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Risk of Second Breast Cancer Events with Chronic Opioid Use in Breast Cancer Survivors

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Abstract

Background: Opioids may increase cancer risk and progression through multiple pathways. Our objective was to estimate the association between chronic opioid use and risk of second breast cancer events (SBCEs).

Methods: Cohort study of women ≥18 years, diagnosed with early stage breast cancer between January 1, 1990 and December 31, 2008, and enrolled in a large health plan for 1+ years before and after (unless died) diagnosis. SBCEs were defined as evidence of recurrence or second primary breast cancer in the medical chart. Chronic opioid use was defined as 75+ days of use in any moving 90-day window after breast cancer diagnosis and varied to 150+ days in a 180-day window in a sensitivity analysis. Using Cox proportional hazards models, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for SBCE and components of SBCE by chronic opioid use.

Results: Almost 10% met the criteria for chronic use and almost a third of users were taking opioids for > 3 years. Risk of SBCEs (HR=1.20; 95% CI: 0.85–1.70), including second primary breast cancer (HR=1.38; 95% CI: 0.71–2.70), was non-significantly higher among chronic users vs non-chronic/non-users. The HR for recurrence was 1.14 (95% CI, 0.76–2.70). Results of the sensitivity analyses on longer opioid use does support an association with SBCE or recurrence.

Conclusion: This first US-based study on chronic opioid use and cancer outcomes provides some reassurance on safety. However, the question warrants further exploration in other populations and settings.

Keywords

Breast cancer; opioids; recurrence; survivorship

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Introduction

Opioids are one of the most commonly prescribed drug classes in the United States (US).[1] The US observed a 50–79% increase in use between 2001 and 2010. In people with cancer, a population where pain is prevalent during and often after treatment, opioid use may be even higher. The long-term effects of opioid use in cancer survivors are unknown, but several biological mechanisms support the hypothesis that opioid use may increase risk of cancer progression and recurrence. [2,3]

Opioids bind directly to opioid receptors in cells. μ-Opioid receptor overexpression, which may influence tumor growth and cancer progression, was noted in several cancers[4–6] including non-small cell lung, prostate, and breast. However, studies of high morphine doses in mice do not demonstrated tumor progression.[5,6] Opioids were shown to stimulate angiogenesis in some, but not all studies of human endothelial cells and mice.[7] Contrary to this, opioids enhance apoptosis in breast cancer, small cell lung cancer, and prostate cancer cells, suggesting opioids may have anti-cancer effects.[7] Finally, opioids may suppress immune function, in particular natural killer cells, which spontaneously recognize and kill a variety of tumor cells.[4–7] Opioids may also increase concentrations of vascular endothelial growth factor, which increases angiogenesis and cell migration. Increases in tumor metastasis with opioids were observed with progression of lung cancer in cell and animal models,[8] and with fentanyl in rats.[9]

The little evidence available in humans is primarily focused on the association between anesthetic techniques with or without opioids during oncologic surgery and cancer survival. [10–13] Two studies suggest that patients receiving opioids during surgical removal of breast and prostate cancer tumors have higher recurrence rates, likely through immune suppression, compared to patients receiving paravertebral analgesia.[12,13] Two other studies failed to find an association between epidural analgesia with opioids and cancer-free survival.[10,11]

We are aware of only one study on post-diagnosis opioid use and long-term cancer outcomes.[14] The study was conducted in Denmark and found no associations between any use of opioids or chronic use and risk of breast cancer recurrence. The results may not be generalizable to US populations because of differences that include variation in types of commonly prescribed opioids.

Any effect of opioids on cancer outcomes has implications for pain management of cancer or non-cancer pain in cancer survivors. Using data from an existing cohort, we examined the trend in regular use of opioids and the association between chronic use and second breast cancer events (SBCE). Given the opioid epidemic and increasing number of cancer survivors, this is a timely, understudied research question of public health importance.

METHODS

Population and Setting

The parent study, COmmonly Used Medications and Breast Cancer Outcomes (COMBO) is a cohort study within Kaiser Permanente Washington (KPWA) (formerly Group Health

Cooperative).[15,16] KPWA is a nonprofit integrated delivery system that provides comprehensive health care and insurance to approximately 600,000 individuals in Washington State. KPWA is located within the geographic reporting region of the western Washington Cancer Surveillance System, a population-based cancer registry and member of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program.[17,18] The COMBO cohort included women ≥18 years, diagnosed with histologically confirmed unilateral stage I or II breast cancer between January 1, 1990 and December 31, 2008, enrolled at KPWA for at least 1 year before and after (unless died) diagnosis, definitive surgery, alive and recurrence-free for 120 days after surgery, and having a medical record for review.[15,16] The final cohort included 4,216 women.

The KPW Institutional Review Board approved the study with a waiver of consent.

Data collection

Data were obtained from medical record review, SEER tumor registry, and electronic health records (EHR) from one year prior to incident breast cancer diagnosis through the end of follow-up defined as the earliest of death, disenrollment from KPWA, or end of study (i.e., chart abstraction date). The EHR includes demographics, enrollment, inpatient and outpatient diagnoses, procedures including breast imaging and results, pharmacy dispensings, laboratory results, vital signs, and death.[19] The pharmacy database includes all medications dispensed at KPW's outpatient pharmacies as well as claims from contracting pharmacies. Pharmacy data are estimated to be 97% complete.[19–21] Death data are obtained from Washington State death certificates, internal sources, and SEER.

Opioid exposure

We identified all opioids dispensed in the year before breast cancer diagnosis through the end of follow-up. The date when the dispensing should run out (runout date) was estimated for each dispensing based on the date of the dispensing plus the days supply. Successive dispensings with ≤2-day gap between the runout date of one dispensing and dispensing date of the subsequent were considered a continuous episode of use. For each day in a continuous use episode, women were considered to have possession of opioids.

To evaluate trends in regular opioid use, a woman was categorized as a regular user (yes, no) in each fixed and independent calendar quarter pre- and post-breast cancer diagnosis if she was in possession of opioids for at least 45 days, regardless of whether it was continuous, in the quarter of interest (Figure 1). Classification as a regular user in each fixed quarter was independent of classification in the other quarters but days of opioid use that extended from one quarter into a subsequent quarter were counted as part of the subsequent quarter.

Chronic opioid therapy after breast cancer diagnosis was our exposure of interest in relation to risk of SBCE. Women were defined, in a time-varying manner, as a chronic user if they had 75+ days possession of opioids within any rolling 90-day window starting at diagnosis through end of follow-up (Figure 2). This is a commonly used definition of chronic opioid therapy [22–25] A moving 90-day window was scanned over the follow-up period, and days with possession of opioids were summed up within each rolling 90-day time window. We lagged exposure by 6-months to reduce protopathic bias. Therefore, women were considered

chronic users from 6 months after the day when they accumulated 75 days of opioid possession in a 90-day window and remained as exposed through the end of follow-up. Chronic opioid use in the year prior to breast cancer diagnosis was also estimated by applying the definition above to the year prior to incident breast cancer diagnosis.

Daly dose in morphine equivalent milligrams (MME) was calculated for each dispensing by first multiplying strength, quantity dispensed and a drug-specific conversion factor and then dividing by days supply.[26] Based on guidelines,[26] we defined high dose as an average daily dose of at least 90 MME/day, mid -dose as 20–90 MME/day and low dose as under 20 MME/day.

Our referent group was non-chronic opioid users and non-users. Ninety-five percent of the referent group filled at least one opioid and we therefore refer to the referent group as non-chronic users.

Outcomes

SBCE were defined as the first of a ductal carcinoma in situ or invasive cancer of the ipsilateral (recurrence) or contralateral (second primary) breast or in any regional or distant sites.[27] A woman was at risk for a SBCE starting 120 days after completing definitive surgery for the incident breast cancer.[28]

Statistical Analysis

Prevalence of regular opioid use (45+ days of use per quarter) was plotted on a histogram for the three quarters prior to breast cancer diagnosis through the last quarter with a full 91 days of follow-up and until 6 months prior to the censoring date. The date of censoring was the earliest of 5 years post diagnosis, first SBCE, death, disenrollment from the health plan, or end of study. Women without at least 6 months of follow-up were excluded from this analysis (n=47). Trends in the number of regular opioid users were estimated from the three fixed quarters prior to incident breast cancer diagnosis (i.e., Quarter 0 was 91 days prior to diagnosis to the day before diagnosis) through the subsequent 20 fixed quarters (5-years) post breast cancer diagnosis (i.e., Quarter 1 was from cancer diagnosis day to the 90th day after cancer diagnosis).

We compared patient, tumor, and treatment characteristics by outcome and by exposure. We estimated the adjusted hazard ratios (HR) and 95% confidence intervals (CI) using the cause-specific Cox proportional hazards model to assess whether chronic use was associated with risk of SBCEs while accounting for competing risks.[29] We modeled time from the incident breast cancer with a delayed entry at 120 days post-surgery[28] to SBCE as a function of a time-varying chronic opioid exposure while adjusting for potential confounders. Women were followed until the earliest of SBCE, death, disenrollment from the health plan, or end of study. We also modeled recurrences and second primaries separately to obtain a comprehensive assessment of outcomes.[29] In analysis of individual events (e.g., recurrence) women were censored at the earliest of disenrollment, end of follow-up, and other competing events (e.g., death and second primary). Chronic use was modeled as time-varying and women were only allowed unidirectional transition (i.e., non-chronic user to chronic user).

Potential confounders were determined a priori. The minimally adjusted model included age at incident breast cancer diagnosis and American Joint Committee on Cancer (AJCC) stage. Similar to other studies and the COMBO cohort, [15,16,30–34] fully adjusted models included age, AJCC stage, calendar year,[35] hormone receptor, primary breast cancer treatment, body mass index (BMI), smoking status, and menopausal status -- all of which were defined at the time of the incident breast cancer diagnosis -- as well as the time-varying covariates including endocrine therapy, Charlson co-morbidity score,[36] diabetes,[37–39] non-steroidal anti-inflammatory medication use, and receipt of surveillance mammogram in the prior 12 months. Chronic use in the year prior to breast cancer diagnosis was highly correlated with chronic use post diagnosis (i.e., 68 of the 87 chronic users) pre-diagnosis were chronic users post diagnosis) and therefore we did not adjust for prior chronic opioid use.

Using methods similar to the main analysis described above, we conducted three sensitivity analysis. We modeled chronic use as 150+ days in any 180-day window, lagged exposure by 12-months, and excluded surveillance mammography as a covariate in the model.

Proportional hazards assumptions were evaluated by testing the interaction between the exposure variable and the logarithm of follow-up time. There was no evidence suggesting a violation of the proportional hazards assumption. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Median age of the cohort at incident breast cancer diagnosis was 63 years. The majority of women were post-menopausal, Caucasian, non-Hispanic, never smokers, and had at least some college education and a Charlson co-morbidity score of zero (Table 1). The majority were AJCC stage I, lymph node negative, estrogen receptor (ER)+/progesterone receptor (PR)+, ≤2 cm in size, HER-2 negative (if tested), treated with breast conserving surgery +/− radiation, not treated with chemotherapy, and treated with endocrine therapy. Median follow-up was 6.3 years (Interquartile range 3.7–9.7 years).

In Figure 3, we display the number of women regularly using opioids in each quarter before and after incident breast cancer diagnosis. The proportion varied from a low of 2.0% in two quarters prior to incident breast cancer diagnosis to a high of 5.0% in the quarter which breast cancer was diagnosed. It consistently hovered around the median of 3.2% during the years following diagnosis and treatment.

Among the 4,216 eligible women, 558 (13.2%) experienced a SBCE (first of: 415 recurrences and 143 second primary breast cancers). Median time to the first SBCE was 3 years. Among recurrences, 67% were distant, 32% local or regional, and 1% DCIS. Among second primary breast cancers, 21% were DCIS, 49% stage I, 21% stage II, 4% stage III/IV, and 5% unknown stage.

Women with a SBCE were more likely to be peri- or premenopausal, AJCC stage II, lymph node positive, ER and/or PR negative, tumor size > 2 cm, HER-2 positive, treated with mastectomy, treated with chemotherapy, and not treated with endocrine therapy than women

without a SBCE (Table 1). Women with SBCEs had few pain diagnoses than disease free women during follow-up.

Approximately 9.7% of women (n=410) met the definition of chronic opioid use during follow-up (Table 2). The most commonly dispensed opioids among the chronic users were oxycodone (33%), hydrocodone (31%), codeine (14%), and morphine (9%). The median duration of use was 23.5 months (interquartile range (IQR): 12.9–42.1). Approximately 45% of chronic users had 1–3 years of use and 32% >3 years of use. The median duration of use in the non-chronic user referent group was 0.8 months (IQR: 0.3–1.9). We did not examine SBCE by duration of opioid use because of large differences in follow up time (i.e., censoring at SBCEs) and small numbers. Compared to non-chronic users, chronic users were older, less educated, and more likely to be menopausal and obese. Chronic users also had more extensive breast surgery and more comorbidities including diabetes than non-users. Chronic users on endocrine therapy were less likely to use aromatase inhibitors than non-chronic users. Adherence to screening surveillance was lower among chronic users than non-chronic users. Chronic users had more diagnoses of pain conditions than non-chronic users.

Among chronic users, the mean and median daily dose of opioids was 31 MME and 20 MME (IQR: 10–35), respectively. Few of the women on chronic therapy (6.1%) were using high doses of ≥ 90 mg MME/day and 50% were using low doses of <20 mg MME/day.

Chronic use was associated with a non-significant increased risk of SBCEs (HR=1.20; 95% CI: 0.85–1.70), including second primary breast cancer (HR=1.38; 95% CI: 0.71–2.70), compared to non-chronic users/non-users (Table 3). The HR for recurrence was 1.14 (95% CI, 0.76–2.70). However, all confidence intervals included 1.0 and were overlapping for recurrence and second primary.

Results from the sensitivity analysis of chronic use as defined as 150+ days in a 180-day window was attenuated toward the null. The adjusted HRs and respective 95% CI were 0.97 (0.62–1.54) for SBCE, 0.87 (0.50–1.49) for recurrence and 1.29 (0.55–3.00) for second primaries. Lagging exposure by 12-months in a sensitivity analysis yielded point estimates closer to the null with HR=1.05 (95% CI; 0.71–1.54) for SBCE, HR=0.98 (95% CI: 0.63–1.55) for recurrence and HR=1.24 (95% CI: 0.64–2.42) for second primaries. Results changed minimally when we took surveillance mammography out of adjusted models.

DISCUSSION

This was the first US based observational study on the association between chronic opioid use and risk of cancer recurrence and second primary breast cancer. Our study may provide some reassurance to women with breast cancer that chronic use post breast cancer diagnosis was not associated with a statistically significant increased risk of SBCEs in this study. However, an elevated risk of SBCEs with chronic opioid therapy cannot be ruled out, in part, due to a limited sample size to detect small differences in risk and a cohort of chronic users with relatively low dose use of non-immunosuppressive opioids.

The only other published study of chronic opioid use and breast cancer recurrence was conducted in Denmark.[14] Cronin-Fenton et al. studied 34,188 women with stage I-III incident breast cancer between 1996 and 2008. The average follow-up was 7 years and 15.6% developed a recurrence. Chronic opioid use was defined as having 1+ opioid dispensing per month for at least six months and approximately 2% met this criteria during follow-up. The study found no association between chronic opioid users (HR=1.1; 95% CI: 0.93–1.4) and risk of recurrence compared to non-chronic users. Risk did not differ by cumulative dose. Contrary to hypotheses, the study results suggest strongly immunosuppressive opioids reduce risk of recurrence (HR=0.75; 95% CI: 0.57–0.99) in comparison to non-users. The authors note that channeling bias among those with high competing risks such as mortality may explain why recurrence rates were lower among users of strong but not weakly immunosuppressive opioids. Tramadol (36%) and codeine (23%) were the most frequently prescribed opioids.

Because of other safety concerns with opioids and lack of evidence on the long-term benefits of opioids,[25] it may be concerning that almost 10% of the women in our cohort met the criteria for chronic use at some point during follow-up and approximately a third of them took opioids for more than 3 years. It is somewhat reassuring that relatively few were high dose users. However, regular use of opioids in the years following breast cancer diagnosis and treatment (~3.2% in any given quarter) was on the high end of estimates reported in the general U.S. population (2–3.5%).[40–43] A large US claims-based study of cancer patients undergoing curative-intent surgery found that 10% of opioid-naïve patients developed persistent opioid use after surgery (defined as 1+ opioid dispensings attributed to surgery plus 1+ opioid dispensings 90–180 days after surgery).[44] This is higher than the 6% to 8% reported for noncancer surgery.[45–47] These patients continued using opioids at modestly high doses (25 MMEs) even one year after cancer surgery. This data taken together should prompt discussions on whether there is a need to reduce excess opioid prescribing during the years post cancer diagnosis and treatment among cancer survivors.

COMBO is one of only a few population-based US cohorts of breast cancer survivors that contains comprehensive and high quality data on incident breast cancer characteristics and treatment through both a registry and medical charts, demographics, unbiased health care utilization including medication use and breast services, breast cancer outcomes, and death. Complete information on death and disenrollment allows the application of robust methods to address potential competing risks and informative censoring. Detailed information on breast cancer screening and relatively long follow-up are other strengths of the study.

However, our study is not without limitations. COMBO uses data from a single health plan and includes an insured, educated, and primarily Caucasian population. This may limit generalizability to some populations but the results are generalizable to a large majority of women and we do not hypothesize a difference in association by race. Loss to follow-up is a possible source of bias with 18% censored due to disenrollment from the health plan. Residual confounding is possible in any observational study. We considered numerous potential confounders, but lacked information on lifestyle factors, over-the-counter medications, and alcohol intake. We lacked data on use of non-prescribed opioids but expect illicit use to be relatively rare in older women. We had no information on opioid use in the

inpatient setting including perioperative use, which was shown to influence recurrence.[12] While not the objective of the study, we are unable to describe lifetime opioid use prior to breast cancer diagnosis. Protopathic bias where opioids are prescribed to treat symptoms of undiagnosed SBCEs is possible but we used standard methods of lagging the exposure to minimize this bias.[48] Due to limited statistical power, we were unable to evaluate associations with SBCEs by cumulative dose, duration of use, individual opioids, and immunosuppressive vs non-immunosuppressive opioids. The majority of chronic users in this study were on low doses and non-immunosuppressive opioids[49–51] (i.e., oxycodone and hydrocodone) which may partly explain the overall null results.

The gap in evidence on the safety of opioids with respect to cancer risk and cancer outcomes is of concern. Even a small increase in risk is of importance given the high prevalence of opioid use. Chronic pain is one of the most common symptoms in cancer survivors, especially in the first few years after treatment.[52–54] For example, half of breast cancer survivors report pain[55,56] and pain remains common even among long-term breast cancer survivors.[57,58] As many as 30% of breast cancer survivors report above-average pain 10 years after treatment.[59] Another example is pelvic pain syndrome arising in patients who undergo radiation therapy for cancers of the rectum, prostate, bladder, and uterus.[60] Neuropathic pain is also commo in cancer survivors who have undergone surgery.[61,62] As cancer survivors live longer, pain from other conditions becomes common.[63,64] A study out of Canada found opioid prescribing to be 1.2 times higher among cancer survivors than matched controls.[61] This coupled with evidence that opioids influence multiple well-established cancer pathways[2,3] such as immune suppression, cell proliferation, cell invasion and angiogenesis, points to a need for clinical studies of the effects of chronic use on cancer outcomes in diverse population and across different cancers. Our results can be used in planning future studies in this area.

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Take home messages:

1. The long-term effects of opioid use in cancer survivors are unknown, but several biological mechanisms support the hypothesis that opioid use may increase risk of cancer progression and recurrence.
2. Regular use of opioids among breast cancer survivors is common. Regular use varied from 2.0% in quarters prior to incident breast cancer diagnosis to a high of 5.0% in the quarter which breast cancer was diagnosed. It consistently hovered around 3.2% during the years following diagnosis and treatment.
3. Chronic use of opioids is common with 10% of breast cancer survivors meeting the definition of chronic opioid use during follow-up. Median duration of chronic use was 23.5 months: 45% had 1–3 years of use and 32% >3 years of use.
4. This first US based study of women with early stage breast cancer provides some reassurance that chronic opioid use does not increase the risk of second breast cancer events (SBCEs). While statistically non-significant, the observed higher risk estimates for SBCEs warrants further study in larger and different populations.

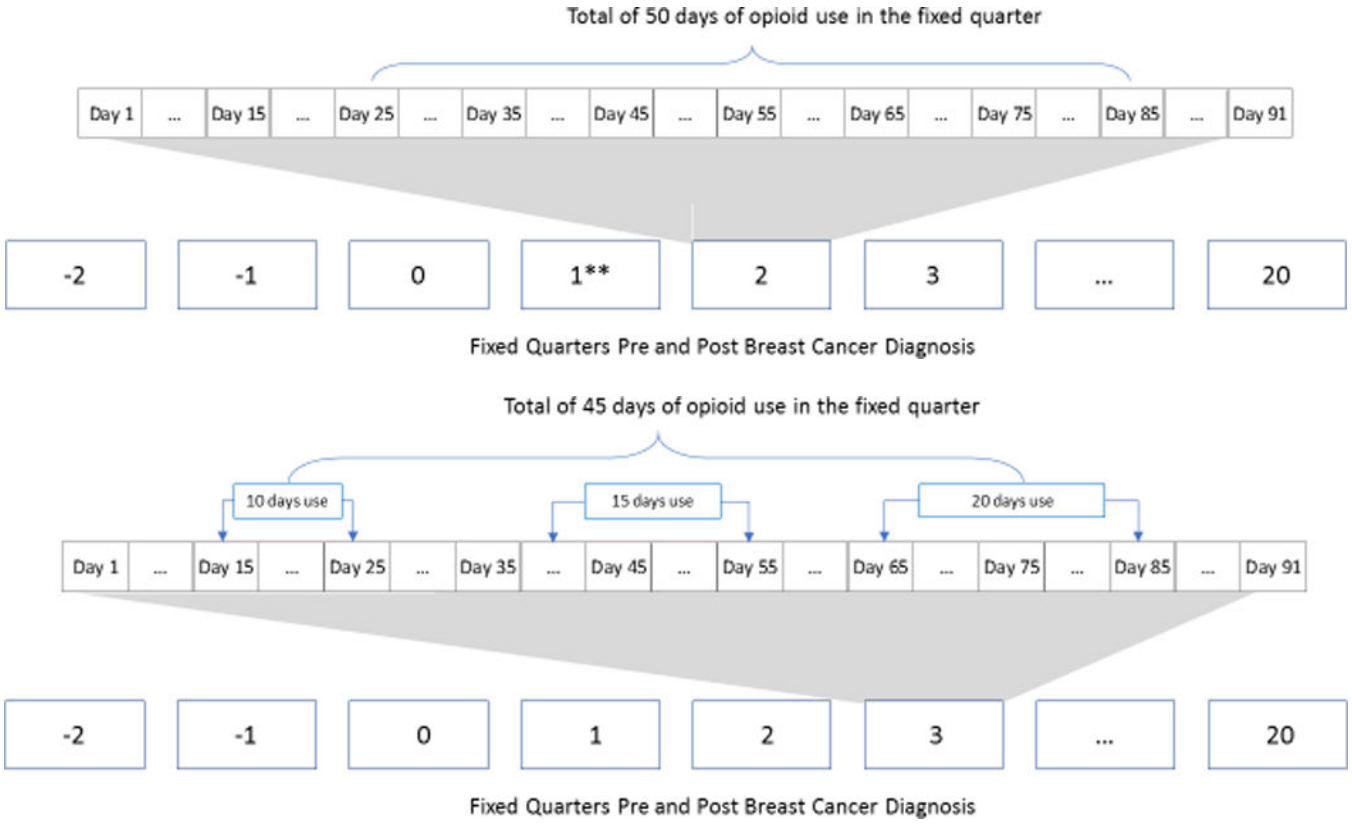

Figure 1.

Two examples of regular opioid use per fixed quarters pre- and post-incident breast cancer diagnosis. Regular use defined as 45+ days of opioid use in fixed and independent quarters of interest. Not to scale.

*Regular user in a fixed quarter if 45+ days of opioid use in the fixed quarter of interest. Count starts over at the beginning of each quarter.

**Q1 = quarter of incident brest cancer diagnosis

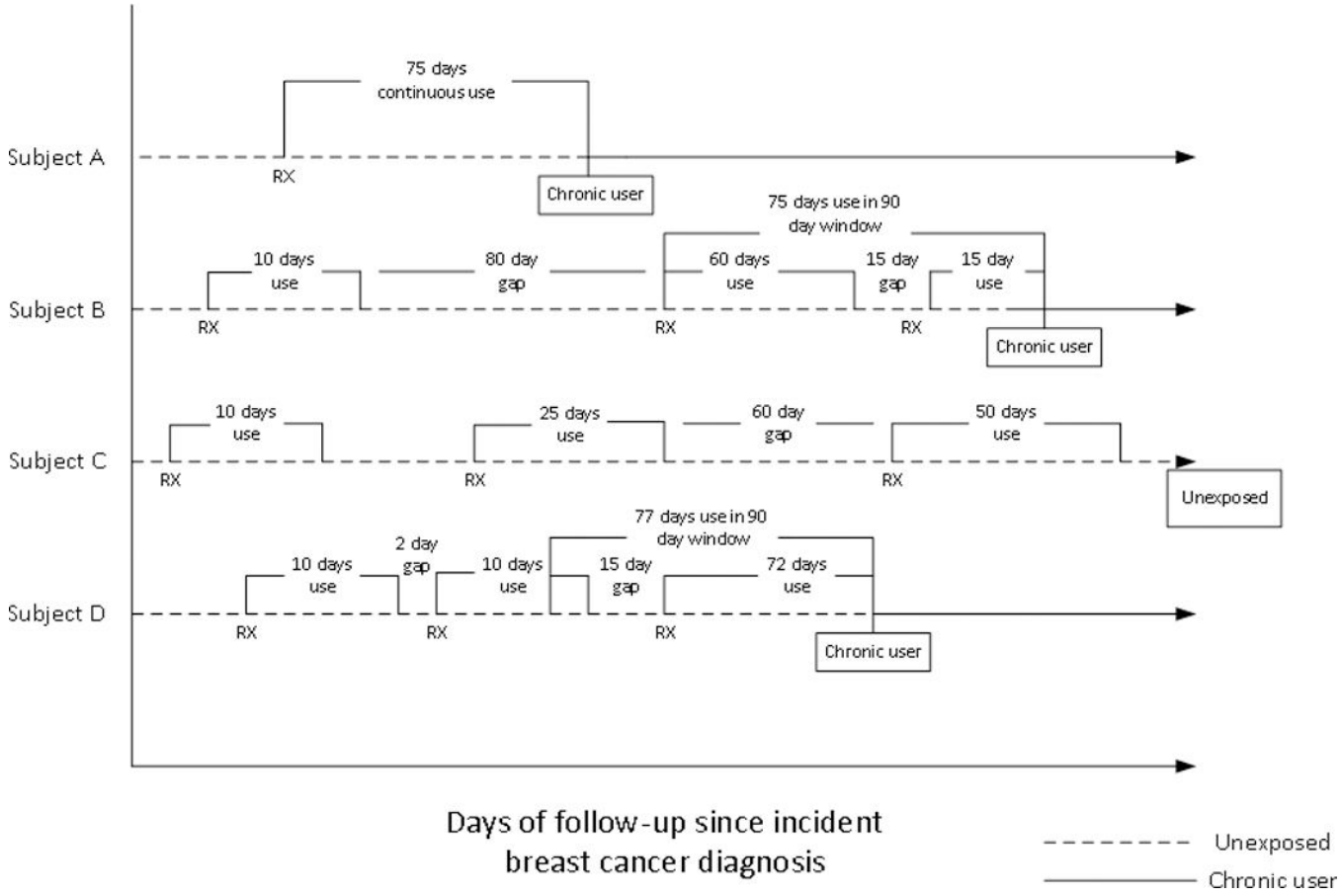

Figure 2.

Examples of chronic opioid use post incident breast cancer diagnosis through end of follow-up. Chronic use defined as 75+ days of use in any rolling 90-day window following diagnosis. Not to scale.

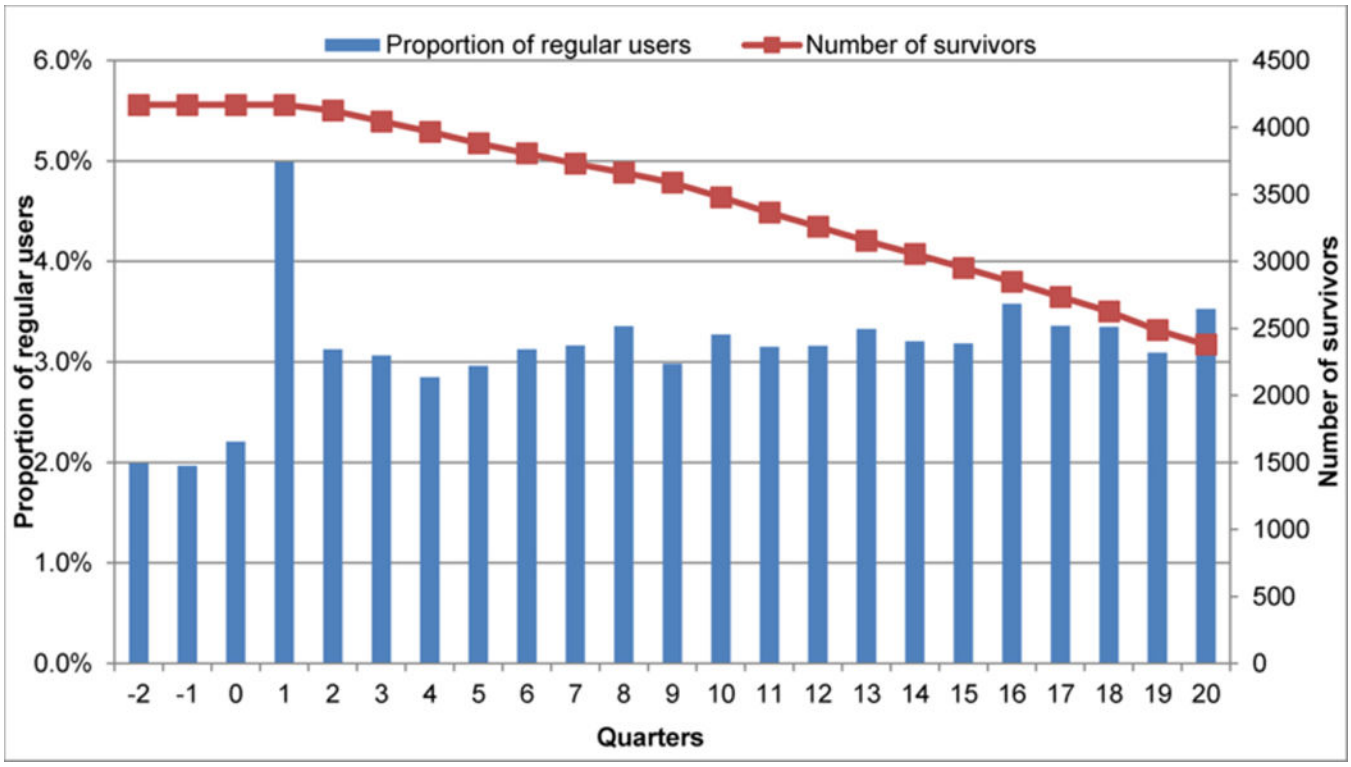

Figure 3.

The proportion of regular opioid users, defined as 45+ days of use in each fixed 91-day quarter, during the quarters pre (0, −1, and −2) and post (quarters 1–20) incident breast cancer diagnosis. The red line denotes the number of breast cancer survivors at each quarter. *Regular opioid use defined as having 45+ days of use in each 91-days quarter.Quarter #1 is the quarter in which the incident brest cancer was diagnosed.

Table 1.

Characteristics of women included in the COMBO study, overall and by second breast cancer event status

	All		*SBCE*[*]			
	n=4216		*No (n=3658)*		*Yes (n=558)*	
Characteristics	**n**	**(column %)**	**n**	**(column %)**	**n**	**(column %)**
At incident breast cancer diagnosis						
Year of diagnosis						
1990–1994	950	(22.5)	755	(20.6)	195	(34.9)
1995–1999	1191	(28.2)	1020	(27.9)	171	(30.6)
2000–2004	1201	(28.5)	1073	(29.3)	128	(22.9)
2005–2008	874	(20.7)	810	(22.1)	64	(11.5)
Age (years)						
Median (Interquartile range)	63	(52–73)	63	(52–73)	62	(50–72)
18–39	139	(3.3)	112	(3.1)	27	(4.8)
40–49	646	(15.3)	544	(14.9)	102	(18.3)
50–59	995	(23.6)	866	(23.7)	129	(23.1)
60–69	1018	(24.1)	889	(24.3)	129	(23.1)
70–79	940	(22.3)	824	(22.5)	116	(20.8)
80+	478	(11.3)	423	(11.6)	55	(9.9)
Menopausal status						
Peri- or Pre-menopausal	1145	(27.2)	956	(26.1)	189	(33.9)
Post-menopausal	3071	(72.8)	2702	(73.9)	369	(66.1)
Race						
White	3719	(88.5)	3232	(88.7)	487	(87.3)
African American	136	(3.2)	104	(2.9)	32	(5.7)
American Indian/Alaska Native	113	(2.7)	104	(2.9)	9	(1.6)
Asian/Pacific Islander	233	(5.5)	203	(5.6)	30	(5.4)
Unknown	15		15		0	
Hispanic ethnicity						
Non-Hispanic	3976	(94.6)	3438	(94.3)	538	(96.4)
Hispanic	229	(5.4)	209	(5.7)	20	(3.6)
Unknown	11		11		0	
Education						
High school or less	418	(23.4)	393	(23.5)	25	(21.4)
Some college	634	(35.4)	594	(35.5)	40	(34.2)
College or post graduates	737	(41.2)	685	(41)	52	(44.4)
Unknown	2427		1986		441	
Body mass index (kg/m^2)						
<18.5	69	(1.6)	55	(1.5)	14	(2.5)

Characteristics	All n=4216		SBCE* No (n=3658)		Yes (n=558)	
	n	(column %)	n	(column %)	n	(column %)
18.5–24.9	1453	(34.6)	1269	(34.8)	184	(33.3)
25–29.9	1362	(32.5)	1186	(32.6)	176	(31.8)
30–34.9	766	(18.3)	666	(18.3)	100	(18.1)
35+	546	(13)	467	(12.8)	79	(14.3)
Unknown	20		15		5	
Smoking status						
Current	253	(6.0)	230	(6.3)	23	(4.1)
Past	352	(8.3)	318	(8.7)	34	(6.1)
Never/Unknown	3611	(85.6)	3110	(85.0)	501	(89.8)
AJCC stage						
I	2648	(62.8)	2384	(65.2)	264	(47.3)
IIA	1078	(25.6)	906	(24.8)	172	(30.8)
IIB	490	(11.6)	368	(10.1)	122	(21.9)
Lymph node						
Negative	2847	(75.6)	2525	(77.4)	322	(64.3)
Positive	918	(24.4)	739	(22.6)	179	(35.7)
Unknown	451		394		57	
ER/PR status**						
ER-/PR-	667	(16.7)	531	(15.3)	136	(25.7)
ER+/PR-	383	(9.6)	319	(9.2)	64	(12.1)
ER-/PR+	61	(1.5)	47	(1.4)	14	(2.6)
ER+/PR+	2888	(72.2)	2572	(74.1)	316	(59.6)
ER and/or PR unknown	217		189		28	
Tumor size						
≤2cm	3110	(73.8)	2785	(76.1)	325	(58.5)
>2cm	1104	(26.2)	873	(23.9)	231	(41.5)
Unknown	2		0		2	
HER2 status						
Test done	2074	(49.2)	1874	(51.2)	200	(35.8)
Positive/borderline	353	(17.0)	311	(16.6)	42	(21.0)
Negative	1714	(82.6)	1556	(83.0)	158	(79.0)
No result	7	(0.3)	7	(0.4)	0	(0)
Surgical treatment						
Mastectomy including radical ± radiation	1521	(36.1)	1289	(35.2)	232	(41.6)
Breast conserving, + radiation	2172	(51.5)	1927	(52.7)	245	(43.9)
Breast conserving, no radiation	523	(12.4)	442	(12.1)	81	(14.5)
Other treatment						

Characteristics	All n=4216		SBCE* No (n=3658)		SBCE* Yes (n=558)	
	n	(column %)	n	(column %)	n	(column %)
Any chemotherapy	1376	(32.6)	1142	(31.2)	234	(41.9)
Any endocrine therapy	2363	(56.0)	2101	(57.4)	262	(47.0)
Tamoxifen only	1394	(59.0)	1297	(61.7)	97	(37.0)
Aromatase inhibitors only	288	(12.2)	275	(13.1)	13	(5.0)
Both tamoxifen and aromatase inhibitors	673	(28.5)	522	(24.9)	151	(57.6)
Unknown	8	(0.3)	7	(0.3)	1	(0.4)
Charlson co-morbidity score						
0	3229	(76.6)	2784	(76.1)	445	(79.7)
1	704	(16.7)	625	(17.1)	79	(14.2)
2+	283	(6.7)	249	(6.8)	34	(6.1)
Throughout study follow-up ***						
Years of follow-up, Median (interquartile range)	6.3	(3.7–9.7)	6.7	(4.2–10.2)	3.3	(1.8–5.9)
Diabetes	610	(14.5)	539	(14.7)	71	(12.7)
% Follow-up years with yearly surveillance mammography						
<50%	939	(22.3)	793	(21.7)	146	(26.2)
50–79%	1439	(34.1)	1284	(35.1)	155	(27.8)
80%+	1838	(43.6)	1581	(43.2)	257	(46.1)
Pain conditions						
Abdominal	1875	(44.5)	1690	(46.2)	185	(33.2)
Arthritis/gout	2993	(71.0)	2700	(73.8)	293	(52.5)
Back	1074	(25.5)	987	(27.0)	87	(15.6)
Chest	2077	(49.3)	1876	(51.3)	201	(36.0)
Fibromyalgia	706	(16.8)	633	(17.3)	73	(13.1)
General chronic	163	(3.9)	157	(4.3)	6	(1.1)
Limb/extremity	1916	(45.4)	1745	(47.7)	171	(30.6)
Neck	369	(8.8)	327	(8.9)	42	(7.5)
Neuropathic	278	(6.6)	254	(6.9)	24	(4.3)
Pelvic	52	(1.2)	42	(1.2)	10	(1.8)
Migraine/TMJ	1213	(28.8)	1099	(30.0)	114	(20.4)

*SBCE=second breast cancer event includes recurrence or second primaries, in-situ and invasive

**ER/PR=Estrogen receptor/progesterone receptor

***Earliest of SBCE, death, disenrollment from health plan, or end of study period.

Table 2.

Characteristics of women included in the COMBO study, overall and by chronic opioid use after breast cancer diagnosis

Characteristics	*Chronic opioid use**			
	No (n=3,806)		*Yes (n=410)*	
	n	**(column %)**	**n**	**(column %)**
At incident breast cancer diagnosis				
Year of diagnosis				
1990–1994	858	(22.5)	92	(22.4)
1995–1999	1062	(27.9)	129	(31.5)
2000–2004	1065	(28)	136	(33.2)
2005–2008	821	(21.6)	53	(12.9)
Age (years)				
Median (Interquartile range)	62	(51–72)	68	(58–76)
18–39	131	(3.4)	8	(2)
40–49	616	(16.2)	30	(7.3)
50–59	917	(24.1)	78	(19)
60–69	905	(23.8)	113	(27.6)
70–79	820	(21.5)	120	(29.3)
80+	417	(11)	61	(14.9)
Menopausal status				
Peri- or Pre-menopausal	1073	(28.2)	72	(17.6)
Post-menopausal	2733	(71.8)	338	(82.4)
Race				
White	3344	(88.2)	375	(91.7)
African American	120	(3.2)	16	(3.9)
American Indian/Alaska Native	101	(2.7)	12	(2.9)
Asian/Pacific Islander	227	(6)	6	(1.5)
Unknown	14		1	
Hispanic ethnicity				
Non-Hispanic	3579	(94.3)	397	(96.8)
Hispanic	216	(5.7)	13	(3.2)
Unknown	11		0	(0)
Education				
High school or less	369	(22.4)	49	(34.3)
Some college	586	(35.6)	48	(33.6)
College or post graduates	691	(42)	46	(32.2)
Unknown	2160		267	
Body mass index (kg/m^2)				

Characteristics	*Chronic opioid use*[*]			
	No (n=3,806)		*Yes (n=410)*	
	n	**(column %)**	**n**	**(column %)**
<18.5	62	(1.6)	7	(1.7)
18.5–24.9	1349	(35.6)	104	(25.4)
25–29.9	1236	(32.6)	126	(30.7)
30–34.9	673	(17.8)	93	(22.7)
35+	466	(12.3)	80	(19.5)
Unknown	20		0	(0)
Smoking status				
Current	221	(5.8)	32	(7.8)
Past	321	(8.4)	31	(7.6)
Never/Unknown	3264	(85.8)	347	(84.6)
AJCC stage				
I	2395	(62.9)	253	(61.7)
IIA	977	(25.7)	101	(24.6)
IIB	434	(11.4)	56	(13.7)
Lymph node				
Negative	2586	(75.9)	261	(73.3)
Positive	823	(24.1)	95	(26.7)
Unknown	397		54	
ER/PR status[**]				
ER-/PR-	612	(16.9)	55	(14.3)
ER+/PR-	342	(9.5)	41	(10.7)
ER-/PR+	54	(1.5)	7	(1.8)
ER+/PR+	2607	(72.1)	281	(73.2)
ER and/or PR unknown	191		26	
Tumor size				
≤2cm	2812	(73.9)	298	(72.7)
>2cm	992	(26.1)	112	(27.3)
Unknown	2		0	(0)
HER2 status				
Test done	1888	(49.6)	186	(45.4)
Positive/borderline	328	(17.4)	25	(13.4)
Negative	1553	(82.3)	161	(86.6)
No result	7	(0.4)	0	(0)
Surgical treatment				
Mastectomy including radical ± radiation	1339	(35.2)	182	(44.4)
Breast conserving, + radiation	1989	(52.3)	183	(44.6)
Breast conserving, no radiation	478	(12.6)	45	(11)

Characteristics	*Chronic opioid use**			
	No (n=3,806)		*Yes (n=410)*	
	n	**(column %)**	**n**	**(column %)**
Other treatment				
Any chemotherapy	1259	(33.1)	117	(28.5)
Any endocrine therapy***	2123	(55.8)	240	(58.5)
Tamoxifen only	1240	(58.4)	154	(64.2)
Aromatase inhibitors only	272	(12.8)	16	(6.7)
Both tamoxifen and aromatase inhibitors	603	(28.4)	70	(29.2)
Unknown	8	(0.4)	0	0
Charlson co-morbidity score				
0	2964	(77.9)	265	(64.6)
1	613	(16.1)	91	(22.2)
2+	229	(6)	54	(13.2)
Throughout study follow-up*				
Years of follow-up, Median (interquartile range)	6.1	(3.6–9.6)	7.5	(4.5–10.6)
Diabetes	519	(13.6)	91	(22.2)
% Follow-up years with yearly surveillance mammography				
<50%	826	(21.7)	113	(27.6)
50–79%	1265	(33.2)	174	(42.4)
80%+	1715	(45.1)	123	(30)
Pain conditions				
Abdominal	1603	(42.2)	272	(66.3)
Arthritis/gout	2632	(69.2)	361	(88.1)
Back	859	(22.6)	215	(52.4)
Chest	1787	(47.0)	290	(70.7)
Fibromyalgia	573	(15.1)	133	(32.4)
General chronic	78	(2.0)	85	(20.7)
Limb/extremity	1686	(44.3)	230	(56.1)
Neck	304	(8.0)	65	(15.9)
Neuropathic	219	(5.8)	59	(14.4)
Pelvic	44	(1.2)	8	(2.0)
Migraine/TMJ	1050	(27.6)	163	(39.8)

*Chronic use defined as 75+ days of use in any 90-day window

**ER/PR=Estrogen receptor/progesterone receptor

***Throughout study follow up - earliest of SBCE, death, disenrollment from health plan, or end of study period

Table 3.

Risk of second breast cancer events (SBCE) by chronic opioid use after breast cancer diagnosis.

Outcomes	Exposure status*	Number of events **	Unadjusted Incidence rate (per 1000-person year)	Minimally adjusted Hazard Ratio ***	95% Confidence Interval	Multivariate adjusted Hazard Ratio†	95% Confidence Interval
SBCE	Non	521	18.4	Reference		Reference	
	Chronic	37	23.6	1.23	0.88–1.72	1.20	0.85–1.70
Recurrence	Non	388	13.7	Reference		Reference	
	Chronic	27	17.2	1.21	0.81–1.79	1.14	0.76–1.70
Second primary	Non	133	4.7	Reference		Reference	
	Chronic	10	6.4	1.28	0.67–2.47	1.38	0.71–2.70

*Chronic opioid use was defined as 75+ days of use in any 90-day window and modeled as a time-varying covariate.

**Second breast cancer event includes recurrence or second primaries, in-situ and invasive. Women were censored at the earliest of disenrollment, death, any SBCE event, or end of study period.

***Adjusted for age at diagnosis (18–49,50–59, 60–69, 70–79, 80+ years) and AJCC stage (I, IIA, IIB).

†Adjusting for age at diagnosis (18–49,50–59, 60–69, 70–79, 80+ years); diagnosis year (1990–1994,1995–1999, 2000–2004, 2005–2008); AJCC stage (I, IIA, IIB); hormone receptor status (estrogen receptor [ER]-/progesterone receptor [PR]-, ER+/PR-, ER-/PR+, ER+/PR+, and ER and/or PR unknown); primary treatment for initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation); endocrine therapy for the incident breast cancer (yes/no, time-varying); body mass index (BMI) at diagnosis (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35+kg/m^2); smoking status at diagnosis (current, past, never/unknown); menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal); Charlson comorbidity score (0, 1, 2+, time-varying); diabetes (yes/no, time-varying); use of NSAIDs (yes/no, time-varying) and receipt of screening mammogram in the 12 months prior to events (yes/no, time-varying).