may play an important role. These findings can direct future research on specific patient populations that may benefit or be harmed by prescription opioid exposure. ***Cancer* 2021;127:1648-1657**. © *2020 American Cancer Society*.

KEYWORDS: cancer, Medicare, opioids, prescription opioids, Surveillance, Epidemiology, and End Results (SEER)-Medicare.

INTRODUCTION

One in 6 deaths is attributed to cancer, making it the second most common cause of death worldwide.[1] Over 18 million new cancer cases and approximately 9.6 deaths and were reported in 2018.[2] Understanding modifiable processes that affect cancer development is fundamental for prevention. Several known, lifestyle-related, modifiable risk factors for cancer development account for approximately 40% of incident cancer cases and include smoking, alcohol, obesity, ultraviolet radiation from sun exposure, and a sedentary lifestyle.[3]

Opioid use is a potentially modifiable risk factor that may affect cancer development. Over the past several decades, animal, in vitro, clinical, and observational studies have demonstrated both protective and harmful effects of opioid administration on cancer development, metastasis, and recurrence. There are limited data from prospective clinical trials to address this issue, in part because of complexity, cost, and ethical considerations. To understand the potential role opioids play in the development of cancer, we analyzed Surveillance, Epidemiology, and End Results (SEER)-Medicare–linked data to examine whether a clinically significant modifiable risk factor, the use of prescription opioids, is associated with incident cancer.

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This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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MATERIALS AND METHODS

Data Sources

Data from the National Cancer Institute's SEER program (https://seer.cancer.gov/data/; accessed February 9, 2019) and from the 5% random-sample Medicare Surveillance Summarized Denominator file were obtained for the years 2007 through 2013. The SEER program is a population-based tumor registry that identifies incident cancers and patient survival in the United States.[4] The SEER cancer registry collects clinical, demographic, and cause of death information. The SEER data are linked to Medicare files based on name, age, date of birth, Social Security number, and sex (http://healthservices.cancer.gov/seermedicare/; accessed April 23, 2019). Approximately 94% of patients in SEER registries are matched to Medicare enrollment records. The percentage of Medicare Part D beneficiaries has increased since inception on January 1, 2006, from 56% of Medicare beneficiaries enrolled in Medicare Part D in 2007 to 68% in 2013 (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMSProgramStatistics/2013/Enrollment.html#Medicare%20Part%20D%20Enrollment; accessed March 8, 2019).

Study Population

The study included patients who were diagnosed with (cases) or without (controls) 1 of 10 incident cancers between January 2008 and December 2013. Incident cancer cases included in the SEER database were collected from 17 cancer registries (Atlanta, Connecticut, Detroit, Greater California, Greater Georgia, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Rural Georgia, San Francisco, San Jose, Seattle, and Utah). Cancer sites were selected based on those with the highest incidence in the United States, peer-reviewed publications suggesting cancer development from opioid use, and theoretical risk suggested in the basic science literature. The 10 selected cancer sites included bladder, brain, breast, colorectal, esophageal, kidney, leukemia, liver, lung, and lymphoma.

Cases and Controls

Cases were defined as patients whose incident cancer was diagnosed between 2008 and 2013 who were identified from 1 of the 10 cancer site-specific SEER-Medicare Patient Entitlement and Diagnosis Summary Files. A case was included in the study if they were continuously enrolled in Medicare Parts A, B, and D for 1 year before their diagnosis year (2007-2012), aged ≥65 years, with nonmissing sex data, and no previous cancer diagnosis. Because the first possible year of enrollment would be 2007, cases diagnosed during 2008 through 2013 were aged ≥66 years (Fig. 1).

Controls were eligible for the study if the patient was aged ≥65 years, continuously enrolled in Medicare Parts A, B, and D for at least 1 year, and with nonmissing sex data between 2007 and 2012. The controls were selected from the pool of noncancer cases identified from the random 5% sample of Medicare beneficiaries in the Medicare Surveillance Summarized Denominator file (Fig. 1).

Patient Characteristics

Patient characteristics included age at calendar year categorized into 5-year age groups (66-70, 71-75, 76-80, 81-85, and ≥86 years), sex (men/women), calendar year (2008-2013), race (categorized as white, black, and other race; other race included Asian, Hispanic, North American Native, other, and unknown), SEER registry (listed above), geographic region (urban/rural), dual eligibility (no/yes), comorbidity index (grouped as 0 [none], 1, and ≥2) based on the National Cancer Institute Comorbidity Index, and a smoking-related variable (smoking, no/yes). Patients jointly enrolled in Medicare and Medicaid who were eligible to receive benefits from both programs were defined as *dual-eligible*. Indicators for smoking were based on *International Statistical Classification of Diseases and Health-Related Problems*, 9th edition, codes for tobacco use disorder, including those related to chronic obstructive pulmonary disease and allied conditions (490.x-492.x, 494.x-496.x), except asthma, personal history of tobacco abuse (V15.82), and nondependent tobacco use disorder (305.1).[5] The comorbidity index was derived from claims during the exposure year using the National Cancer Institute comorbidity index Klabunde adaptation to the Charlson comorbidity score.[6]

Length of Exposure Time

The period preceding cancer onset during which the exposure (prescription opioid use) could alter the risk was defined as the *exposure window*. By design, opioid use was only measured during the exposure year. The length of time for the exposure window of 12 months was determined by the minimum time during which the presence of the exposure (prescription opioid use) could alter the risk of a patient with cancer whose diagnosis date was January 1, 2008. Exposure year was defined as 12 months of continuous enrollment in Medicare Parts A, B, and D for the years 2007 through 2012. For cases, the exposure year was the year preceding the cancer diagnosis year. Calendar year was defined as the year after the exposure year.

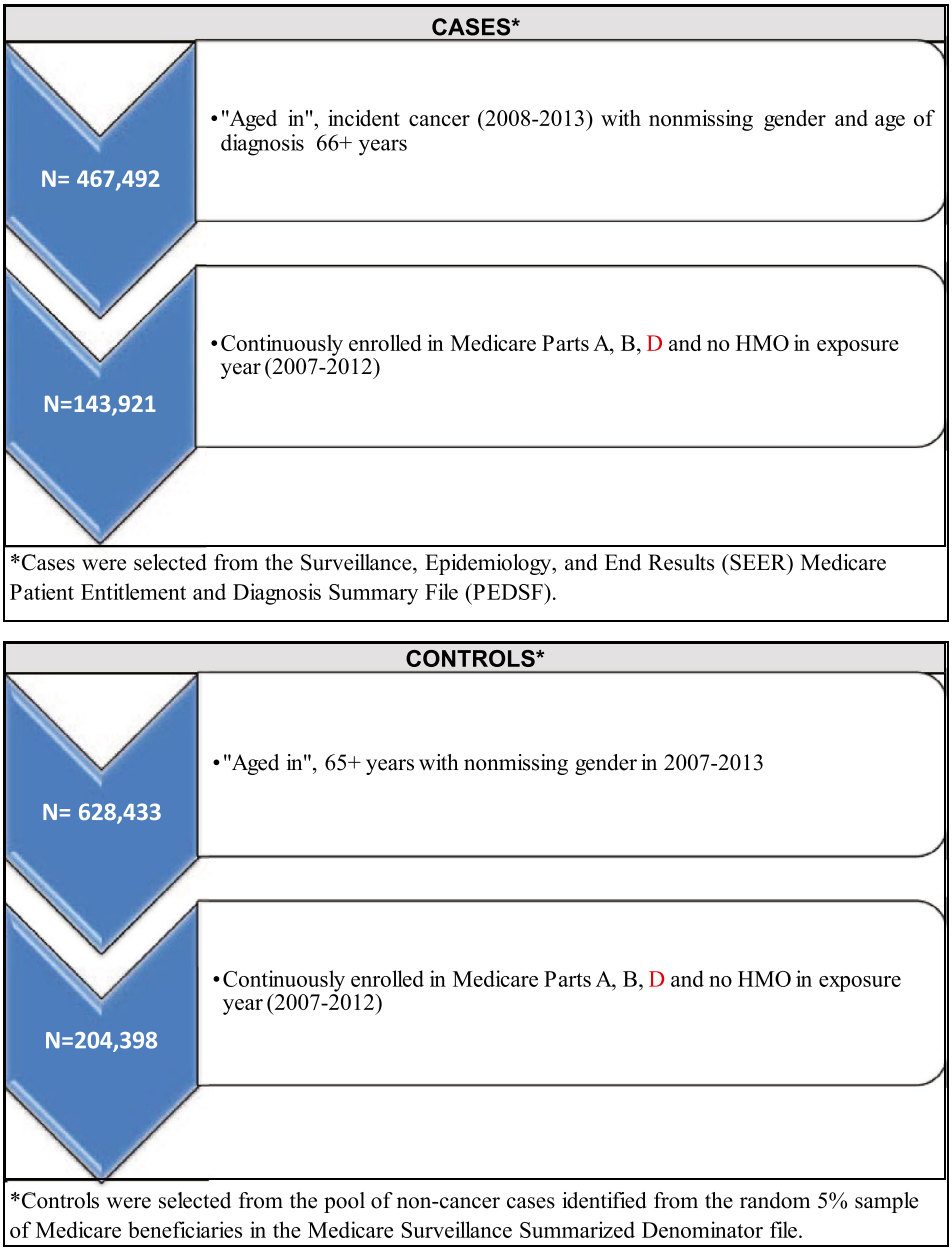

Figure 1. Case-control eligibility criteria for the current study are illustrated.

Exposure

Opioid use was defined as the presence or absence of any prescription opioids in the Medicare Part D Prescription Drug event files. The exposure year was used to search for any prescription opioid use from 1 of the 13,661 prescription opioids listed as national drug codes in the Centers for Disease Control and Prevention resource files (https://www.cdc.gov/drugoverdose/data-files/cdc_mme_table_sept2017.sas7bdat; accessed October 26, 2018).

Statistical Analysis

Cancer cases were frequency matched to the controls by age group, sex, and calendar year. By matching on calendar year, the controls reflected the underlying population distribution of the cases. Frequency distributions (numbers and percentages) for the cancer cases and controls by prescription opioid use and patient characteristics are reported. In addition, prescription opioid distributions by patient characteristics were determined. Stratification was

used to reveal the possible effect modification between exposure (opioid use), outcome (cancer), and a smoking-related diagnosis (smoking). Smoking was a confounder, and we adjusted by including this factor in the multivariate models. To determine whether there was an association between prescription opioids and the development of cancer, multivariable logistic regression models adjusting for patient characteristics were conducted. Model results are reported as odds ratios (ORs) and 95% CIs. Cancer site-specific models examined the effect of prescription opioid use on each of the 10 cancers. Analyses were conducted in SAS (version SAS 9.4 System Options, 2nd edition; SAS Institute Inc).

RESULTS

Of the 348,319 patients who met the eligibility criteria, 143,921 (41.3%) were patients with cancer and 204,398 (58.7%) were controls. The majority (79.5%) of the overall study population race was white, 13% lived in a rural area, 36.9% were dually eligible for Medicare and Medicaid, 52.7% had at least 1 comorbidity, and 16% had smoking-related diagnoses (Table 1). Compared with controls, cases were more likely to be white (81.8% vs 77.8%), to live in a rural area (13.7% vs 12.4%), to have more than 1 comorbidity (30.3% vs 26.6%), and to have a smoking-related diagnosis (20.7% vs 12.6%).

Overall, 34% of the study's Medicare population had a claim for prescription opioids (35.2% among cases, 33.2% among controls). An increase in prescription opioid use was observed among women, those who were black, those with a rural residential status, those who were dually eligible, those with more comorbid conditions, and those who had a smoking-related diagnosis compared with individuals who had no prescription opioid use (Table 2). Patients with a smoking-related diagnosis were more likely to receive prescription opioids (53% vs 31%) and to develop cancer (50% vs 31%; data not shown).

The use of prescription opioids was associated with a significant increase in incident cancers for patients matched on age, sex, and calendar year (OR, 1.10; 95% CI, 1.09-1.12). The results of the fully adjusted analyses indicated that exposure to prescription opioids did not increase the odds of cancer incidence (OR, 1.01; 95% CI, 0.99-1.03). However, an analysis of cancer site in relation to opioid use varied from reduced odds, to no impact, to increased odds, depending on cancer site. Distribution of the 10 incident cancer sites were as follows: bladder (n = 11,623; 8%), brain (n = 2678; 2%), breast (n = 34,123;

TABLE 1. Overall and Cancer Status (Cases/Controls) Distributions by Prescription Opioid Use and Patient Characteristics Among a Surveillance, Epidemiology, and End Results-Medicare Population (N = 348,319) Diagnosed With and Without an Incident Cancer (2008-2013)[a]

	No. (%)		
Variable	Total, N = 348,319 (100.0)	Cases, N = 143,921 (41.3)	Controls, N = 204,398 (58.7)
Prescription opioid use			
No	229,860 (66.0)	93,274 (64.8)	136,586 (66.8)
Yes	118,459 (34.0)	50,647 (35.2)	67,812 (33.2)
Patient characteristics[b]			
Age, y			
66-70	109,709 (31.5)	35,649 (24.8)	74,060 (36.2)
71-75	76,552 (22.0)	34,776 (24.2)	41,776 (20.4)
76-80	62,924 (18.0)	29,692 (20.6)	33,232 (16.3)
81-85	50,688 (14.6)	23,932 (16.6)	26,756 (13.1)
≥86	48,446 (13.9)	19,872 (13.8)	28,574 (14.0)
Sex			
Women	222,716 (63.9)	91,730 (63.7)	130,986 (64.1)
Men	125,603 (36.1)	52,191 (36.3)	73,412 (35.9)
Calendar year			
2008	56,974 (16.4)	23,233 (16.1)	33,741 (16.5)
2009	57,745 (16.6)	23,355 (16.2)	34,390 (16.8)
2010	57,300 (16.5)	23,233 (16.1)	34,067 (16.7)
2011	57,457 (16.5)	23,390 (16.3)	34,007 (16.7)
2012	58,560 (16.8)	24,494 (17.0)	34,066 (16.7)
2013	60,283 (17.3)	26,216 (18.2)	34,067 (16.7)
Race			
White	276,813 (79.5)	117,793 (81.8)	159,020 (77.8)
Black	29,088 (8.4)	11,804 (8.2)	17,284 (8.5)
Other[c]	42,418 (12.2)	14,324 (10.0)	28,094 (13.7)
SEER registry			
Connecticut	21,355 (6.1)	8352 (5.8)	13,003 (6.4)
Detroit	15,865 (4.6)	6949 (4.8)	8916 (4.4)
Iowa	23,225 (6.7)	10,717 (7.5)	12,508 (6.1)
Seattle	16,574 (4.8)	6827 (4.7)	9747 (4.8)
Los Angeles	28,852 (8.3)	11,148 (7.8)	17,704 (8.7)
Greater California	62,331 (17.9)	24,760 (17.2)	37,571 (18.4)
Kentucky	28,117 (8.1)	13,046 (9.1)	15,071 (7.4)
New Jersey	49,784 (14.3)	20,695 (14.4)	29,089 (14.2)
Greater Georgia	30,343 (8.7)	12,995 (9.0)	17,348 (8.5)
Other[d]	71,873 (20.6)	28,432 (19.8)	43,441 (21.3)
Urban/rural status			
Urban	302,903 (87.0)	124,179 (86.3)	178,724 (87.6)
Rural	45,059 (13.0)	19,716 (13.7)	25,343 (12.4)
Dual eligibility			
No	219,838 (63.1)	91,859 (63.8)	127,979 (62.6)
Yes	128,481 (36.9)	52,062 (36.2)	76,419 (37.4)
Comorbidity index			
0	164,807 (47.3)	62,940 (43.7)	101,867 (49.8)
1	85,501 (24.6)	37,359 (26.0)	48,142 (23.6)
≥2	98,011 (28.1)	43,622 (30.3)	54,389 (26.6)
Smoking			
No	292,620 (84.0)	114,053 (79.3)	178,567 (87.4)
Yes	55,699 (16.0)	29,868 (20.7)	25,831 (12.6)

Abbreviation: SEER, Surveillance, Epidemiology, and End Results program of the US National Cancer Institute.

[a]Cancer types included bladder, brain, breast, colon, esophagus, kidney, leukemia, liver, lung, and lymphoma.

[b]Urban/rural status was missing for n =357.

[c]Other race included unknown race (n = 987).

[d]Other registries included San Francisco, Hawaii, New Mexico, Utah, Atlanta, San Jose, Rural Georgia, and Louisiana.

TABLE 2. Prescription Opioid Use by Patient Characteristics Among a Surveillance, Epidemiology, and End Results-Medicare Population, N = 348,319

Patient Characteristics[a]	No. (%)	
	No Prescription Opioid Use, N = 229,860 (66.0%)	Prescription Opioid Use, N = 118,459 (34.0%)
Age, y		
66-70	72,636 (31.6)	37,073 (31.3)
71-75	50,280 (21.9)	26,272 (22.2)
76-80	41,410 (18.0)	21,514 (18.2)
81-85	33,379 (14.5)	17,309 (14.6)
≥86	32,155 (13.8)	16,291 (13.8)
Sex		
Women	142,059 (61.8)	80,657 (68.1)
Men	87,801 (38.2)	37,802 (31.9)
Calendar year		
2008	38,144 (16.6)	18,830 (15.9)
2009	37,661 (16.4)	20,084 (17.0)
2010	37,247 (16.2)	20,053 (16.9)
2011	37,774 (16.4)	19,683 (16.6)
2012	38,664 (16.8)	19,896 (16.8)
2013	40,370 (17.6)	19,913 (16.8)
Race		
White	181,472 (79.0)	95,341 (80.5)
Black	17,403 (7.6)	11,685 (9.9)
Other[b]	30,985 (13.5)	11,433 (9.7)
SEER registry		
Connecticut	15,243 (6.7)	5932 (5.0)
Detroit	10,016 (4.4)	5849 (4.9)
Iowa	16,061 (7.0)	7164 (6.1)
Seattle	10,823 (4.7)	5751 (4.9)
Los Angeles	19,950 (8.7)	8902 (7.5)
Greater California	40,315 (17.5)	22,016 (18.6)
Kentucky	16,659 (7.3)	11,458 (9.7)
New Jersey	36,450 (15.9)	13,334 (11.3)
Greater Georgia	17,048 (7.4)	13,295 (11.2)
Other[c]	47,115 (20.5)	24,758 (20.9)
Urban/rural status		
Urban	202,298 (88.1)	100,605 (85.0)
Rural	27,276 (11.9)	17,783 (15.0)
Dual eligibility		
No	153,138 (66.6)	66,700 (56.3)
Yes	76,722 (33.4)	51,759 (43.7)
Comorbidity index		
0	123,220 (53.6)	41,587 (35.1)
1	54,421 (23.7)	31,080 (26.2)
≥2	52,219 (22.7)	45,792 (23.8)
Smoking		
No	202,291 (88.0)	90,329 (76.3)
Yes	27,569 (12.0)	28,130 (23.8)

Abbreviation: SEER, Surveillance, Epidemiology, and End Results program of the US National Cancer Institute.
[a]Urban/rural status was missing for n =357.
[b]Other race included unknown race (n = 987).
[c]Other registries included San Francisco, Hawaii, New Mexico, Utah, Atlanta, San Jose, Rural Georgia, and Louisiana.

24%), colon (n = 24,540; 17%), esophagus (n = 2311; 2%), kidney (n = 6718; 5%), leukemia (n = 6725; 5%), liver (n = 4457; 3%), lung (n = 40,311; 28%), and lymphoma (n = 10,435; 7%). Patients who received prescription opioids had lower ORs associated with breast cancer (OR, 0.96; 95% CI, 0.92-0.99) and colon cancer (OR, 0.90; 95% CI, 0.86-0.93) (Fig. 2). Patients who were exposed to prescription opioids had higher ORs associated with kidney cancer, leukemia, liver cancer, lung cancer, and lymphoma, ranging from an OR of 1.04 (95% CI, 1.01-1.07) for lung cancer to an OR of 1.19 (95% CI, 1.08-1.21) for liver cancer (Fig. 2). Prescription opioid exposure was not associated with bladder, brain, or esophageal cancers.

Adjusted for patient characteristics, a subgroup analysis of the subpopulation of patients with breast and colon cancers and matched controls revealed lower odds of cancer among those who were prescribed prescription opioids

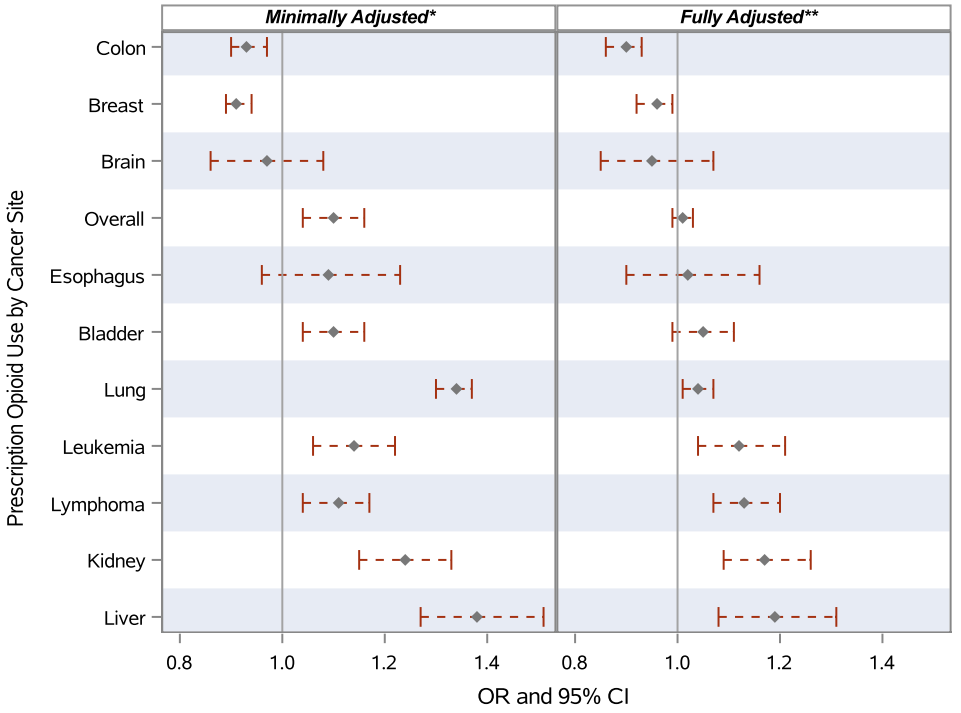

Figure 2. Odds ratios (ORs) and 95% CIs are illustrated for the association between cancer status (cases/controls; overall and by cancer site) and prescription opioid use with models that were minimally adjusted and fully adjusted for patient characteristics. *The model was minimally adjusted for age, sex, and calendar year. **The model was fully adjusted for age; sex; calendar year; race; Surveillance, Epidemiology, and End Results registry; urban/rural status; dual eligibility; comorbidity index; and smoking status.

(OR, 0.93; 95% CI, 0.91-0.95) (Fig. 3). Prescription opioid use was associated with a higher incidence of kidney cancer, liver cancer, lung cancer, leukemia, and lymphoma (OR, 1.08; 95% CI, 1.06-1.10) (Fig. 3). Adjustment by a smoking-related diagnosis did not significantly affect the development of colon or breast cancer in patients who received prescription opioids (OR, 1.03; 95% CI, 0.99-1.07), but it did have a strong, positive relation with patients who were diagnosed with cancers associated with the use of prescription opioids (OR, 2.44; 95% CI, 2.37-2.50) (Fig. 3).

DISCUSSION

Our current results suggest an association between prescription opioids and incident cancer that varies by cancer site. We examined 10 preselected cancer sites based on evidence published in the medical literature and observed a complicated relation between prescription opioid use and incident cancer. In both the crude and adjusted models, patients exposed to prescription opioids had a lower OR associated with breast and colon cancer but a higher OR for incident lung cancer, leukemia, lymphoma, renal cancer, and liver cancer. We did not find any association between prescription opioids and esophageal, brain, or bladder cancers in the adjusted models; however, an increased OR was noted in patients diagnosed with bladder cancer in the minimally adjusted model. Among patients who had a higher likelihood of incident cancer (lung cancer, leukemia, lymphoma, renal cancer, and liver cancer), an increased OR was noted in those who had a smoking-related diagnosis compared with those who had incident breast or colon cancer.

The controversy surrounding the effect opioids exert on cancer incidence has spanned several decades. Multiple biologic mechanisms have been proposed based on laboratory and clinical research that support and contradict the hypothesis that opioids affect cancer development, metastasis, and recurrence.

One theory suggests that opioids exert a direct positive or negative effect on cancer development, metastasis, and recurrence by binding to μ-opioid receptors on specific cancer cells. These μ-opioid receptors are present in lung cancer, breast cancer, neural tumors, leukemia, gastrointestinal cancers, and bladder cancers.[7-15] This theory is supported by research examining the effect of opioid antagonists on cancer. Janku et al reported an increased median overall survival in

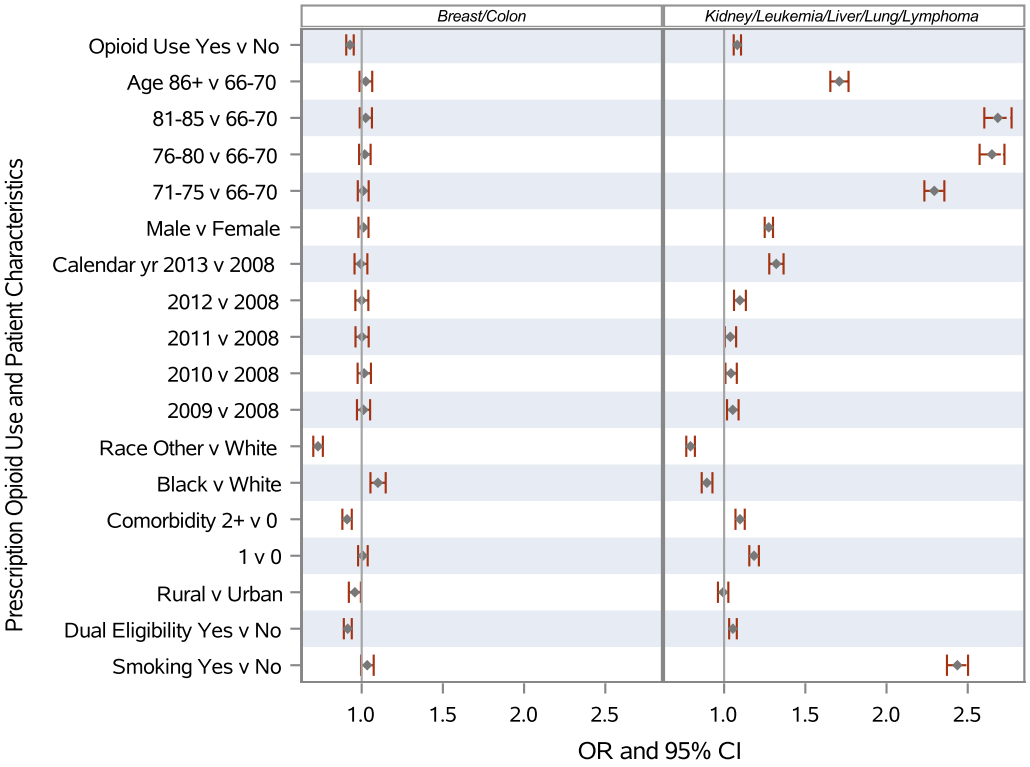

Figure 3. Odds ratios (ORs) and 95% CIs are illustrated for the association between cancer status (cases/controls) and prescription opioid use according to characteristics among subpopulations of patients in the Surveillance, Epidemiology, and End Results-Medicare database with breast cancer and colon cancer (n = 117,220) and with kidney cancer, leukemia, liver cancer, lung cancer, and lymphoma (n = 197,550).

patients with advanced cancer who received the opioid antagonist methylnaltrexone to treat opioid-induced constipation.[16] Bimonte and colleagues demonstrated that morphine increased tumor size in mice, and these effects were counteracted by the administration of naloxone.[17,18] Although those investigators reported a negative effect of opioids on cancer, other researchers have suggested that opioids may exert a protective effect. Friesen et al reported that the administration of methadone induced cell death in leukemia cells, including apoptosis-resistant and multidrug-resistant leukemia cells.[19] In addition, Maneckjee and Minna reported that methadone inhibited the growth of lung cancer cells, and this effect was reversed by the administration of naltrexone.[20] Our study suggests that these contradictory findings may result from various effects that opioids have on specific cancer sites.

These differences in cancer sites are not entirely apparent; however, other researchers have published similar results, although in different populations. Randall and colleagues reported that, in opioid-dependent individuals enrolled on a substitution therapy program in Australia, mortality from liver, lung, and anorectal cancer was higher; however, death from breast cancer was significantly lower than in the general population.[21] In a population-based study conducted in Denmark examining breast cancer recurrence, Cronin-Fenton et al observed that opioid use was not associated with breast cancer recurrence and that patients who received high-dose opioids had lower recurrence rates.[22] Several researchers have suggested that the increased numbers of opioid receptors and opioid requirements are associated with recurrence or decreased overall survival in patients with cancer.[23-27] Furthermore, several investigators have suggested targeting μ receptors on cancer cells as a possible adjunct for cancer treatment.[7,28]

In addition to the direct effects of opioids on cancer cells, the indirect effects of opioids on cancer development, recurrence, and metastasis have been postulated. Opioids exert immunosuppressive effects, particularly on natural killer cells, which are considered the first line of defense in cancer surveillance.[29-33] Investigators have suggested

that opioids negatively affect the immune system through several mechanisms, including impaired function of lymphocytes, neutrophils, and dendritic cells.[34-41] Another biologically plausible theory suggested is that opioids promote tumor angiogenesis and foster cancer occurrence by modulating the immune system through the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis.[18,42-46]

Several publications have reported an association between opioids, opium, and esophageal cancer.[47,48] Our current study did not demonstrate a significant effect of prescription opioids in patients diagnosed with esophageal cancer in the fully adjusted models. Interestingly, Du et al reported that high-dose intraoperative opioids were associated with more prolonged survival in patients who had squamous cell carcinoma of the esophagus but demonstrated no difference in those who had esophageal adenocarcinoma. Those authors suggested that opioids may exert different outcomes, depending on the type of histologic cancer.[49] Our study did not differentiate the cancers based on histology. We had relatively low numbers of patients diagnosed with esophageal cancer (n = 2311), and the numbers may be insufficient to demonstrate any significant finding.

Smoking is a known risk factor for cancer development and is considered a possible confounder in observational studies that should be addressed whenever possible. Stratification is used as an analytic tool used to reveal possible effect modification between exposure (opioid use), outcome (cancer), and a third characteristic (smoking), which may have a different relation with both the exposure and the outcome. We assessed both possible relations. The smoking-related diagnosis was a confounder, thus we adjusted by including this factor in the multivariate models. Patients who received 1 or more opioid prescriptions and had a smoking-related diagnosis demonstrated a significantly increased OR of kidney cancer, leukemia, lymphoma, liver cancer, and lung cancer, which contrasts with patients who had incident breast or colon cancer. Although these results are biologically plausible, they should be interpreted with caution because only patients with a smoking-related diagnosis are designated as smokers in our model.

There are several other limitations to our study. The use of Medicare Part D prescription opioid data does not include prescription opioid use from other sources, such as private insurance or the Veterans Administration. The database does not collect information on the use of nonprescription opioids or monitor opioid consumption. As is typical of observational studies, residual confounding is possible. Our study population was limited to Medicare patients aged >65 years, and these results may not be generalizable to younger populations. It is possible that the patient received an opioid prescription for a cancer that had not been diagnosed. There may be a temporal limitation of our research. For this study, we could have obtained different results if we had selected a different time of exposure. Finally, this study is subject to limitations of the SEER-Medicare database, including the incomplete coding of health conditions in the administrative data. Our findings suggest the need for large, population-based, longitudinal studies over many years that can reliably and validly ascertain both opioid use and cancer incidence, along with important covariates, such as smoking.

The clinical effect of opioids on cancer is a complex issue that is not well understood. It has been argued that studies focusing on the association or causal relation between opioids and cancer development have been conducted on animals, in vitro models, or in young, healthy volunteers and may not be clinically applicable to the general or at-risk populations. Our goal was to determine whether a clinical association could be determined between prescription opioid use and incident cancer development in the population at risk for cancer development.

There are multiple strengths to our study. The Medicare-SEER database is a large, validated, representative sample of the US population. Approximately 98% of patients aged >64 years are enrolled in Medicare; and, in 2019, 44.1% of Medicare patients were enrolled in Part D.[50] The SEER registries must adhere to strict reporting standards and capture nearly all incident cancers.[4] The longitudinal aspect of the database enabled us to verify that patients were not diagnosed with cancer before the study and were exposed to prescription opioids before a cancer diagnosis. Also, advanced age is a known risk factor for cancer. All patients were matched on age, sex, and calendar year to negate trends in prescribing patterns and control for confounders. The adjusted models controlled for socioeconomic status, diagnoses associated with smoking, and comorbidities index. To our knowledge, we are the first to examine the relation between prescription opioids and incident cancer.

Conclusions

Our current results suggest that prescription opioids may affect incident cancer rates, and the specific cancer site is likely an important determinant. In both the crude and adjusted models, patients who received 1 or more opioid prescriptions had a lower OR associated with breast and colon cancer but a higher OR for incident lung cancer, leukemia, lymphoma, renal cancer, and liver cancer.

Because cancer is the second leading cause of death worldwide and opioid use by the general public is common, we believe further research in this area is warranted.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jeana E. Havidich: Developed conceptual framework, conceived and designed the analysis, responsible for data acquisition from Surveillance, Epidemiology, and End Results-Medicare, contributed to data analysis, wrote the article (primary author), supervised the project, and commented on and approved the final version. **Julie Weiss:** Developed conceptual framework, conceived and designed the analysis, analyzed the data, created the figures and tables, wrote the article, and commented on and approved the final version. **Tracy L. Onega:** Developed conceptual framework, conceived and designed the analysis, contributed to data analysis, wrote the article, and commented on and approved the final version. **Ying H. Low:** Developed conceptual framework, provided feedback on framework and analysis, wrote the article, and commented on and approved the final version. **Martha E. Goodrich:** Contributed to data acquisition and storage, contributed to design of analysis, wrote the article, and commented on and approved the final version. **Mathew A. Davis:** Provided feedback on the framework and analysis, commented on the article, and approved the final analysis. **Brian D. Sites:** Obtained funding from Department of Anesthesiology, contributed to conceptual framework and study design, wrote the article, and commented on and approved the final version.

REFERENCES

1. World Health Organization (WHO). WHO Cancer Fact Sheets. Accessed June 6, 2019. https://www.who.int/news-room/fact-sheets/detail/cancer
2. World Health Organization (WHO). Number of New Cases, 2018. Accessed June 6, 2019. http://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf
3. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018;68:31-54.
4. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Practice of epidemiology use of Surveillance, Epidemiology, and End Results-Medicare data to conduct case-control studies of cancer among the US elderly. *Am J Epidemiol*. 2011;174:860-870.
5. Mahale P, Torres HA, Kramer JR, et al. Hepatitis C virus infection and the risk of cancer among elderly US adults: a registry-based case-control study. *Cancer*. 2017;123:1202-1211.
6. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000;53:1258-1267.
7. Mathew B, Lennon FE, Siegler JH, et al. Novel role of the mu opioid receptor in lung cancer progression: a laboratory study. *Anesth Analg*. 2011;112:558-567.
8. Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. μ-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. *Anesthesiology*. 2012;116:896-902.
9. Weingaertner IR, Koutnik S, Ammer H. Chronic morphine treatment attenuates cell growth of human BT474 breast cancer cells by rearrangement of the ErbB signalling network. *PLoS One*. 2013;8:e53510.
10. Wang S, Li Y, Liu XD, Zhao CX, Yang KQ. Polymorphism of A118G in μ-opioid receptor gene is associated with risk of esophageal squamous cell carcinoma in a Chinese population. *Int J Clin Oncol*. 2013;18:666-669.
11. Zhang YF, Xu QX, Liao LD, et al. Association of mu-opioid receptor expression with lymph node metastasis in esophageal squamous cell carcinoma. *Dis Esophagus*. 2015;28:196-203.
12. Diaz-Cambronero O, Mazzinari G, Giner F, et al. Mu opioid receptor 1 (MOR-1) expression in colorectal cancer and oncological long-term outcomes: a five-year retrospective longitudinal cohort study. *Cancers (Basel)*. 2020;12:134.
13. Hatzoglou A, Bakogeorgou E, Kampa M, et al. Somatostatin and opioid receptors in mammary tissue. Role in cancer cell growth. *Adv Exp Med Biol*. 2000;480:55-63.
14. Gach K, Szemraj J, Stasikowska-Kanicka O, Danilewicz M, Janecka A. Opioid-receptor gene expression and localization in cancer cells. *Cent Eur J Biol*. 2011;6:10-15.
15. Li C, Li L, Qin Y, et al. Exogenous morphine inhibits the growth of human gastric tumor in vivo. *Ann Transl Med*. 2020;8:385.
16. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. *Ann Oncol*. 2016;27:2032-2038.
17. Bimonte S, Barbieri A, Cascella M, et al. Naloxone counteracts the promoting tumor growth effects induced by morphine in an animal model of triple-negative breast cancer. *In Vivo*. 2019;33:821-825.
18. Bimonte S, Barbieri A, Rea D, et al. Morphine promotes tumor angiogenesis and increases breast cancer progression. *Biomed Res Int*. 2015;2015:161508.
19. Friesen C, Roscher M, Alt A, Miltner E. Methadone, commonly used as maintenance medication for outpatient treatment of opioid dependence, kills leukemia cells and overcomes chemoresistance. *Cancer Res*. 2008;68:6059-6064.
20. Maneckjee R, Minna JD. Nonconventional opioid binding sites mediate growth inhibitory effects of methadone on human lung cancer cells. *Proc Natl Adad Sci U S A*. 1992;89:1169-1173.
21. Randall D, Degenhardt L, Vajdic CM, et al. Increasing cancer mortality among opioid-dependent persons in Australia: a new public health challenge for a disadvantaged population. *Aust N Z J Public Health*. 2011;35:220-225.
22. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, et al. Opioids and breast cancer recurrence: a Danish population-based cohort study. *Cancer*. 2015;121:3507-3514.
23. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-opioid receptor expression in metastatic lung cancer. *Br J Anaesth*. 2014;113(suppl 1):i103-i108.
24. Wang K, Qu X, Wang Y, Shen H, Liu Q, Du J. Effect of mu agonists on long-term survival and recurrence in nonsmall cell lung cancer patients. *Medicine (Baltimore)*. 2015;94:e1333.
25. Maher D, Wong W, White P, et al. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis. *Br J Anaesth*. 2014;113(suppl 1):i88-i94.
26. Lennon FE, Mirzapoiazova T, Mambetsariev B, Salgia R, Moss J, Singleton PA. Overexpression of the μ-opioid receptor in human nonsmall cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. *Anesthesiology*. 2012;116:857-867.
27. Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. *Cancer Med*. 2014;3:900-908.
28. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: a new target for cancer therapy? *Cancer*. 2015;121:2681-2688.
29. Brittenden J, Heys SD, Ross J, Eremin O. Natural killer cells and cancer. *Cancer*. 1996;77:1226-1243.
30. Vivier E, Ugolini S, Blaise D, Chabannon C, Brossay L. Targeting natural killer cells and natural killer T cells in cancer. *Nat Rev Immunol*. 2012;12:239-252.
31. Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. *Nat Immunol*. 2016;17:1025-1036.
32. Whiteside TL, Herberman RB. The role of natural killer cells in immune surveillance of cancer. *Curr Opin Immunol*. 1995;7:704-710.
33. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B. Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study. *Neuroimmunomodulation*. 2004;11:255-260.

34. Yeager MP, Colacchio TA, Yu CT, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology*. 1995;83:500-508.
35. Tai LH, de Souza CT, Belanger S, et al. Preventing postoperative metastatic disease by inhibiting surgery-induced dysfunction in natural killer cells. *Cancer Res*. 2013;73:97-107.
36. Nguyen J, Luk K, Vang D, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. *Br J Anaesth*. 2014;113(suppl 1):i4-i13.
37. Lennon FE, Moss J, Singleton PA. The μ-opioid receptor in cancer progressions there a direct effect? *Anesthesiology*. 2012;116:940-945.
38. Beilin B, Shavit Y, Hart J, et al. Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. *Anesth Analg*. 1996;82:492-497.
39. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *Br J Anaesth*. 2014;113(suppl 1):i56-i62.
40. Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol*. 1998;83:36-44.
41. Maher DP, Walia D, Heller NM. Suppression of human natural killer cells by different classes of opioids. *Anesth Analg*. 2019;128:1013-1021.
42. Mellon RD, Bayer BM. Evidence for central opioid receptors in the immunomodulatory effects of morphine: review of potential mechanism(s) of action. *J Neuroimmunol*. 1998;83:19-28.
43. Matta S, Saphier D, Dunn AJ. The brain-immune axis and drugs of abuse cytokines as mediators of infection-induced stress. *J Neuroimmunol*. 1996;69:P25-P39.
44. Neeman E, Zmora O, Ben-Eliyahu S. A new approach to reducing postsurgical cancer recurrence: perioperative targeting of catecholamines and prostaglandins. *Clin Cancer Res*. 2012;18:4895-4902.
45. Neeman E, Ben-Eliyahu S. Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. *Brain Behav Immun*. 2013;30(suppl):S32-S40.
46. Farooqui M, Li Y, Rogers T, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. *Br J Cancer*. 2007;97:1523-1531.
47. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*. 2007;165:1424-1433.
48. Nasrollahzadeh D, Kamangar F, Aghcheli K, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*. 2008;98:1857-1863.
49. Du KN, Feng L, Newhouse A, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with esophageal ade7nocarcinoma and squamous cell carcinoma. *Anesth Analg*. 2018;127:210-216.
50. Davis K, Schoen C, Bandeali F. Medicare: 50 Years of Ensuring Coverage and Care. The Commonwealth Fund; 2015. Accessed July 21, 2019. https://www.commonwealthfund.org/publications/fund-reports/2015/apr/medicare-50-years-ensuring-coverage-and-care