

# Letters

## RESEARCH LETTER

### Incidence of Opioid-Associated Deaths in Cancer Survivors in the United States, 2006-2016: A Population Study of the Opioid Epidemic

More than 40 000 people in the US died owing to opioids in 2016; the epidemic tops public health concerns. Opioids are commonly used for cancer-associated pain, and there has been a call for oncologists to become more aware of opioid-related risks and benefits.<sup>1</sup> It is unknown, however, if opioid-related deaths in cancer survivors are rising at the same rate as in the general population.

**Methods** | Death certificate data were obtained from the National Center for Health Statistics (NCHS). Death certificates contain 1 underlying cause of death, up to 20 contributing causes, and demographic data. All deaths owing to opioids were included from 2006 through 2016; if present, cancer was noted as a contributing cause. Opioid-related death incidence was



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calculated from the US population and estimated cancer survivor population,<sup>2</sup> both via NCHS data. To assess for differences,  $\chi^2$  and  $R^2$  tests were used. Statistical significance was defined as  $\alpha < .05$  on a 2-sided significance level. All statistical analyses were performed with SPSS, version 21 (IBM). The Duke University Medical Center Institutional Review Board provided a waiver (Pro00045337) for this study, given that it is publicly available deidentified data. Informed consent is waived for publicly available, deidentified databases. Data were collected from May through August 2018, and analysis was completed in September 2019.

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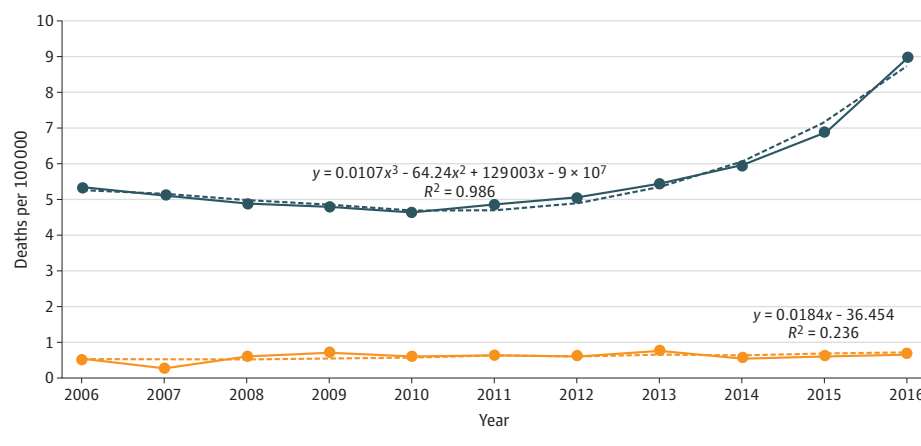
**Results** | From 2006 through 2016, there were 193 500 deaths owing to opioids in the general population and 895 in the cancer population. The number of opioid-related deaths increased from 5.33 to 8.97 per 100 000 people in the general population ( $P < .001$ ;  $R^2 = 0.99$ ) and from 0.52 to 0.66 per 100 000 ( $P < .001$ ;  $R^2 = 0.24$ ) in the cancer population (**Figure**).

Demographic characteristics of cancer survivors with opioid-related deaths differed from those in the general population including higher education (12.7% vs 6.9% with at least a college degree), more women (38.5% vs 29.2%), fewer white individuals (82.3% vs 84.2%), more non-Hispanic individuals (94.5% vs 90.7%), and fewer single patients (24.2% vs 48.1%) (all  $P < .001$ ; except race,  $P = .03$ ) (**Table**). Cancer survivors also were older (median age, 57 years vs 42 years). The underlying primary cancer for those with opioid-related deaths was lung (22.3%), gastrointestinal (20.9%), head and neck (11.7%), and hematologic (11.3%), among others (**Table**).

**Discussion** | Death from opioids as the primary cause as documented in death certificates is 10 times less likely to occur in cancer survivors vs the general population. In the past decade, there was a slight increase in opioid-related deaths in cancer survivors; however, it was not the sharp growth seen in the general population. These findings confirm prior research showing that opioid-related hospitalizations among patients with cancer are rare but slowly increasing over time.<sup>3</sup> This may be because of increased survivorship rates with commensurately higher rates of chronic pain or increased abuse of opioid medications.

Cancer survivors at risk for opioid overdose may be different from people in the general population, including being older with higher educational attainment; these differences may, in part, reflect the diagnosed cancer population.

Figure. Opioid-Related Deaths per 100 000



Deaths per 100 000 in the general population (blue) and in those with cancer as a contributing cause (orange). The solid lines are the data points, and the dashed lines are the best-fit lines for which the equations are listed and the  $R^2$  is calculated.

Table. Patient Characteristics

Characteristic	No. (%)		P value
	Overdose deaths in the general public (n = 193 500)	Overdose deaths with cancer as contributing cause (n = 895)	
Age, median (IQR) [range]	42 (31-51) [1-103]	57 (50-65) [13-98]	<.001
Sex			
Male	136 988 (70.8)	550 (61.5)	<.001
Female	56 512 (29.2)	345 (38.5)	
Race			
White	163 014 (84.2)	737 (82.3)	.027
Black	27 104 (14.0)	131 (14.6)	
Asian	2107 (1.1)	18 (2.0)	
American Indian	1275 (0.7)	9 (1.0)	
Ethnicity			
Non-Hispanic	175 453 (90.7)	844 (94.3)	<.001
Hispanic	16 760 (8.7)	49 (5.5)	
Unknown	1287 (0.7)	2 (0.2)	
Marital status			
Single	93 020 (48.1)	217 (24.2)	<.001
Not single <sup>a</sup>	100 426 (51.9)	678 (75.8)	
Education			
At least a college education	13 352 (6.9)	114 (12.7)	<.001
Less than a college education	135 609 (70.1)	625 (69.8)	
Unknown	44 539 (23.0)	156 (17.4)	
Underlying primary cancer			
	New diagnoses in US <sup>b</sup> (n = 1 735 350)	Diagnosis in opioid-related death (n = 895)	
Lung	234 030 (13.5)	200 (22.3)	NA
Gastrointestinal	319 160 (18.4)	187 (20.9)	
Head and neck	64 690 (3.7)	105 (11.7)	
Hematologic	174 250 (10.0)	101 (11.3)	
Prostate/urinary	326 670 (18.8)	90 (10.1)	
Breast	268 670 (15.5)	63 (7.0)	
Gynecologic	92 070 (5.3)	44 (4.9)	

Abbreviations: IQR, interquartile range; NA, not applicable.

<sup>a</sup> Including married, widowed, and separated.

<sup>b</sup> Cancer statistics from American Cancer Society, *Cancer Facts and Figures 2018*.

Additionally, some diagnoses may carry higher proportional risk; patients with head and neck cancer represent 12% of opioid-related deaths but less than 4% of new cancer diagnoses (Table).

One-third of patients experience cancer-related pain after curative treatment,<sup>4</sup> and prescribing restrictions tied to the opioid epidemic may be reducing access for both long-term survivors and those on active treatment. One study of patients referred to palliative care found that opioid doses decreased by almost half from 2010 to 2015,<sup>5</sup> another found that the number of patients with cancer and survivors with opioid prescriptions decreased by more than half from 2016 to 2018, with almost half told that their treatment options were limited by laws, guidelines, or insurance coverage.<sup>6</sup>

Our study is limited by its dependence on accurate documentation of cancer as a contributing cause when present. It may underestimate the number of opioid-related deaths in those on active cancer treatment if clinicians assume all deaths are owing to cancer as underlying cause; it may also underestimate survivor risk if cancer was a distant diagnosis and not noted at the time of an opioid-related death.

In summary, opioid-related deaths in the cancer population are much rarer than in the general population. Continued care should be taken when treating cancer-related pain.

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*Study concept and design:* All authors.

*Acquisition, analysis, or interpretation of data:* F. Chino, J. Chino.

*Drafting of the manuscript:* All authors.  
*Critical revision of the manuscript for important intellectual content:* All authors.  
*Statistical analysis:* J. Chino.  
*Administrative, technical, or material support:* Kamal, J. Chino.  
*Study supervision:* J. Chino.

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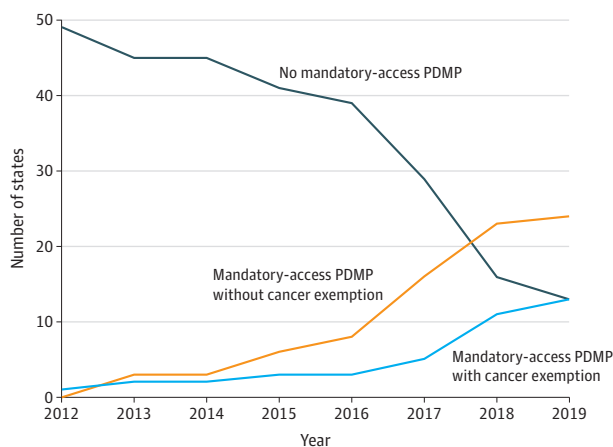
### Association of Mandatory-Access Prescription Drug Monitoring Programs With Opioid Prescriptions Among Medicare Patients Treated by a Medical or Hematologic Oncologist

More than 30 states have enacted laws mandating use of prescription drug monitoring programs (PDMP) to reduce inappropriate opioid prescribing. Clinicians in those states must check the PDMP database before writing opioid prescriptions. These mandates vary substantially across states in their timing and scope; for example, some exempt patients with cancer.<sup>1,2</sup> We examine the association between state mandatory-access PDMPs and changes in the percent of oncologists' Medicare patients with any opioid prescription fills.

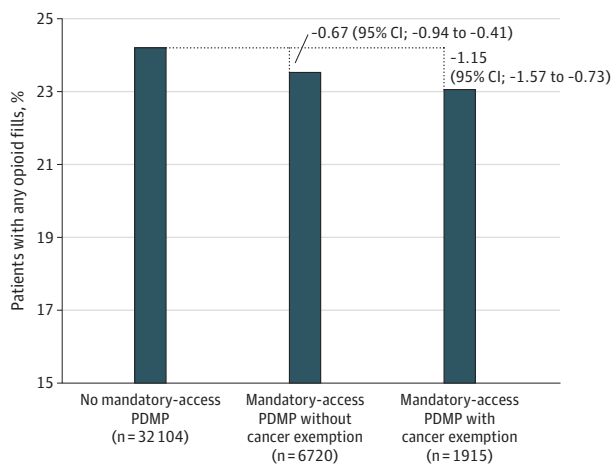
**Methods** | We used the physician-level Medicare Part D prescriber files for 2013 to 2017 and restricted the sample to physicians specialized in medical or hematologic oncology. For each year, we classified states as having: no mandatory-access PDMP or a mandatory-access PDMP with or without a cancer exemption.

We used linear regression with physician and year fixed effects to assess the association between PDMP mandates with and without a cancer exemption and the percent of oncologists' patients with any opioid prescription covered by Medicare Part D. This approach measured within-physician changes in opioid prescribing after the implementation of mandated

**Figure 1. Timeline of Number of States That Implemented Mandatory-Access Prescription Drug Monitoring Programs (PDMP)**



**Figure 2. Adjusted Percent of 40 739 Patients Treated by a Medical or Hematologic Oncologist With Any Opioid Prescription**



PDMPs compared with physicians in states without mandates, adjusting for secular time trends.

The institutional review board of Emory University determined that study approval was not required because all data analyzed were publicly available and deidentified.

**Results** | By 2017, 21 states had implemented mandatory-access PDMPs, including 5 states that explicitly exempted the reviewing requirement for patients with cancer (Figure 1). Compared with oncologists in states with no mandated PDMP, the proportion of oncologists' patients who filled an opioid prescription declined by 1.15 percentage points (95% CI, -1.57% to -0.73%; a 4.8% decline) and by 0.67 percentage points (95% CI, -0.94% to -0.41%; a 2.8% decline) in states that implemented PDMP mandates with and without cancer exemptions, respectively (Figure 2). To protect the privacy of Medicare beneficiaries, this data set suppresses observations when physicians had 1 to 10 Part D claims in a year with an opioid prescription (12 297 of 53 036 [23.1%]). Results from models

where we imputed the missing number of patients with any opioid prescription as either 1, 5, or 10 were similar in magnitude and significance to the presented results with missing values omitted.

**Discussion** | The share of oncology patients who filled an opioid prescription declined by 4.8% and 2.8% in states that enacted mandatory-access PDMPs—with and without exemptions for patients with cancer, respectively. Although recent studies<sup>3,4</sup> have shown that mandated PDMPs are associated with an 8% to 12% reduction in opioid prescribing, this is the first to show that mandated PDMPs—with or without an explicit exemption for patients with a cancer diagnosis—are associated with decreases in opioid prescribing by medical and hematologic oncologists.

Implementation of PDMPs was intended to curb inappropriate opioid prescribing, not legitimate use among patients undergoing oncology treatment, who are often undertreated for pain.<sup>5</sup> From our early results, we find that exemptions for patients with a cancer diagnosis did not shield Medicare patients treated by a medical or hematologic oncologist from the unintended spillovers of mandated PDMP requirements. This analysis was limited by lack of patient-level data, including cancer type and stage, and short follow-up period. In addition we did not examine changes in per-patient opioid dose. Future studies should examine the effect of PDMP policies with more years of follow-up data and adjusting patient-level characteristics. It is possible that with more time to learn about the nuances of the PDMP mandate, prescriber practices will adjust.

**Conclusions** | Although policymakers are motivated to prevent opioid misuse, there is growing concern that some physicians—burdened by the task of consulting a PDMP and added scrutiny over their prescribing—have reduced their opioid prescribing even for patients with legitimate pain management needs.<sup>6</sup> These results show that with or without an exemption for patients with cancer, the percent of patients treated by a medical or hematologic oncologist receiving opioids declined after mandatory-access PDMPs were implemented. As more states contemplate policies to alleviate the opioid crisis, it is critical to understand how they affect both problematic and legitimate opioid use.

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**Concept and design:** Graetz, Yarbrough, Hu.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Graetz, Yarbrough, Hu.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** All authors.

**Administrative, technical, or material support:** Graetz.

**Supervision:** Graetz.

**Conflict of Interest Disclosures:** None reported.

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#### Invited Commentary

### Managing Cancer Pain During the Opioid Epidemic—Balancing Caution and Compassion

Opioid prescribing patterns have come under increased scrutiny in the setting of the ongoing opioid epidemic as rates of opioid prescription, overdose, and mortality have risen in the United States.<sup>1</sup> The opioid epidemic has appropriately led to new guidelines, regulations, and policies that attempt to curtail the inappropriate use of opioids in clinical practice. However, these policies in part arise from prior research of opioid-related adverse effects in the noncancer population, and we lack an understanding of how the opioid epidemic and related opioid policies will influence patients with cancer.

In this issue of *JAMA Oncology*, 2 Research Letters address timely and important questions surrounding trends in opioid prescribing and toxic effects among patients with cancer. Chino and colleagues<sup>2</sup> evaluated death certificates from the National Center for Health Statistics and found that the risk of opioid-related deaths among patients with cancer was substantially lower than in patients who did not have cancer. Between 2006 and 2016, the rates of opioid-related deaths among the noncancer population increased from 5.33 to 8.97 per 100 000. Over the same time period, the rates of opioid-related death among patients with cancer increased slightly (0.52-0.66 per 100 000), though notably, the rates of opioid-related death in patients with cancer were 10-fold less in magnitude compared with the rates among patients without cancer. As noted by the authors, health care providers could be less likely to attribute opioid use as a cause of death among patients with cancer, and this misattribution bias could lead



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to underreporting of opioid-related mortality among patients in this population. Despite this potential limitation, these data provide reassurance that opioid-related deaths are rare in patients with cancer and that rates are not rapidly increasing.

The study by Graetz and colleagues<sup>3</sup> evaluated the influence of prescription drug monitoring programs (PDMPs) on opioid prescription rates for patients with cancer by using Medicare claims data from 2013 through 2017. More than 30 states have mandated PDMPs with the goal of reducing inappropriate opioid prescribing, though these initiatives, when implemented, can add to the administrative burden of prescribing opioids. These potential barriers to prescribing opioids could lead to reduced use of appropriate opiates among patients with cancer (undertreatment), and as such, a select minority of states exempt patients with cancer from these programs. Graetz and colleagues evaluated Medicare Part D data between 2013 and 2017, and found that states enacting PDMPs had reduced opioid prescriptions among patients with cancer compared with states without PDMPs. Of note, the decrease in patients filling an opioid prescription appeared numerically greater among states with PDMPs that exempted patients with cancer (4.8% decrease) as opposed to states with PDMPs without cancer exemptions (2.8% decrease). This study only evaluated the prescribing behaviors of oncology care providers and did not account for opioid prescriptions from primary care, pain, palliative care, or other specialist providers. Regardless of this limitation, the study by Graetz and colleagues highlights the fact that opioid-related policies in general could have unintended consequences on pain management among patients with cancer. At the same time, this study demonstrated a modest reduction on prescription rates with PDMPs, which suggests that oncologists continue to prioritize pain management.

Pain management represents a critical aspect in the practice of clinical oncology, with up to 40% of patients experiencing moderate to severe pain that warrants use of opioid analgesics.<sup>4</sup> Additionally, up to 50% of patients with cancer have undertreated pain,<sup>1</sup> and this number may be higher among minority and elderly patients.<sup>5</sup> Given the vast range of symptoms, treatments, prognoses, and long-term toxic effects experienced by patients with cancer, it comes as little surprise that research demonstrates higher rates of long-term opioid use among cancer survivors compared with controls without cancer.<sup>5</sup> As in the general population, a small minority of cancer survivors are at high risk for adverse opioid outcomes, including abuse and toxic effects.<sup>6</sup> Of note, these adverse events may be increasing in frequency: a study by Jairam and colleagues<sup>7</sup> found that the incidence of emergency department visits for opioid overdoses in patients with cancer doubled from 2006 to 2015. These studies point to a need for approaches to identify the small proportion of patients with cancer at risk of opioid-related adverse events. However, patients and health care providers should keep in mind that the absolute risks associated with opioid use among patients with cancer remain relatively rare.

Oncologists worry that overly conservative practice trends, guidelines, or policies may revert the field to an era when cancer-related pain was systematically undertreated. Taken to-

gether, the studies in this issue of *JAMA Oncology* by Chino and colleagues<sup>2</sup> and Graetz and colleagues<sup>3</sup> help provide important context with respect to the opioid conversation as it pertains to patients with cancer. In the coming years, we will appropriately see the introduction of opioid-related policies that aim to reduce misuse, addiction, and death. These policies will arise within clinics and hospitals, as well as at the state and national levels. The available research demonstrates the uniqueness of patients with cancer with respect to opioids, which underscores the fact that the needs and risks of patients with cancer diverge from the general noncancer population. Policy makers need to consider the cancer population when creating opioid-related policies, and researchers need to continue evaluating the effect of enacted policies on patients with cancer. The opioid epidemic represents a critical public health concern, though in battling this epidemic we need to make sure we protect individuals with cancer.

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### Association of Behavioral Nudges With High-Value Evidence-Based Prescribing in Oncology

Identifying effective strategies to promote high-value, evidence-based prescribing is critical in oncology, where spending is projected to surpass \$150 billion in 2020, driven in large part by cancer drugs.<sup>1</sup> By intentionally modifying the way choices are framed, behavioral nudges can lead to desirable