

# Persistent prescription opioid use and all-cause mortality following the first-year breast cancer survivorship

Rulin C. Hechter , MD, PhD<sup>\*1,2</sup>, Lie Hong Chen , DrPH<sup>1</sup>, Jiaxiao Shi , PhD<sup>1</sup>, Zheng Gu , MPH<sup>1</sup>, Moira Brady-Rogers , MA, LMFT<sup>3</sup>, Rowan T. Chlebowski , MD, PhD<sup>4,5</sup>, Reina Haque , PhD<sup>1,2</sup>

<sup>1</sup>Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States

<sup>2</sup>Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, United States

<sup>3</sup>Alive & Well Women, South Pasadena, CA, United States

<sup>4</sup>The Lundquist Research Institute for Biomedical Innovation, UCLA-Harbor, Torrance, CA, United States

<sup>5</sup>Division of Medical Oncology and Hematology, UCLA-Harbor, Torrance, CA, United States

\*Corresponding author: Rulin C. Hechter, MD, PhD, Department of Research & Evaluation, Kaiser Permanente Southern California, 100 South Los Robles, Second Floor, Pasadena, CA 91101, United States ([rulin.c.hechter@kp.org](mailto:rulin.c.hechter@kp.org))

## Abstract

**Background:** Harm associated with persistent opioid use beyond the first-year intensive cancer treatment is underinvestigated in cancer survivors. We examined rates and risk factors for persistent opioid use and all-cause mortality after the first-year breast cancer survivorship.

**Methods:** This retrospective cohort study used electronic health record data from Kaiser Permanente Southern California for women diagnosed with a nonmetastatic breast cancer between 2009 and 2019 who filled 2 or more opioid prescriptions. Rates of persistent opioid use were estimated from first-year survivorship through December 31, 2021. Rate ratios (RRs) and 95% confidence intervals (CIs) for factors associated with persistent use were estimated using a multivariable Poisson regression model. Hazard ratios (HRs) for all-cause mortality associated with persistent opioid use were estimated using multivariable Cox regression models.

**Results:** Of 14 347 eligible individuals (mean [SD] age = 61.9 [12.5]), 2285 (15.9%) developed persistent opioid use, with an incident rate of 25.5 per 1000 person-years. Risk factors included older age ( $\geq 65$  vs  $< 65$  years: RR = 1.63, 95% CI = 1.24 to 2.14), smoking (current: 1.89, 1.68 to 2.13; former: 1.30, 1.20 to 1.41), baseline comorbidities (Elixhauser Comorbidity Index 5+ vs 0: 1.70, 1.29 to 2.24), and substance use disorders (1.58, 1.43 to 1.74). All-cause mortality was doubled among individuals with persistent use (51.6, 48.0 to 55.6 per 1000 person-years) than in those without (25.3, 24.2 to 26.4). Persistent use was associated with an increased all-cause mortality (adjusted HR = 1.84, 1.66 to 2.04).

**Conclusions:** Persistent opioid use was common in breast cancer survivors and associated with increased mortality. Further research is needed to explore factors that may be contributing to increased mortality.

## Introduction

An estimated 40%-89% of the 3 million breast cancer survivors in the United States suffer from chronic pain following breast cancer treatments.<sup>1-4</sup> Many breast cancer survivors suffer severe pain following extensive breast surgery and lymph node removal or after initiation of adjuvant endocrine therapy (aromatase inhibitors), which may induce bone pain, and they often initiate opioids for pain management and continue well after primary cancer treatment. Moreover, breast cancer survivors are more likely to be prescribed opioids than other cancer survivors because they often experience chronic pain long after initial cancer surgeries and adjuvant treatments.<sup>2</sup> Prescription drug misuse, especially opioid misuse and overdose, has been a major public health crisis in the past 2 decades in the United States.<sup>5,6</sup> Prior studies on opioid-related mortality in the general population suggested that polydrug toxicity contributes to an increased risk of death.<sup>6</sup> However, data on consequent health outcomes in breast cancer survivors related to opioid use disorder are limited.<sup>6-15</sup> Although potential adverse events associated with persistent prescription opioid use has become an area of concern in cancer survivorship research, patterns of opioid use in breast

cancer survivors and subsequent adverse events including deaths are understudied.

In this study, we addressed these research gaps and examined rates and risk factors of persistent opioid use in a large diverse cohort of survivors with nonmetastatic breast cancer after active cancer treatment and assessed the association between persistent opioid use and risk of all-cause mortality.

## Methods

We conducted a retrospective longitudinal cohort study of breast cancer survivors enrolled at Kaiser Permanente Southern California (KPSC), a not-for-profit vertically integrated health-care system with approximately diverse 4.8 million members. Kaiser Permanente Southern California members receive virtually all their health care within the system with prepaid insurance health plans. Patient demographic characteristics, tumor registry, pharmacy order and dispensing record, laboratory tests, health-care utilization including diagnostic codes at outpatient, inpatient, and emergency department, census tract level neighborhood education and household income (linked with members'

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address), and death data were ascertained through KPSC's comprehensive electronic health records (EHRs). Deaths were identified from a database that incorporates information from the health plan membership and National Death Index databases. The health plan's National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)—affiliated cancer registry—was used to identify women with breast cancer, and tumor characteristics and surgical and adjuvant treatments. The study protocol was reviewed and approved by the Institutional Review Boards at KPSC, with a waiver of informed consent (45 C.F.R. part 46.114; 21 C.F.R. part 56.114). Reporting followed Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

## Study population

The study population included women ( $\geq 18$  years) diagnosed with a nonmetastatic breast cancer (in situ, localized, or regional) during 2009-2019, with at least 1 year survivorship after their initial breast cancer diagnosis. As almost all breast cancer patients (approximately 97%) received prescription opioids following cancer surgery in this population, we further restricted the analysis to cancer survivors who had filled at least 2 opioid prescriptions after the first year of cancer survivorship. The study cohort was followed from the date immediately following the 1-year survivorship anniversary (index date), until occurrence of the outcomes of interest, membership disenrollment, death, or December 2021 (administrative censoring of the study observation), whichever occurred first.

## Main outcomes

Prescription opioid use was ascertained from the outpatient pharmacy dispensing records for hydrocodone, hydromorphone, oxycodone, tramadol, morphine, and fentanyl, including drug generic names, dosages, medication filled dates, and days supplied. Persistent opioid use was defined as receipt of at least 2 continuous opioid dispensing with a consecutive  $\geq 90$  days' supply (allowing a maximum of 15-day gap in supply).<sup>16</sup> Annualized cumulative days supplied was calculated during the follow-up period. The maximum daily morphine milligram equivalent (MME) of the dosage was computed based on prescription strength and days of supply, using the Centers for Disease Control and Prevention's oral MME conversion factor.<sup>17</sup> All-cause mortality rate (per 1000 person-years) was calculated during the follow-up period through December 2021.

## Covariates

To determine the covariates included in this study, we considered opioid use at baseline (ie, opioid use during the first year after cancer diagnosis as well as factors associated with opioid misuse in the literature and prescription medications often concurrently used for pain or stress management).<sup>1-16</sup> Baseline covariates during the first year of breast cancer survivorship included age; self-reported race and ethnicity; geocoded median annual household income at census block level; smoking status (never, former, current); body mass index (BMI; kg/m<sup>2</sup>); and opioid use at baseline (yes/no). We also included history of substance use disorders in the 5 years prior to index date (ascertained using International Classification of Diseases codes [Table S1]). A modified baseline Elixhauser Comorbidity Index (ECI) was calculated after excluding cancer diagnosis from the algorithm, with a possible range of the score between 0 and 31.<sup>18</sup> Tumor characteristics including SEER summary stage, diagnosis year, and primary treatment (ie, surgery type, adjuvant chemotherapy, adjuvant

radiation, and adjuvant endocrine therapy) were ascertained from the cancer registry. Additionally, concurrent use of psychiatric medications (antidepressants, anxiolytics, sedatives/sleep aids) and other prescribed pain medications (nonsteroidal anti-inflammatory drugs [NSAIDs]; cannabinoids; gabapentin) during follow-up were included as time-updated covariates in the analysis for all-cause mortality. The percentage of missing value was low ( $< 2\%$ ) for most covariates except for baseline smoking status; thus, a dummy variable for missing smoking status was generated to maintain the full sample size in multivariable analysis.

## Statistical analysis

We compared baseline characteristics between breast cancer survivors who developed persistent opioid use and those who did not during follow-up, using  $\chi^2$  test for categorical variables. We estimated rates (per 1000 person-years) and 95% confidence intervals (CIs) of persistent opioid use status. We plotted the cumulative percentages of those who developed persistent opioid use by year of follow-up in the overall study population and stratified by age group ( $< 65$  vs  $\geq 65$  years).

Risk factors and calculated rate ratios (RRs) and 95% CI associated with persistent opioid use were evaluated using Poisson regression models with robust variance. Multivariable analyses included the following potential risk factors: sociodemographic characteristics including age (at index date), race/ethnicity, geocoded median annual household income, BMI, smoking status, opioid use at baseline, history of substance use disorders, tumor characteristics, and cancer treatment variables (including SEER summary stage, year of diagnosis, surgery type, adjuvant chemotherapy, radiation, and endocrine therapy).

Three sets of nested multivariable analyses were conducted using Cox proportional hazards models to estimate the hazard ratio (HR) and 95% CI for association between persistent opioid use and all-cause mortality during follow-up. Model 1 adjusted for baseline sociodemographic characteristics, BMI, smoking status, opioid use at baseline, and history of substance use disorders. Model 2 adjusted for all covariates in Model 1 plus tumor characteristics and cancer treatment variables (SEER summary stage, year of diagnosis, surgery type, adjuvant chemotherapy, radiation, and endocrine therapy). Model 3 further incorporated time-updated variables of persistent opioid use and concurrent use of prescription pain or psychiatric medications during follow-up. Assumption of proportional hazard was evaluated, and no evidence of violation was found. Collinearity of covariates was also checked. Results were deemed statistically significant at a level of 2-sided  $P < .05$ . All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC). Data collection and analyses were conducted from January 2023 to March 2024.

## Results

Among 33 989 eligible breast cancer survivors, 14 347 women with 2 or more opioid dispense records after the first-year survivorship were included for this study, with a median age of 61.9 years (q1-q3 = 53.0-71.0 years). There were 53.6% non-Hispanic White, 22.2% Hispanic, 14.3% non-Hispanic Black, 8.9% Asian/Pacific Islanders, and 1.0% of other/mixed/unknown races.

### Persistent opioid use

After the first-year survival, a total of 2285 (15.9%) women developed persistent opioid use, with a rate of 25.5/1000 person-years (95% CI = 24.5 to 26.5). The median duration of opioid use per year was 160 days (q1-q3 = 75.3-273.8 days) among those with

**Table 1.** Baseline sociodemographic and clinical characteristics among women diagnosed with a nonmetastatic breast cancer during 2009-2019.

	Total, No. (%)	With persistent opioid users, No. (%)	Without persistent opioid use, No. (%)	P
<b>Characteristics</b>	N = 14 347	n = 2285	n = 12 062	
Age, year <sup>a</sup>				<.001
<40	557 (3.9)	47 (2.1)	510 (4.2)	
40-64	7468 (52.1)	1043 (45.6)	6425 (53.3)	
≥65	6322 (44.1)	1195 (52.3)	5127 (42.5)	
Race/ethnicity				<.001
Asian/Pacific Islander	1277 (8.9)	88 (3.9)	1189 (9.9)	
Hispanic	3179 (22.2)	318 (13.9)	2861 (23.7)	
Non-Hispanic Black	2047 (14.3)	340 (14.9)	1707 (14.2)	
Non-Hispanic White	7695 (53.6)	1511 (66.1)	6184 (51.3)	
Other or unknown <sup>b</sup>	149 (1.0)	28 (1.2)	121 (1.0)	
Median annual household income, \$				<.001
<40 000	1964 (13.7)	351 (15.4)	1613 (13.4)	
40 000-65 000	5187 (36.2)	876 (38.3)	4311 (35.7)	
>65 000	7196 (50.2)	1058 (46.3)	6138 (50.9)	
Elixhauser Comorbidity Index <sup>c</sup>				<.001
0	567 (4.0)	46 (2.0)	521 (4.3)	
1	1750 (12.2)	132 (5.8)	1618 (13.4)	
2	2675 (18.6)	289 (12.6)	2386 (19.8)	
3	2659 (18.5)	366 (16.0)	2293 (19.0)	
4	2260 (15.8)	362 (15.8)	1898 (15.7)	
5+	4436 (30.9)	1090 (47.7)	3346 (27.7)	
Body mass index <sup>d</sup>				<0.001
<18.5	151 (1.1)	33 (1.4)	118 (1.0)	
18.5 to <25	3420 (23.8)	505 (22.1)	2915 (24.2)	
25 to <30	4534 (31.6)	640 (28.0)	3894 (32.3)	
≥30	6242 (43.5)	1107 (48.4)	5135 (42.6)	
Smoking				<.001
Never	9046 (63.1)	1083 (47.4)	7963 (66.0)	
Current	655 (4.6)	216 (9.5)	439 (3.6)	
Former	3882 (27.1)	843 (36.9)	3039 (25.2)	
Missing	764 (5.3)	143 (6.3)	621 (5.1)	
Opioid use at baseline <sup>e</sup>				<.001
No	573 (4.0)	46 (2.0)	527 (4.4)	
Yes	13 774 (96.0)	2239 (98.0)	11 535 (95.6)	
Substance use disorders <sup>f</sup>				<.001
No	13 611 (94.9)	1988 (87.0)	11 623 (96.4)	
Yes	736 (5.1)	297 (13.0)	439 (3.6)	

<sup>a</sup> Age was calculated at the index date, the day of the 1-year cancer survivorship.

<sup>b</sup> Other captured all other races and ethnicity categories, including multiple races and Native American.

<sup>c</sup> Assessed in the 12 months prior to the index date; Elixhauser Comorbidity Index (range = 0-31, with higher values indicating greater comorbid disease burden) was calculated after excluding cancer diagnosis from the algorithm.

<sup>d</sup> Calculated as weight in kilograms divided by height in meters squared (kg/m<sup>2</sup>).

<sup>e</sup> Opioid use during the first year after cancer diagnosis.

<sup>f</sup> Assessed in the 5 years prior to the index date.

persistent use. [Table 1](#) summarizes baseline characteristics by the status of persistent opioid use during follow-up. Compared with breast cancer survivors who did not develop persistent opioid use, individuals who developed persistent opioid use were more likely to be older (52.3% vs 42.5% ≥65 years;  $P < .001$ ); of White race (66.1% vs 51.3%;  $P < .001$ ); with obesity (BMI ≥ 30 kg/m<sup>2</sup>, 48.4% vs 42.6%;  $P < .001$ ); being a former smoker (36.9% vs 25.2%;  $P < .001$ ) or current smoker (9.5% vs 3.6%;  $P < .001$ ); with a history of substance use disorders (13.0% vs 3.6%;  $P < .001$ ); and had more comorbidities (ECI 5+: 47.7% vs 27.7%;  $P < .001$ ). In general, tumor characteristics including stage (localized: 54.5% vs 54.3%) and use of adjuvant therapies (eg, chemotherapy: 37.6% vs 38.8%; radiation: 44.2% vs 45.1%) were similar in those who developed persistent opioid use compared with individuals who did not ([Table S2](#)). The cumulative percentage of those who developed persistent opioid use rose steadily over time during cancer survivorship, with a steeper rise in persistent use among individuals aged 65 years and older ([Figure S1](#)).

Persistent opioid users received a higher median maximum daily MME compared with those without persistent opioid use

(75.0 vs 50.0 MME,  $P < .001$ ) ([Table 2](#)). In both groups, the most commonly used opioids were hydrocodone (86.8% vs 84.0%,  $P < .001$ ) and oxycodone (46.1% vs 26.9%,  $P < .001$ ), respectively. In general, a greater proportion of individuals with persistent opioid use also had concurrent use of other prescription pain or psychiatric medications. Breast cancer survivors with persistent opioid use were more likely to have concurrent NSAIDs use (61.4% vs 58.2%,  $P = .005$ ) and gabapentin use (50.3% vs 27.8%,  $P < .001$ ) compared with those without persistent opioid use, respectively. Cannabinoids use was low in both groups (2.6% in persistent opioid users vs 1.0% in nonpersistent opioid users,  $P < .001$ ). Persistent opioid users were more likely to use other psychiatric drugs including anxiolytics (29.7% vs 15.8%), antidepressants (75.6% vs 49.5%,  $P < .001$ ), and sedatives or sleep aids (61.1% vs 42.1%,  $P < .001$ ) than nonpersistent opioid users, respectively.

[Figure 1](#) presents risk factors and adjusted rate ratios (aRRs) associated with developing persistent opioid use in the multivariable analysis. Compared with individuals without persistent opioid use, breast cancer survivors with persistent opioid use

**Table 2.** Duration and type of opioid use, maximum daily dosage, and concurrent use of other pain and psychiatric drugs during follow-up.

	Total N = 14 347	With persistent opioid use n = 2285	Without persistent opioid use n = 12 062	P <sup>a</sup>
Annualized duration of opioid use, days				
Median (IQR)	6.1 (2.7 to 22.6)	160 (75.3 to 273.8)	4.5 (2.3 to 10.5)	<.001 <sup>1</sup>
Maximum daily dosage, MME				
Median (IQR)	53.6 (32.1 to 80.0)	75 (45.0 to 128.6)	50 (30.0 to 75.0)	<.001 <sup>1</sup>
Type of opioid <sup>b</sup> , No. (%)				
Hydrocodone	12 115 (84.4)	1983 (86.8)	10 132 (84.0)	<.001 <sup>2</sup>
Oxycodone	4304 (30.0)	1054 (46.1)	3250 (26.9)	<.001 <sup>2</sup>
Tramadol	5346 (37.3)	830 (36.3)	4516 (37.4)	.312 <sup>2</sup>
Other opioids	5818 (40.6)	1210 (53.0)	4608 (38.2)	<.001 <sup>2</sup>
Other pain and psychiatric medication use <sup>c</sup> , No. (%)				
Cannabinoids	180 (1.3)	60 (2.6)	120 (1.0)	<.001 <sup>2</sup>
NSAIDs	8422 (58.7)	1402 (61.4)	7020 (58.2)	.005 <sup>2</sup>
Gabapentin	4502 (31.4)	1150 (50.3)	3352 (27.8)	<.001 <sup>2</sup>
Antidepressants	7702 (53.7)	1727 (75.6)	5975 (49.5)	<.001 <sup>2</sup>
Anxiolytics	2583 (18.0)	678 (29.7)	1905 (15.8)	<.001 <sup>2</sup>
Sedatives or sleep aids	6470 (45.1)	1397 (61.1)	5073 (42.1)	<.001 <sup>2</sup>

Abbreviation: IQR = interquartile range; MME = morphine milligram equivalent; NSAIDs = nonsteroidal anti-inflammatory drugs.

<sup>a</sup> P-value was calculated using Wilcoxon-Mann-Whitney test for continuous variables and  $\chi^2$  test for categorical variables.

<sup>b</sup> The distribution is not mutually exclusive, an individual could take more than 1 type of opioid.

<sup>c</sup> Use of any of the following drugs during follow-up: cannabinoids, NSAIDs, gabapentin, antidepressants, anxiolytics, and sedatives or sleep aids. The percentage may exceed 100% as a person may take more than 1 medication.

were more likely to be older ( $\geq 65$  years vs  $< 40$  years: aRR = 1.63, 95% CI = 1.24 to 2.14); being current or former smokers (current vs never: aRR = 1.89, 95% CI = 1.68 to 2.13; former vs never: aRR = 1.30, 95% CI = 1.20 to 1.41); with more comorbidities (ECI 5+ vs ECI = 0: aRR = 1.70, 95% CI = 1.29 to 2.24); baseline opioid use (aRR = 1.67, 95% CI = 1.27 to 2.19) and substance use disorders (aRR = 1.58, 95% CI = 1.43 to 1.74). In the multivariable analysis incorporating time-varying covariates, use of stronger opioids (eg, hydrocodone: aRR = 1.30, 95% CI = 1.17 to 1.45; and oxycodone: aRR = 1.60, 95% CI = 1.48 to 1.72) were associated with an increased risk of persistent opioid use. Similarly, gabapentin use was associated with a 63% increased risk of developing persistent opioid use (aRR = 1.62, 95% CI = 1.50 to 1.75), and prescription cannabinoid use was associated with an 43% increased risk (aRR = 1.43, 95% CI = 1.17 to 1.75). Additionally, use of psychiatric medication during follow-up such as antidepressants (aRR = 1.73, 95% CI = 1.58 to 1.90), anxiolytics (aRR = 1.34, 95% CI = 1.24 to 1.45) and sedatives/sleep aids (aRR = 1.20, 95% CI = 1.11 to 1.30) were also associated with increased risk for developing persistent opioid use.

### All-cause mortality

Compared with breast cancer survivors without persistent opioid use (rate [95% CI]: 25.3 [24.2 to 26.4], per 1000 person-years), those who developed persistent opioid use after the first-year survival had a much higher all-cause mortality rate (51.6 [48.0 to 55.6], per 1000 person-years) (Table 3). This difference was more prominent among individuals younger than 65 years such that the mortality rate was approximately 2.8 times higher among those who developed persistent opioid use (41.3 [36.8 to 46.3], per 1000 person-years) than those who did not (14.8 [13.8 to 15.9], per 1000 person-years).

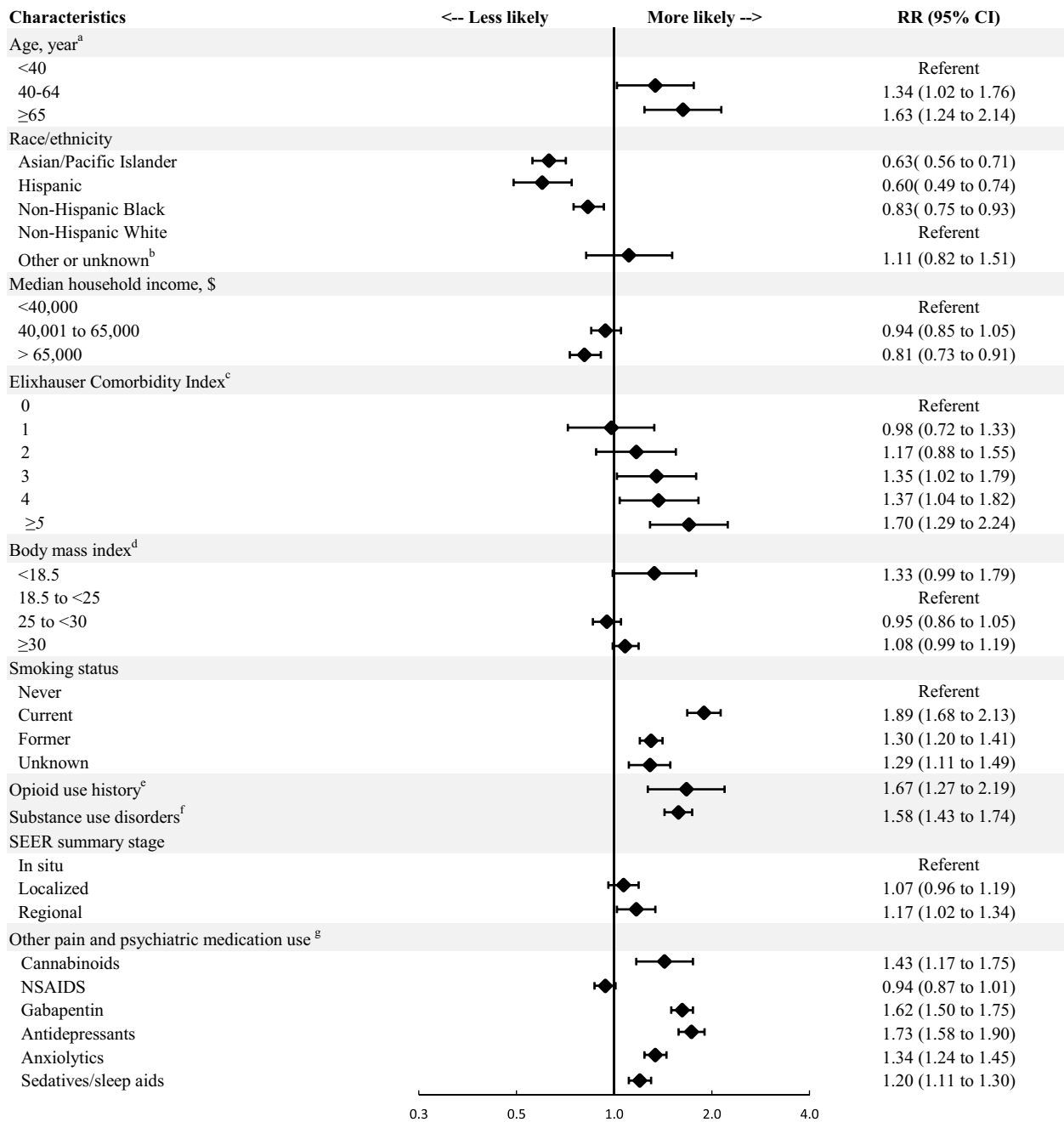
Table 4 summarizes results of estimated crude and adjusted HR (aHR) and 95% CIs for the association between persistent opioid use and all-cause mortality. In the crude analysis, persistent opioid use was associated with more than 2-fold increase in all-cause mortality (crude HR = 2.06, 95% CI = 1.89 to 2.24). The association remained statistically significant in the multivariable

analyses adjusted for baseline age, race/ethnicity, geocoded median annual household income, BMI, history of smoking, opioid use at baseline, and substance use disorder (model 1: aHR = 1.69, 95% CI = 1.54 to 1.85), with further adjustment for cancer stage, diagnosis year, cancer surgery type, and adjuvant cancer treatments (model 2: aHR = 1.66, 95% CI = 1.52 to 1.82), and use of other pain and psychiatric medication during follow-up (model 3: aHR = 1.84, 95% CI = 1.66 to 2.04). In a stratified analysis by age, the association between persistent opioid use and all-cause mortality rate was consistently greater among younger breast cancer survivors (age  $< 65$  years) than among those older than 65 years (eg, in model 3: HR = 2.11, 95% CI = 1.77 to 2.52, among  $< 65$  years vs HR; 1.69, 95% CI = 1.49 to 1.91, among  $\geq 65$  years).

### Discussion

In this longitudinal cohort study using data from a large integrated health-care organization, opioid use among nonmetastatic breast cancer survivors often continued beyond the first year of intensive cancer treatment and many individuals remained on prescription opioid and developed persistent opioid use after the first-year survivorship. Furthermore, in this insured population with relatively equal access to comprehensive general medical care and oncology care, breast cancer survivors who developed persistent opioid use had a substantially higher all-cause mortality rate compared with those who did not develop persistent opioid use, with a much stronger association observed among younger survivors ( $< 65$  years) than older survivors ( $\geq 65$  years).

Prolonged opioid use after surgery has been a substantial burden in the general population with injuries and surgical procedures. Majority of breast cancer patients undergo surgeries and other therapies in the first year of cancer diagnosis. In previous studies of general populations, the receipt of preoperative prescription opioids as well as high prescribed daily opioid doses were correlated with increased risk for persistent opioid use.<sup>19,20</sup> A meta-analysis of 33 studies including more than 1.9 million



**Figure 1.** Rate ratios and 95% confidence intervals (CIs) of factors associated with persistent opioid use after the first-year cancer survivorship among women diagnosed with a nonmetastatic breast cancer during 2009-2019. Abbreviations: NSAIDs = nonsteroidal anti-inflammatory drugs; SEER = National Cancer Institute’s Surveillance, Epidemiology, and End Results. <sup>a</sup>Age was calculated at the index date, the day of the 1-year cancer survivorship. <sup>b</sup>Other captured all other races and ethnicity categories, including multiple races and Native American. <sup>c</sup>Assessed in the 12 months prior to the index date; Elixhauser Comorbidity Index (range = 0-31, with higher values indicating greater comorbid disease burden) was calculated after excluding cancer diagnosis from the algorithm. <sup>d</sup>Calculated as weight in kilograms divided by height in meters squared (kg/m<sup>2</sup>). <sup>e</sup>Assessed in the first year of breast cancer survivorship. <sup>f</sup>Assessed in the 5 years prior to the index date. <sup>g</sup>Any use during the follow-up period, nonusers served as the reference group.

individuals in the general population reported a pooled rate of prolonged opioid use after surgery (opioid use for 3 or more months after surgery) was 6.7% (95% CI = 4.5% to 9.8%) but decreased to 1.2% (95% CI = 0.4% to 3.9%) in restricted analyses involving only opioid-naïve participants at baseline.<sup>21</sup> We observed a higher percentage of our study population who developed persistent opioid use after the first-year survivorship (15.9%) compared with the patients after noncancer surgeries in those previous studies, and we also found that individuals with

persistent use also received a much higher daily dosage. The difference in the rates of persistent use may be caused by several factors including varying definitions of persistent opioid use, different demographic, and clinical factors (eg, surgery type), but the higher rate in our study is expected as breast cancer survivors often undergo major surgeries and endure more severe pain associated with cancer and its treatments than noncancer patients. In our study population, individuals older than 65 years were more likely to develop persistent use compared with those

**Table 3.** All-cause mortality rates (per 1000 person-years) and 95% confidence intervals (CIs) among nonmetastatic breast cancer survivors in the overall study population, by persistent opioid use status, and by age group.

	Total		With persistent opioid use		Without persistent opioid use	
	N = 14 347		n = 2285		n = 12 062	
All-cause deaths	No.	Rates per 1000 PY (95% CI)	No.	Rates per 1000 PY (95% CI)	No.	Rates per 1000 PY (95% CI)
Overall	2742	29.1 (28.1 to 30.3)	714	51.6 (48.0 to 55.6)	2028	25.3 (24.2 to 26.4)
Age <65 years	1001	18.2 (17.1 to 19.3)	288	41.3 (36.8 to 46.3)	713	14.8 (13.8 to 15.9)
Age ≥65 years	1741	44.7 (42.7 to 46.9)	426	62.2 (56.5 to 68.4)	1315	41.0 (38.8 to 43.3)

Abbreviations: CI = confidence interval; PY = person-year.

**Table 4.** Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality associated with persistent opioid use in nonmetastatic breast cancer survivors.

	Overall population HR (95% CI)	Age < 65 years HR (95% CI)	Age ≥ 65 years HR (95% CI)
Crude analysis	2.06 (1.89 to 2.24)	2.79 (2.43 to 3.20)	1.50 (1.38 to 1.72)
Model 1 <sup>a</sup>	1.69 (1.54 to 1.85)	2.81 (2.43 to 3.25)	1.31 (1.17 to 1.46)
Model 2 <sup>b</sup>	1.66 (1.52 to 1.82)	2.56 (2.21 to 2.96)	1.30 (1.16 to 1.46)
Model 3 <sup>c</sup>	1.84 (1.66 to 2.04)	2.11 (1.77 to 2.52)	1.69 (1.49 to 1.91)

<sup>a</sup> Model 1 adjusted for baseline age, race/ethnicity, median annual income, body mass index (kg/m<sup>2</sup>), Elixhauser index score, opioid use at baseline and history of smoking and any substance use disorders documented in the 5 years prior to the index date.

<sup>b</sup> Model 2 adjusted for all covariates in model 1, plus tumor SEER (National Cancer Institute's Surveillance, Epidemiology, and End Results) summary stage, year of diagnosis, surgery type, adjuvant chemotherapy, radiation, and endocrine therapy.

<sup>c</sup> Model 3 adjusted for all covariates in model 2, plus time-dependent status of persistent opioid use and any concurrent use of cannabinoids, nonsteroidal anti-inflammatory drugs, gabapentin, antidepressants, anxiolytics, sedatives or sleep aids (including benzodiazepines) during follow-up.

younger than 65 years. This finding adds to the current literature of the trends in persistent opioid use and serious adverse events among cancer survivors aged 65 years and older.<sup>22,23</sup> Our findings suggest that breast cancer survivors of all age groups should be carefully monitored for high daily dosage use and persistent opioid use and potential harms.

## Strengths and limitations

This large cohort study leveraged comprehensive EHR of diverse breast cancer survivors to enhance the internal validity of the results. We found risk factors associated with development of persistent opioid use included older age (≥65 years), greater comorbidity burden (as indicated by ECI ≥5), smoking, opioid use at baseline, history of substance use disorders, and use of other pain and psychiatric medications. These findings are consistent with previous studies of patients with surgeries.<sup>19,20,24</sup>

Survival for breast cancer is generally good, given greater screening and improved treatments. According to the American Cancer Society, the 5-year relative survival rate for women with localized breast cancer at the time of diagnosis is about 99%, and about 91% for all SEER stages combined.<sup>25</sup> In this insured population of breast cancer survivors who had relatively equal access to oncology specialty care and other comprehensive health-care services, all-cause mortality rate was much higher in survivors who developed persistent opioid use than those who did not. Furthermore, it is particularly concerning that the adverse impact of persistent opioid use on mortality was much greater among those younger than 65 years. This finding emphasizes the importance of monitoring newly developed persistent opioid use

among younger breast cancer survivors and offer alternative pain management as needed to mitigate potential harms.

Several study limitations need to be considered. First, exposure to opioid medications, daily dosage, and concurrent use of other pain and psychiatric medications were ascertained through pharmacy dispensing records; therefore, we cannot be sure that patients took the medications as prescribed. However, we defined persistent opioid use based on the records of dispensed medications; thus, misclassification of persistent use is anticipated to be lower than solely relying on prescription records or self-reported use. Second, we could not measure pain severity in this study, as this information was not coded in the EHR. In addition, some illicit drug use might not be documented in the EHR, which may potentially impact the interpretation of the results. Third, although our findings are likely generalizable to other commercially insured populations diagnosed with breast cancer, prescription opioid use may be lower among those with less access to health care, including individuals who are uninsured. However, members of this health-care system are representative of southern California in terms of race/ethnicity and socioeconomic status.<sup>26</sup> Fourth, we acknowledge that development of persistent opioid use might have been driven by patients' progression to metastatic disease; however, the fraction of such patients is expected to be small. Finally, we assessed all-cause death without information on deaths associated with opioid overdose, because there was a long lag of data on underlying cause of death. However, we were able to identify death events that occurred out-of-health plan hospitals through the national death databases to mitigate misclassification.

Persistent opioid use beyond first-year survivorship was common in women with a nonmetastatic breast cancer and was associated with an increased risk of all-cause mortality. Further research is needed to explore factors that may be contributing to increased mortality in patients with persistent opioid use.

## Author contributions

Rulin C. Hechter (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing—original draft), Lie Hong Chen (Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Writing—review & editing), Jiaxiao Shi (Data curation, Formal analysis, Methodology, Writing—review & editing), Zheng Gu (Data curation, Formal analysis, Software, Writing—review & editing), Moira Brady-Rogers (Writing—review & editing), Rowan Chlebowski (Writing—review & editing), and Reina Haque (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft).

## Supplementary material

Supplementary material is available at *JNCI Cancer Spectrum* online.

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## Conflicts of interest

All authors claimed no direct COI related to the submitted work. R. C.H. received research grant paid to her institution from the Opioid Post Marketing Requirements Consortium for an unrelated opioid use outcome research. R.T.C. served in a consulting or advisory role with Pfizer and UpToDate (unrelated to study topic). R.H. received research grant paid to her institution from AstraZeneca and Pfizer Inc. for research unrelated to the study topic. No disclosure from other co-authors.

## Data availability

Individual level data from this study are unavailable for public access. However, a deidentified dataset for research purposes may be made available to requestors following data use agreements and KPSC IRB approval. The corresponding author can be contacted for guidelines on how to access data.

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