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Opioids and Breast Cancer Recurrence: A Danish population-based cohort study

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Abstract

Background—Opioids may alter immune function and thereby potentially affect cancer recurrence. We investigated the association between post-diagnosis opioid use and breast cancer recurrence.

Methods—We identified incident early-stage breast cancer patients, diagnosed 1996-2008 in Denmark, registered in the Danish Breast Cancer Cooperative Group Registry. Opioid prescriptions were ascertained from the Danish National Prescription Registry. Follow-up began on the date of breast cancer primary surgery and continued until breast cancer recurrence, death, emigration, ten years, or 31 July 2013, whichever occurred first. We used Cox regression models to compute hazard ratios (HRs) and 95% confidence intervals (95%CI) associating breast cancer recurrence with opioid prescription use overall, and by opioid type and strength, immunosuppressive effect, chronic use (>=6 months continuous exposure), and cumulative morphine-equivalent dose, adjusting for confounders.

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Results—We identified 34,188 patients who together contributed 283,666 person-years of follow-up. There was no association between ever use of opioids and breast cancer recurrence (HR_{crude}=0.98, 95% CI=0.90 - 1.1, and $HR_{adjusted}$=1.0, 95% CI=0.92 - 1.1), regardless of opioid type, strength, chronicity of use, and cumulative dose. Breast cancer recurrence rates were lower among users of strong but not weakly immunosuppressive opioids, possibly due to channeling bias among those with high competing risk as mortality was higher among users of this drug type.

Conclusions—This large prospective cohort study provided no clinically relevant evidence of an association between opioid prescriptions and breast cancer recurrence. Our findings are important to cancer survivorship, as opioids are frequently used to manage pain associated with comorbid conditions.

Keywords

Breast cancer; breast cancer recurrence; cohort study; epidemiology; opioids; risk

INTRODUCTION

Opioids are frequently and increasingly used as analgesics for treating moderate to severe pain in patients with malignant and non-malignant conditions.[1,2] Opioids inhibit cell-mediated immunity—a principal defense against cancer.[3] Laboratory studies suggest that opioids induce tumor growth, by promoting angiogenesis, cell cycle progression, migration, and metastasis.[3,4] These mechanisms may increase the rate of cancer recurrence. However, some *in vitro* studies have shown that morphine and other opioids prevent angiogenesis, inhibit matrix metalloproteinase expression,[3] and promote apoptosis, albeit at high doses that may not be relevant for clinical practice.[4] Murine breast cancer models have shown that morphine does not affect tumorigenesis, but does appear to promote growth of existing tumors.[5] Methylnaltrexone, a μ-opioid receptor antagonist used to treat opioid side effects, inhibits the growth of lung carcinoma and lung metastasis.[6] This evidence suggests that opioids may modify cancer progression, although whether the balance of effects favors increased or decreased recurrence risk remains unclear.

Studies of opioids and cancer progression in humans almost exclusively evaluated the effect of opioid-based anesthesia on cancer survival.[7-11] During the perioperative period opioids may be administered in high doses, and tumor cells may have higher risk of disseminating into the general circulation.[4,12] Some studies,[9-11] but not all,[7,8] indicate poorer survival among patients who received general anesthesia with morphine compared with those who received regional anesthesia (*i.e.*, local, paravertebral, or epidural). A μ-opioid receptor gene polymorphism, which diminishes response to opioids, has been correlated with better survival in breast cancer patients,[13] and high μ-opioid receptor expression has been correlated with poorer survival in prostate cancer.[14] A study based on 99 non-small cell lung cancer patients found a higher five-year recurrence rate among patients who used opioids in the first 96 hours post-surgery.[15]

Any role of opioids in cancer progression would have important clinical implications for pain management of patients with cancer or comorbid conditions.[16] The potential for such pain management to exacerbate malignant disease requires clarification. We therefore

measured the association between use of prescribed opioids and breast cancer recurrence in a large Danish population-based study of breast cancer survivors.

METHODS

This study was approved by the Danish Data Protection Agency (record 2012-41-0793), the Danish Medicines Agency, and the Danish Breast Cancer Cooperative Group (DBCG).

Source population and data collection

This cohort study included all women residing in Denmark who were diagnosed with incident invasive breast cancer between 1996 and 2008 and whose diagnosis was registered with the DBCG. The DBCG has captured most cases of invasive breast cancer since its establishment in 1976, with completeness of registration increasing over time from 87% in 1986 to 96% in 1997.[17] The DBCG obtains prospective, pre-specified data on tumor, treatment, and patient characteristics from treating physicians. Patients with operable breast cancer registered in the DBCG undergo semi-annual follow-up exams for the first five years after diagnosis, and annual exams for the next five years. Follow-up exams include a physical and, if indicated, a chest x-ray, bone scan, or other diagnostic procedure to detect recurrent disease.[18] Patients who develop recurrent disease between follow-up exams are also reported to the DBCG. From the DBCG we retrieved surgery date, age at diagnosis, menopausal status at diagnosis, stage based on WHO histologic tumor type and lymph node status, histologic grade, tumor estrogen receptor (ER) status, type of primary surgery, chemotherapy, radiotherapy, or endocrine therapy (ET), and date and anatomical site of recurrence. Information on age on the surgery date and all-cause mortality was retrieved from the Danish Civil Registration System (DCRS).[19]

The National Prescription Registry (NPR) maintained by Statistics Denmark has recorded all prescriptions redeemed at Danish pharmacies since 1995, including the date dispensed, drug prescribed (according to the Anatomical Therapeutic Chemical classification (ATC)), and fill quantity.[20] Data can be linked among registries using the civil personal registration number (CPR), a unique personal identification number assigned to each Danish citizen by the DCRS at birth or upon immigration.[19] We used the NPR to ascertain information on prescriptions for opioids, and potentially confounding co-prescriptions including simvastatin, aspirin, and hormone replacement therapy (HRT) (Supplementary Information 1).

We obtained information on comorbidities from the Danish National Registry of Patients (DNRP), which has recorded data on non-psychiatric hospital admissions since 1977 and on outpatient hospital contacts since 1995, including CPR number, dates of admission and discharge, and up to 20 discharge diagnoses.[21] We examined specific comorbid diseases prevalent on the date of breast cancer surgery, including rheumatoid arthritis, osteoarthritis, diabetes, cancer diagnoses other than breast cancer, peripheral and cerebral vascular disease, myocardial infarction, and congestive heart failure. Specific ICD–8 and ICD–10 codes used in the study are listed in Supplementary Information 2.

Analytic variables

Age at diagnosis was included as a continuous variable in multivariable models. Histological grade was classified as low, moderate, or high. We defined primary therapy as either mastectomy or breast conserving surgery with radiotherapy, chemotherapy as a dichotomous variable, and ER and endocrine therapy (ET) as a design variable (ER+/ET+, ER+/ET−, ER −/ET−, ET−/ET+).

Opioid prescriptions were modelled as a time-dependent exposure updated daily during follow-up and lagged by one year. We have chosen an initial lag time of one year and conducted sensitivity analyses where models were lagged by two years but saw no change in the effect estimates. Opioid exposure overall was defined as at least one opioid prescription in the year before exposure assessment. Thus, a patient was considered exposed to opioids at a given time when she was prescribed an opioid more than one but less than two years before each assessment point. Similarly, prescriptions in the two years before diagnosis counted towards the risk period in the first two years after diagnosis. Opioid exposure was also classified by opioid strength [prescriptions for weak opioids (tramadol, codeine, dextropropoxyphene), strong opioids (all others), and both strong and weak opioids], and modeled again as a time-varying exposure lagged by one year. We also conducted sensitivity analyses changing the definition of opioid exposure from one prescription to two prescriptions, and again, lagging models by one and two years.

To investigate the potential immunosuppressive effects of opioids (classified according to their *in vitro* immunosuppressive effects),[22] the following categories of opioid exposure were examined: non-use; exclusive use of strongly immunosuppressive opioids (codeine, morphine, fentanyl); exclusive use of weakly immunosuppressive opioids (oxycodone, tramadol, buprenorphine, hydromorphone); and a single category for a combination of strong and weak immunosuppressive opioids and other opioids (ketobemidone, nicomorphine, pethidine, pentazocine, tapentadol, dextropropoxyphene).

Chronic long-term opioid consumption, incorporating both quantity and duration of opioids exposure, was defined as filling at least one opioid prescription per month for at least six months of the prescribing year.[2] Specifically, this was operationalized as: six or more prescriptions with two of these at least 150 days apart (180 days apart in a sensitivity analysis), and no two consecutive prescriptions more than 37 days apart. We calculated morphine-equivalent dose based on morphine-equivalent fractions as described by Jarlbæk *et al*..[23] The cumulative morphine-equivalent dose was equal to the product of the number and dose of tablets (or injections) dispensed, and the morphine-equivalent conversion factors associated with each prescription's ATC code. These values were aggregated and updated in each follow-up cycle according to the following categories: non-use, 1mg–500 mg (low), 501 mg–5000 mg (medium), and >5000 mg (high).

Potential confounding drugs, including prescriptions for simvastatin and aspirin, which have been found to modify breast cancer prognosis,[24,25] were defined as time-varying covariates lagged by one year. As for opioids, exposure to aspirin and simvastatin was lagged with a moving one-year exposure period. HRT was defined as a baseline covariate.

Information on breast cancer recurrence was ascertained from the DBCG and defined by DBCG as locoregional or distant recurrence, or contralateral breast cancer.[17] Follow-up began on the date of breast cancer primary surgery and continued until the first of recurrence, death, emigration, completion of ten years of follow-up, or 31st July 2013. We censored patients at ten years in accordance with the patients' active follow-up program.[18]

Statistical analyses

We examined the frequency and proportion of ever and never users of opioids within categories of covariates (Table 1).

We used Cox regression models to estimate associations with breast cancer recurrence, computed as hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) (α=0.05), calculated by the Wald method. Estimated associations were adjusted for the following confounders: age, menopausal status, histologic grade, ER/ET status, stage, primary surgery type, chemotherapy, time-varying exposures to simvastatin and aspirin, baseline HRT, and comorbid diseases, as described above. All time-varying covariates were lagged by one year in the Cox models, both to allow for an induction period and to avoid the possibility that subclinical recurrence could affect prescribing patterns. Effect measure modification was evaluated by stratifying analyses on ER/ET status, menopausal status, and surgery type. Additionally, Cox models were used to investigate the effect of cumulative opioid exposure, chronic long-term opioid exposure, and the potential immunosuppressive effect of opioids [22] on breast cancer recurrence. Cox models were also used to investigate the association between the immunosuppressive effect of opioids and all-cause mortality. All analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC).

RESULTS

This study included 34,188 patients diagnosed with invasive breast cancer between 1996 and 2008 (Table 1). Overall, 47% of patients were ever users of opioids and 5,325 patients were diagnosed with a recurrence over a median of 7.1 years of follow-up. Opioid users were generally older at diagnosis (median age 61.8 versus 57.8 years), more likely to be post-menopausal. Overall, 20%, 21%, and 31% of the breast cancer cohort were ever prescribed aspirin, simvastatin, and HRT, respectively. Compared with non-opioid users, opioid users were more likely to be concurrent users of simvastatin, aspirin, and HRT. A higher proportion of opioid users versus non-users had stage I disease (39% versus 37%), grade I tumors (29% versus 26%), and ER+/ET+ disease (54% versus 51%). Opioid users were less likely than non-users to be treated with chemotherapy (26% versus 37%) and had a higher frequency of comorbid diseases than non-users.

Tramadol was the most frequently prescribed opioid, accounting for 36% of all opioid prescriptions. Codeine accounted for 23% of prescriptions (Supplementary Information 3). Oxycodone, ketobemidone, and morphine were the most frequently prescribed strong opioids (11%, 10%, and 9% of all opioid prescriptions, respectively).

Among the 5,325 patients who developed recurrent disease, 1,693 (32%) had ever used opioids. Compared with non-use, use of opioids was not associated with breast cancer

recurrence in both crude and adjusted models (HR_{crude}=0.98, 95% CI=0.90 - 1.1, and $HR_{adjusted}$=1.0, 95% CI=0.92 - 1.1) (Table 3). Similar null associations were seen for weak and strong opioid use, and among patients who used both types of opioids (Table 2). There was no evidence of an association between opioids and recurrence in sensitivity analyses where drug exposure was lagged by two years (Supplementary Information 4). There was also no association between opioids and breast cancer recurrence according to low, medium or high morphine-equivalent cumulative dose (Table 2).

There was no evidence of an association between chronic long-term or short-term opioid exposure and breast cancer recurrence ($HR_{adjusted}$=1.1, 95% CI=0.93 - 1.4; and $HR_{adjusted}$=0.99, 95% CI=0.91 - 1.1, respectively).

In contrast, use of assumed strongly immunosuppressive opioids correlated with a decreased rate of breast cancer recurrence ($HR_{adjusted}$=0.75, 95% CI=0.57 - 0.99), while weakly immunosuppressive opioids, or other/both types of opioids had no association with breast cancer recurrence (Table 2). However, we observed a four-fold increase in the rate of all-cause mortality associated with use of strongly immunosuppressive opioids (Supplementary Information 5).

Finally, there was no evidence of effect modification in models stratified by ER/ET status, menopausal status, surgery type, and chemotherapy receipt (Table 3).

DISCUSSION

Our study shows no evidence of an association between post-diagnosis opioid prescriptions and breast cancer recurrence. The effect estimates did not differ according to opioid strength, cumulative dose, chronic long-term exposure, or in analyses stratified by ER/ET status, menopausal status, and surgery type. Although we observed a decreased rate of recurrence associated with the use of strongly immunosuppressive opioids, such exposure correlated with an increased rate of all-cause mortality in our population, consistent with previous reports.[2] The apparent effect of these opioids on recurrence therefore may be attributable to channeling bias where persons with high competing risk for mortality are those prescribed strong opioids.[26] In these patients, symptoms of recurrent disease may be masked by the opioids, or may be misattributed to comorbid diseases.

Several issues should be considered when interpreting our results. The large size and population-based design of our study, in a country with universal tax-supported healthcare, minimized the potential for selection bias. The DBCG manages a breast cancer clinical database considered to be one of the most comprehensive in the world, with data quality comparable to that of a clinical trial.[17] The use of a prospective, population-based prescription registry eliminated the potential for recall bias. With the exception of HRT, we characterized prescribed opioids and co-medications as time-varying exposures, which allowed for fluctuations in drug exposure during follow-up. We note that over 99% of aspirin exposure in the current study was for low-dose aspirin prescriptions. Low-dose aspirin is almost exclusively prescribed for cardiovascular disease prophylaxis/prevention. Patients pay a proportion of the cost of their prescriptions and aspirin is reimbursable via the

Danish national health insurance system,[27] so it seems likely that our estimates for aspirin, as well as the other confounder drugs (HRT and simvastatin) reflect actual use. We lagged the opioid and confounder drug exposures by one year, and conducted sensitivity analyses lagging opioid exposure by two years, to allow for a latency period between opioid exposure and breast cancer recurrence, and to minimize any potential reverse causation.

A potential concern is misclassification of opioid exposure due to non-prescription opioid use. Opioids are legally only available by prescription in Denmark. While we could not assess possible use of diverted opioid medications among cohort members, we do not expect a high prevalence of illegal drug use among breast cancer patients. Prescription compliance is also a concern. We assessed drug exposure *via* redeemed prescriptions, for which patients had to pay a proportion of the costs. Therefore our estimates are likely to reflect actual use. Although we had no data on the specific indication for an opioid prescription, or the severity of the pain experienced, we saw no overall change in effect estimates when we adjusted our analyses for specific comorbid conditions.

Other types of opioid exposure misclassification are also possible. We had no information on in-hospital or perioperative opioid use, which, as noted above, may influence cancer survival.[7,9-11,28] However, its effect on recurrence may be negligible as length of hospital stay is short for breast cancer patients in Denmark.[29] We also lacked a measure of endogenous opioids such as β-endorphin, which is induced by physiological stress and may have anti-neoplastic properties.[12] β-endorphin expression may vary particularly around the time of breast cancer surgery due to the physiological stress of surgery. Taken together, unmeasured effects of anesthesia and endogenous opioids may work in concert with prescribed exogenous opioids to alter the risk of cancer recurrence.

Our results are at odds with findings from some published studies, which have reported survival differences according to methods of opioid-mediated anesthesia and analgesia in cancer patients.[9,10] Experimental research suggests that extended exposure to high opioid concentrations may suppress tumor growth, whereas clinically relevant use of opioids may promote cancer growth.[30] Accordingly, our null findings may reflect the evidently paradoxical effects of opioids on cancer cell growth, with growth-promoting effects negated by growth-inhibitory effects. We sought to address the potential self-neutralizing effect of opioids on breast cancer recurrence by lagging and continuously updating our drug exposure definitions, by distinguishing between the strong and weak opioids, by assessing the cumulative morphine-equivalent dose and the immunosuppressive effects of opioids, and by evaluating the effect of chronic long-term opioids exposure.

Our large study, which included over 34,000 breast cancer patients, extends current knowledge by providing new evidence on the effect of routine opioid use in breast cancer patients after hospital discharge.[2] This evidence is particularly important given the increasing prevalence of opioid consumption in western populations;[2,23] the increasing incidence of breast cancer; and consequently the increasing numbers of people faced with decisions regarding treatment for pain related to their cancer or comorbid conditions. As the setting of our study was a non-metastatic cancer population, our findings are important to

cancer survivorship settings, since opioids are frequently used to manage pain associated with comorbid conditions.

In conclusion, findings from our large clinical population-based study show no evidence of an association between prescribed opioids and breast cancer recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of patients diagnosed with stage I, II and III breast cancer in Denmark during 1996 to 2008 (n=34,188), according to post-diagnosis opioid use and breast cancer recurrence.

	Patients n (%)		Patients with recurrence n (%)			Total person-years	
	Opioid non-users (n = 18,231)	Opioid users (n = 15,957)	No recurrence; No opioids (n=28,863)	Recurrence during opioid non-exposure (n=4,469)	Recurrence during opioid exposure (n=856)	Opioid non-users (n = 195,339)	Opioid users (n=37,791)
Age at diagnosis (years)							
≤29	81 (0.4)	39 (0.2)	83 (0.3)	33 (0.7)	4 (0.5)	657	63
30–39	1,007 (5.5)	584 (3.7)	1,218 (4.2)	324 (7.3)	49 (5.8)	9,742	1,072
40–49	3,580 (20)	2,382 (15)	4,685 (17)	861 (19)	116 (14)	38,922	4,998
50–59	5,816 (32)	4,579 (29)	8,709 (30)	1,457 (33)	229 (27)	63,874	10,707
60–69	5,307 (29)	5,143 (32)	8,912 (31)	1,261 (28)	277 (32)	57,164	12,830
70–79	2,066 (11)	2,676 (17)	4,099 (14)	492 (11)	151 (18)	22,021	6,930
≥80	374 (2.1)	554 (3.5)	857 (3)	41 (0.9)	30 (3.5)	2,960	1,192
Menopausal status at diagnosis							
Pre-menopausal	5,818 (32)	3,804 (24)	8,007 (28)	1,435 (32)	180 (21)	62,661	7,755
Post-menopausal	12,405 (68)	12,146 (76)	20,842 (72)	3,033 (68)	676 (79)	132,622	30,010
Unknown	8 (0.04)	7 (0.04)	14 (<0.1)	1 (<0.1)	0	56	26
UICC stage							
Stage 1	6,785 (37)	6,177 (39)	11,553 (40)	1,198 (27)	211 (25)	80,218	15,327
Stage 2	8,136 (45)	7,118 (45)	13,136 (46)	1,790 (40)	328 (38)	88,968	17,026
Stage 3	3,310 (18)	2,662 (17)	4,174 (17)	1,481 (33)	317 (37)	26,152	5,439
Histologic grade							
Specimen not suitable for grading	67 (0.4)	62 (0.4)	116 (0.4)	9 (0.2)	4 (0.5)	793	118
Grade I	4,821 (26)	4,650 (29)	8,400 (29)	884 (20)	187 (22)	56,573	11,742
Grade II	6,878 (38)	6,041 (38)	10,938 (38)	1,640 (37)	341 (40)	72,933	14,186
Grade III	4,006 (22)	3,024 (19)	5,521 (19)	1,290 (29)	219 (26)	35,938	6,279
Unknown	2,459 (14)	2,180 (14)	3,888 (13)	646 (14)	105 (12)	29,101	5,467
ER/ET status							
ER+/ET+	9,299 (51)	8,567 (54)	15,402 (53)	2,017 (45)	447 (52)	98,539	20,278
ER+/ET−	4,524 (25)	4,040 (25)	7,263 (35)	1,111 (25)	190 (22)	54,313	10,281
ER−/ET+	109 (0.6)	95 (0.6)	170 (0.6)	32 (0.7)	2 (0.2)	1,218	278
ER−/ET−	3,815 (21)	2,839 (18)	5,322 (18)	1,143 (26)	189 (22)	35,756	5,908
Unknown	484 (2.7)	416 (2.6)	706 (2.5)	166 (3.7)	28 (3.3)	5,512	1,047
Type of primary surgery							
Mastectomy	10,116 (55)	9,246 (58)	15,656 (54)	3,075 (69)	631 (74)	108,563	22,457
Breast conserving surgery & radiotherapy	8,111 (45)	6,709 (42)	13,202 (46)	1,393 (31)	225 (26)	86,754	15,332
Unknown or other	4 (0.02)	2 (0.01)	5 (<0.1)	1 (<0.1)	0	22	2
Chemotherapy							

	Patients n (%)		Patients with recurrence n (%)			Total person-years	
	Opioid non-users (n = 18,231)	Opioid users (n = 15,957)	No recurrence; No opioids (n=28,863)	Recurrence during opioid non-exposure (n=4,469)	Recurrence during opioid exposure (n=856)	Opioid non-users (n = 195,339)	Opioid users (n=37,791)
No	11,428 (63)	11,321 (71)	19,267 (67)	2,854 (64)	628 (73)	129,587	28,666
Yes	6,803 (37)	4,636 (29)	9,596 (33)	1,615 (36)	228 (27)	65,752	9,125
Other drug exposures							
Simvastatin	3,073 (17)	4,045 (25)	6,724 (23)	307 (7)	87 (10)	42,868	10,756
Aspirin	2,576 (14)	4,226 (27)	6,175 (21)	446 (10)	181 (21)	36,993	11,770
Hormone replacement therapy	4,697 (26)	5,860 (37)	9,080 (31)	1,168 (26)	309 (36)	60,274	16,083
Medical history at diagnosis							
Myocardial infarction	112 (0.6)	241 (1.5)	316 (1.1)	28 (0.6)	9 (1.1)	1,547	586
Congestive heart failure	93 (0.5)	200 (1.3)	264 (0.9)	19 (0.4)	10 (1.2)	938	570
Peripheral vascular disease	138 (0.8)	386 (2.4)	462 (1.6)	33 (0.7)	29 (3.4)	1,845	1,077
Cerebrovascular Disease	370 (2.0)	621 (3.9)	883 (3.1)	72 (1.6)	36 (4.2)	4,024	1,607
(Metastatic) Solid tumor, leukemia, or lymphoma	937 (5.1)	950 (6.0)	1,610 (5.6)	218 (4.9)	59 (6.9)	9,563	2,281
Diabetes type I	106 (0.6)	155 (1.0)	219 (0.8)	27 (0.6)	15 (1.8)	1,040	423
Diabetes type II	192 (1.1)	380 (2.4)	498 (1.7)	52 (1.2)	22 (2.6)	2,204	1,027
Rheumatoid arthritis	88 (0.5)	224 (1.4)	270 (0.9)	28 (0.6)	14 (1.6)	1,201	740
Osteoarthritis	473 (2.6)	1,425 (8.9)	1,646 (5.7)	158 (3.5)	94 (11)	7,332	4,460

Table 2

Breast cancer recurrence up to ten years after diagnosis, hazard ratios and associated 95% confidence intervals (95% CI) for stage I, II, or III breast cancer patients in Denmark from 1996 through 2008 by type of opioid use (weak and strong opioids).

Opioid exposure definition	Number of recurrences (person-years)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Non-users	4469 (195,339)	1.0	1.0
Users of any opioid^	856 (37,791)	0.98 (0.90 - 1.1)	1.0 (0.92 - 1.1)
Strength of opioids exposure			
Non-users	4469 (195,339)	1.0	1.0
Only weak opioids	636 (27,765)	0.99 (0.90 - 1.1)	1.0 (0.92 - 1.1)
Only strong opioids	112 (5,396)	0.94 (0.76 - 1.1)	0.95 (0.77 - 1.2)
Both weak and strong opioids	108 (4,632)	0.93 (0.74 - 1.2)	0.95 (0.75 - 1.2)
Cumulative dose (morphine equivalents)			
Non-users#	3802#(162,107)	1.0	1.0
Low (1–≤500)	753 (32,415)	1.1 (0.98 - 1.2)	1.1 (0.99 - 1.2)
Medium (501–≤5000)	481 (23,914)	0.94 (0.86 - 1.0)	0.98 (0.89 - 1.1)
High (>5000)	289 (14,694)	0.93 (0.82 - 1.1)	0.96 (0.84 - 1.1)
Opioid exposure by immunosuppressive effect§			
Non-users	4469 (195,354)	1.0	1.0
Strongly immunosuppressive	358 (16,293)	0.73 (0.55 - 0.95)	0.75 (0.57 - 0.99)
Weakly immunosuppressive	286 (12,514)	0.99 (0.91 - 1.1)	1.0 (0.94 - 1.1)
Other¤	212 (8,986)	1.0 (0.90 - 1.2)	1.0 (0.89 - 1.2)
Chronicity of use			
Non-users	4469 (195,341)	1.0	1.0
Chronic long-term use	118 (4,741)	1.1 (0.93 - 1.3)	1.1 (0.93 - 1.4)
Short-term use	738 (33,053)	0.96 (0.89 - 1.0)	0.99 (0.91 - 1.1)

^Breast cancer recurrence during opioid exposure.

*Adjusted for age at diagnosis (as a continuous variable), menopausal status at diagnosis (pre- or post-menopausal), stage (I, II, or III), histologic grade (low, moderate, high), surgery type and radiotherapy receipt (mastectomy, breast-conserving surgery with radiotherapy), ER status and endocrine therapy receipt (ER+/ET−, ER+/ET−, ER−/ET−, ER−/ET+), receipt of chemotherapy (yes/no), post-diagnostic simvastatin use and post-diagnostic aspirin use (both as time-varying covariates lagged by one year and updated yearly), pre-diagnostic HRT (yes/no), myocardial infarction and congestive heart failure (yes/no), peripheral and cerebrovascular disease (yes/no), malignant disease (yes/no), diabetes mellitus (yes/no), rheumatoid arthritis (yes/no), and osteoarthritis (yes/no).

§Opioids were classified as strongly immunosuppressive (codeine, morphine, fentanyl) and weakly immunosuppressive (buprenorphine, hydromorphone, oxycodone, tramadol) according to Sacerdote et al.[22]

¤Other opioids included mixed exposure to strongly and weakly immunosuppressive opioids, and/or exposure to ketobemidone, pethidine, pentazocine, tapentadol, nicomorphine, or dextropropoxyphene.

[#]In the cumulative dose model, the number of “non-users” appears lower than in the other models. This is because once patients were exposed to opioids, they could not go back to being unexposed. Howeve,r in the other categories, “non-users” encompass a mixture of individuals who were exposed to opioids but were not exposed to opioids when they developed recurrent disease, and individuals who were never exposed to opioids.

Table 3

Hazard ratios and 95% confidence intervals associating prescriptions for strong or weak opioids and breast cancer recurrence up to ten years after diagnosis, stratified by ER/ET status, menopausal status, and type of primary therapy among women with stage I, II, or III breast cancer in Denmark (1996–2008).

Statistical model and variable analyzed	Total recurrences n (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Stratified models			
Total no. recurrences analyzed	5,325	NA	NA
ER/ET status			
ER+/ET+	2,464 (46)	1.1 (0.96 - 1.2)	1.0 (0.93 - 1.2)
ER+/ET−	1,301 (24)	0.89 (0.76 - 1.0)	1.0 (0.86 - 1.2)
ER−/ET−	1,332 (25)	0.96 (0.82 - 1.1)	0.95 (0.81 - 1.1)
Menopausal status			
Premenopausal	1,615 (30)	0.98 (0.84 - 1.1)	0.97 (0.83 - 1.1)
Postmenopausal	3,709 (70)	0.98 (0.90 - 1.1)	1.0 (0.92 - 1.1)
Type of primary therapy			
Mastectomy	3,706 (70)	0.98 (0.90 - 1.1)	1.0 (0.93 - 1.1)
BCS + RT	1,618 (30)	0.90 (0.78 - 1.0)	0.96 (0.83 - 1.1)
Receipt of chemotherapy			
No	3,483 (65)	0.99 (0.91 – 1.1)	1.0 (0.94 – 1.1)
Yes	1,843 (35)	0.97 (0.84 – 1.1)	0.93 (0.80 – 1.1)

§Excluded from the models that were stratified on these factors.

*Adjusted for age at diagnosis (as a continuous variable), menopausal status at diagnosis (pre- or post-menopausal), stage (I, II, or III), histologic grade (low, moderate, high), surgery type and radiotherapy receipt (mastectomy, breast-conserving surgery with radiotherapy), ER status and endocrine therapy receipt (ER+/ET−, ER+/ET−, ER−/ET−, ER−/ET+), receipt of chemotherapy (yes/no), post-diagnostic simvastatin use and post-diagnostic aspirin use (both as time-varying covariates lagged by one year and updated yearly), pre-diagnostic HRT (yes/no), myocardial infarction and congestive heart failure (yes/no), peripheral and cerebrovascular disease (yes/no), malignant disease (yes/no), diabetes mellitus (yes/no), rheumatoid arthritis (yes/no), and osteoarthritis (yes/no).