Original Articles

Trajectories of Opioid Use Before and After Cancer Diagnosis: A Population-Based Cohort Study

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Abstract

Background. Opioid use prior to cancer diagnosis increases the likelihood of long-term use during survivorship, however, patterns of use before and after diagnosis are not understood.

Methods. We used population-based dispensing data linked with cancer and death notifications to identify two cohorts of adults residing in New South Wales initiating opioids within 24 months prior to a first cancer diagnosed between 2014 and 2016: 'survivors' (alive 24 months following diagnosis) and 'decedents' (died within 24 months). We used group-based trajectory modelling to identify trajectories of monthly opioid dispensings and dispensed oral morphine equivalent milligrams (OMEmg) during the 24 months before/after cancer diagnosis.

Results. There were 21,843 survivors with four prediagnosis opioid dispensing trajectories: infrequent (58% of the cohort), late increasing (26%), moderate (10%), and sustained dispensing (6%). We observed an overall increase in dispensed OMEmg of 83 OMEmg (95% CI: 76–91) during the month of diagnosis, with strong opioid formulations comprising most treatment postdiagnosis. Within each prediagnosis opioid trajectory group, we observed five to six postdiagnosis trajectory groups, including no opioid dispensing. Moderate and sustained prediagnosis groups had large proportions of people continuing or increasing opioid dispensing after diagnosis, while small proportions discontinued opioid treatment. We observed similar trajectories in the decedent cohort.

Conclusions. There is considerable heterogeneity in opioid use before and after cancer diagnosis. Our findings suggest noncancer factors drive a significant proportion of postdiagnosis opioid use, but use increased significantly from the month of cancer diagnosis and never returned to prediagnosis levels. J Pain Symptom Manage 2024;68:282–291.

Key Words

Cancer, opioids, group-based trajectory model, cohort study

Key Message

This article describes different precancer diagnosis opioid dispensing trajectories and how preexisting dispensing changes from cancer diagnosis. The results highlight that use both before and after diagnosis is heterogeneous, with higher levels of use likely driven by noncancer factors. Increased levels of postdiagnosis opioid use never returned to prediagnosis levels.

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Introduction

Pain is a common and distressing symptom experienced by people living with cancer.[1] Clinical practice guidelines recommend opioids as first-line pain management for people experiencing moderate or severe cancer pain.[2–4] However, there are concerns around harms associated with opioid treatment, due to the potential for misuse, dependence, and overdose associated with these medicines.[5] While these concerns have been focused on opioid use in the context of chronic noncancer pain (CNCP), risks for people with cancer may also be growing as medical advances translate to people are living longer with the 'chronic' phase of advanced disease and continuing on opioid therapy for extended periods.[6–8]

Several recent studies have found that opioid use prior to a cancer diagnosis significantly increases the likelihood of long-term opioid use following cancer treatment, as well as the use of a larger number of different opioid medicines.[9–11] However, these studies did not account for the heterogeneity of opioid use preceding a cancer diagnosis, which may influence ongoing patterns of use. Studies using more complex methods to examine patterns of opioid use have either excluded people with cancer or lacked the ability to identify them.[12–15] Finally, few studies have examined the specific impacts of cancer diagnosis on existing opioid use and whether patterns of use change following diagnosis. We aimed to describe opioid treatment trajectories for patients receiving opioid medicines during the 24 months prior to cancer diagnosis and the 24 months following diagnosis.

Methods

Setting and Data Sources

The Australian healthcare setting and datasets used in this study have been described in the POPPY II research protocol.[16,17] Briefly, Australia maintains a publicly funded, universal healthcare system entitling citizens and permanent residents to subsidised medicines through the Pharmaceutical Benefits Scheme (PBS). Cancer is a notifiable disease in Australia (excepting basal and squamous cell carcinomas), and each state reports cancer diagnoses to the Australian Cancer Database (ACD).[18]

We used data from the POPPY II cohort, comprising all adults initiating opioid medicines between 2012 and 2018 in New South Wales (NSW).[16,17] The linked data sets include PBS dispensing records (dispensed medicines, quantity, and date of dispensing for opioids and all other prescription medicines); date of death from the National Death Index (NDI); and cancer notifications from the ACD (date of diagnosis, topography and morphology codes).[16] The observation period in the PBS and NDI data was July 2012 through December 2018;. Diagnoses in the ACD ranged from January 1982 through December 2016.

Study Design and Participants

Our population-based, retrospective cohort study included all adults (≥ 18 years) initiating opioid medicines (Supplementary Table a) within the 24 months prior to a first cancer diagnosis between July 2014 and December 2016. Included cancers are listed in Supplementary Table b.

We created two sub-cohorts based on whether or not a person died within 24 months of cancer diagnosis. Opioid use at the end of life tends to exhibit a distinct pattern of increasing to the month of death.[19] Prolonged and escalating use of opioids during the months preceding death from cancer are generally considered less concerning with regard to risk of dependence and addiction than that in patients treated with curative intent. Our primary, 'survivor' cohort consisted of people who were alive at 24 months following first cancer diagnosis; our secondary, 'decedent' cohort consisted of those who died during the 24 months following cancer diagnosis. While our data do not contain information on disease stage, it is likely that more patients treated with curative intent comprise the survivor cohort.

We examined 24 months before and after cancer diagnosis to balance the length of our available observation period and maximise the number of cancer cases in our study—examining a larger period, for instance, 36 months, would have limited our cohort just those diagnosed between July and December 2015. This period also ensured capture of opioid use prior to the emergence of cancer symptoms as well as during the early survivorship period, when opioid treatment for surgery-related pain is likely to have dissipated for many patients.

Outcomes and Statistical Analyses

Clustering patients based on patterns of opioid dispensing. We clustered patients based on monthly patterns of opioid dispensings for the 24 months preceding first cancer diagnosis using logistic group-based trajectory modelling (GBTM).[20] GBTMs are unsupervised models that identify latent groups of people following similar trajectories across a longitudinal outcome (in this case, opioid dispensings). We created 24 binary variables, one for each prediagnosis month, where "one" indicated an opioid dispensing and "zero" indicated no dispensing in the month. GBTMs require the researcher to supply the number of groups to be fit in the model and we explored three to seven latent groups for prediagnosis opioid dispensing, theorising that less than three would be too few to capture

potentially meaningful variation and more than seven would be difficult to meaningfully interpret. GBTMs model time as a function of the longitudinal outcome and also require that the researcher supply the polynomial order of the function. We explored zero-order to quartic polynomials while building our models. We determined the optimal number of groups and polynomial order by evaluating model fit using the Bayesian information criterion, average posterior probability of group membership (> 0.7), and clinical relevance for all models.[21]

Within each resulting prediagnosis trajectory group, we used further GBTMs to examine trajectories of postdiagnosis opioid dispensing according to the procedures described above.

Cohort and treatment characteristics. To better understand opioid use in the resulting trajectory groups, we presented outputs in terms of monthly dispensed oral morphine equivalent milligrams (OMEmg).[22] For each prediagnosis trajectory group we summarised: sex; age at diagnosis; use of nonopioid analgesics (paracetamol, pregabalin, gabapentin, pizotifen), nonsteroidal anti-inflammatory medicines (NSAIDs; nonselective NSAIDs and Selective COX-2 inhibitors), and psychotropic medicines (antidepressants [including serotonin and norepinephrine reuptake inhibitors (SNRIs), which may have analgesic effects], antiepileptics, antipsychotics, anxiolytics, hypnotics/sedatives), in the 24 months before and after cancer diagnosis; cancer site; average dispensed OMEmg; and type of opioid dispensed (strong opioids: buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, oxycodone and naloxone, tapentadol, and methadone; other opioids: codeine, paracetamol and codeine, and tramadol). Many people may receive opioids and nonopioid pain medicines for noncancer comorbidities and we ascertained comorbidity burden using the RxRisk algorithm—a measure for determining comorbidities based on prescription medicine dispensing—applied to dispensing records (excluding dispensings of cancer medicines and opioid medicines) from each of the pre and postdiagnosis periods.[23] For each prediagnosis trajectory group we calculated the prevalence of cohort and treatment characteristics relative to the entire cohort (e.g., the proportion of males in trajectory group X / the proportion of males in the survivor cohort). We used generalised estimating equations to estimate the change in monthly dispensed OMEmg during the month beginning with the date of cancer diagnosis. We used the PROC TRAJ package in SAS v9.4 (SAS Institute, Cary, NC) to construct the GBTMs[24] and performed all other analyses in R v4.0.

Ethics approvals and data access. The Australian Institute of Health and Welfare (AIHW) Ethics Committee (EO2016/4/314), NSW Population and Health Services Research Committee (2017/HRE0208), and the ACT Health Human Research Ethics Committee (ETHLR.18.094) approved the study. The data are not publicly available and access is subject to approval by the relevant data custodians.

Results

Survivor Cohort

Our survivor cohort included 21,843 people diagnosed with a first cancer between 2014 and 2016 initiating an opioid during the 24 months preceding diagnosis. Overall, 52% were male; median age at diagnosis was 66 years (interquartile range (IQR): 57; 74); and the most common cancers were male reproductive (20%), breast (17%), and blood and connective/soft tissue cancers (16%; Table 1). Prior to diagnosis, an average of 16% of the cohort was dispensed an opioid during each month, with an average of 153 OMEmg per dispensing (standard deviation [SD]: 916 OMEmg; Fig. 1, Table 2). Following diagnosis, an average of 19% of the cohort was dispensed an opioid during each month, with an average of 248 OMEmg (SD: 1191 OMEmg) per dispensing.

We identified four prediagnosis opioid dispensing trajectories: (1) Infrequent use (less than monthly dispensing, small amounts of OMEs dispensed; 58% of the survivor cohort); (2) Late increasing use (less than monthly dispensing, small amounts of OMEs dispensed until the six months preceding diagnosis; 26%); (3) Moderate use (monthly dispensings, larger quantities of OMEs dispensed; 10%); and (4) Sustained use (monthly dispensings, large quantities of OMEs dispensed; 6%; Supplementary Fig. a). There were larger proportions of male reproductive cancers in the Infrequent and Late increasing use trajectory groups and larger proportions of lung cancers in the Moderate and Sustained use trajectory groups (Table 1, Supplementary Fig. b). Males comprised the majority of all trajectory groups except for the Sustained use trajectory group (51% female; Table 1). The Moderate and Sustained use trajectory groups had larger proportions of older patients (75 + years); nonopioid analgesic and psychotropic use; and patients dispensed five or more medicines to treat comorbidities (Table 1, Supplementary Figs. b and c).

During the month of diagnosis, we observed an overall increase in dispensed OMEmg of 83 OMEmg (95% CI: 76−91; Table 2). Each prediagnosis trajectory group, except the Sustained use trajectory group, experienced an increase in dispensed OMEmg during the month of diagnosis, with the largest occurring in the Late increasing use trajectory group (221 OMEmg [95% CI: 214−228]) and the smallest occurring in the Infrequent use trajectory group (51 OMEmg [95% CI:

Table 1
Survivor Cohort Patient and Treatment Characteristics at, Before, and After Cancer Diagnosis

	Survivor Cohort	Trajectory 1: Infrequent Use	Trajectory 2: Late Increasing Use	Trajectory 3: Moderate Use	Trajectory 4: Sustained Use
No. (%)	21,843	12,726 (58)	5751 (26)	2034 (10)	1332 (6)
median age at cancer diagnosis (IQR)	66 (57; 74)	66 (57; 74)	65 (54; 73)	69 (61; 77)	70 (61; 79)
Age group, n (%):					
< 35	625 (3)	369 (3)	225 (4)	25 (1)	6 (< 1)
35–54	3881 (18)	2257 (18)	1220 (21)	258 (13)	146 (11)
55–74	12,036 (55)	7135 (56)	3113 (54)	1099 (54)	689 (52)
75 +	5301 (24)	2965 (23)	1193 (21)	652 (32)	491 (37)
Sex, n (%)					
Male	11,260 (52)	2419 (53)	4226 (51)	2364 (53)	900 (49)
Dispensed an analgesic medicine, n (%):					
Prediagnosis	8732 (40)	4602 (36)	1847 (32)	1312 (65)	971 (73)
Postdiagnosis	8417 (39)	4201 (33)	2088 (36)	1199 (59)	929 (70)
Dispensed paracetamol, n (%):					
Prediagnosis	7325 (34)	3904 (31)	1519 (26)	1108 (54)	794 (60)
Postdiagnosis	5713 (26)	2918 (23)	1321 (23)	835 (41)	639 (48)
Dispensed pregabalin, n (%):					
Prediagnosis	2809 (13)	1244 (10)	572 (10)	545 (27)	448 (34)
Postdiagnosis	4295 (20)	1914 (15)	1164 (20)	661 (32)	556 (42)
Dispensed gabapentin, n (%):					
Prediagnosis	129 (1)	52 (< 1)	17 (< 1)	26 (1)	34 (3)
Postdiagnosis	166 (1)	71 (1)	28 (< 1)	36 (2)	31 (2)
Dispensed pizotifen, n (%):					
Prediagnosis	117 (1)	61 (< 1)	22 (< 1)	15 (1)	19 (1)
Postdiagnosis	101 (< 1)	54 (< 1)	17 (< 1)	12 (1)	18 (1)
Dispensed a psychotropic medicine, n. (%):					
Prediagnosis	9830 (45)	5245 (41)	2242 (39)	1342 (66)	1001 (75)
Postdiagnosis	11,370 (52)	6012 (47)	2847 (50)	1459 (72)	1052 (79)
Dispensed an antidepressant, n (%):					
Prediagnosis	6428 (29)	3301 (26)	1401 (24)	957 (47)	769 (58)
Postdiagnosis	7691 (35)	3984 (31)	1822 (32)	1063 (52)	822 (62)
Dispensed an antiepileptic, n (%):					
Prediagnosis	868 (4)	419 (3)	188 (3)	131 (6)	130 (10)
Postdiagnosis	978 (4)	480 (4)	246 (4)	133 (7)	119 (9)
Dispensed an antipsychotic, n (%):					
Prediagnosis	662 (3)	313 (2)	147 (3)	110 (5)	92 (7)
Postdiagnosis	1093 (5)	511 (4)	298 (5)	150 (7)	134 (10)
Dispensed an anxiolytic, n (%):					
Prediagnosis	3190 (15)	1598 (13)	691 (12)	494 (24)	407 (31)
Postdiagnosis	3371 (15)	1669 (13)	816 (14)	491 (24)	395 (30)
Dispensed a hypnotic and/or sedative, n (%):					
Prediagnosis	3159 (14)	1603 (13)	690 (12)	498 (24)	368 (28)
Postdiagnosis	4562 (21)	2337 (18)	1207 (21)	607 (30)	411 (31)
Dispensed an NSAID, n (%):					
Prediagnosis	9374 (43)	5389 (42)	2290 (40)	1117 (55)	578 (43)
Postdiagnosis	7203 (33)	4115 (32)	1741 (30)	848 (42)	499 (37)
Dispensed nonselective NSAIDs, n (%)					
Prediagnosis	4600 (21)	2674 (21)	1154 (20)	522 (26)	250 (19)
Postdiagnosis	3236 (15)	1792 (14)	839 (15)	393 (19)	212 (16)
Dispensed selective COX-2 inhibitors, n (%)					
Prediagnosis	6096 (28)	3467 (27)	1435 (25)	778 (38)	416 (31)
Postdiagnosis	4869 (22)	2836 (22)	1118 (19)	581 (29)	334 (25)
First cancer diagnosis, n (%)					
Bone	60 (< 1)	[a]	[a]	[a]	[a]
Brain & CNS	164 (1)	86 (1)	58 (1)	11 (1)	9 (1)
Breast	3773 (17)	2419 (19)	760 (13)	351 (17)	243 (18)
Connective/soft tissue	3430 (16)	1878 (15)	923 (16)	376 (18)	253 (19)
Colorectal	2727 (12)	1640 (13)	687 (12)	238 (12)	162 (12)
Eye	69 (< 1)	38 (< 1)	17 (< 1)	7 (< 1)	7 (1)
Female reproductive	1001 (5)	545 (4)	310 (5)	91 (4)	55 (4)
Head, face, and/or neck	18 (< 1)	[a]	[a]	[a]	[a]
Liver/digestive other	1021 (5)	579 (5)	271 (5)	110 (5)	61 (5)
Lung	1161 (5)	572 (4)	339 (6)	138 (7)	112 (8)
Male reproductive	4453 (20)	2831 (22)	1093 (19)	342 (17)	187 (14)
Oral	598 (3)	308 (2)	193 (3)	63 (3)	34 (3)
Renal	1303 (6)	664 (5)	390 (7)	150 (7)	99 (7)
Respiratory/intrathoracic	232 (1)	117 (1)	70 (1)	27 (1)	18 (1)
Thyroid/adrenal/endocrine	1833 (8)	1021 (8)	603 (10)	126 (6)	83 (6)

(*Continued*)

Table 1
Continued

	Survivor Cohort	Trajectory 1: Infrequent Use	Trajectory 2: Late Increasing Use	Trajectory 3: Moderate Use	Trajectory 4: Sustained Use
Prediagnosis RxRisk conditions/dispensings, n (%): (excluding opioids and cancer medicines)					
0	1439 (7)	882 (7)	534 (9)	12 (1)	11 (1)
1–5	13,253 (61)	8143 (64)	3752 (65)	864 (42)	494 (37)
5 +	7151 (33)	3701 (29)	1465 (25)	1158 (57)	827 (62)
Postdiagnosis RxRisk conditions/dispensings, n (%): (excluding opioids and cancer medicines)					
0	801 (4)	546 (4)	235 (4)	[a]	[a]
1–5	12,011 (55)	7510 (59)	3361 (58)	[a]	[a]
5 +	9031 (41)	4670 (37)	2155 (37)	1270 (62)	936 (70)

[a]Cells with counts < 6 and those that may allow counts of < 6 to be inferred have been suppressed per ethical conditions of the study.

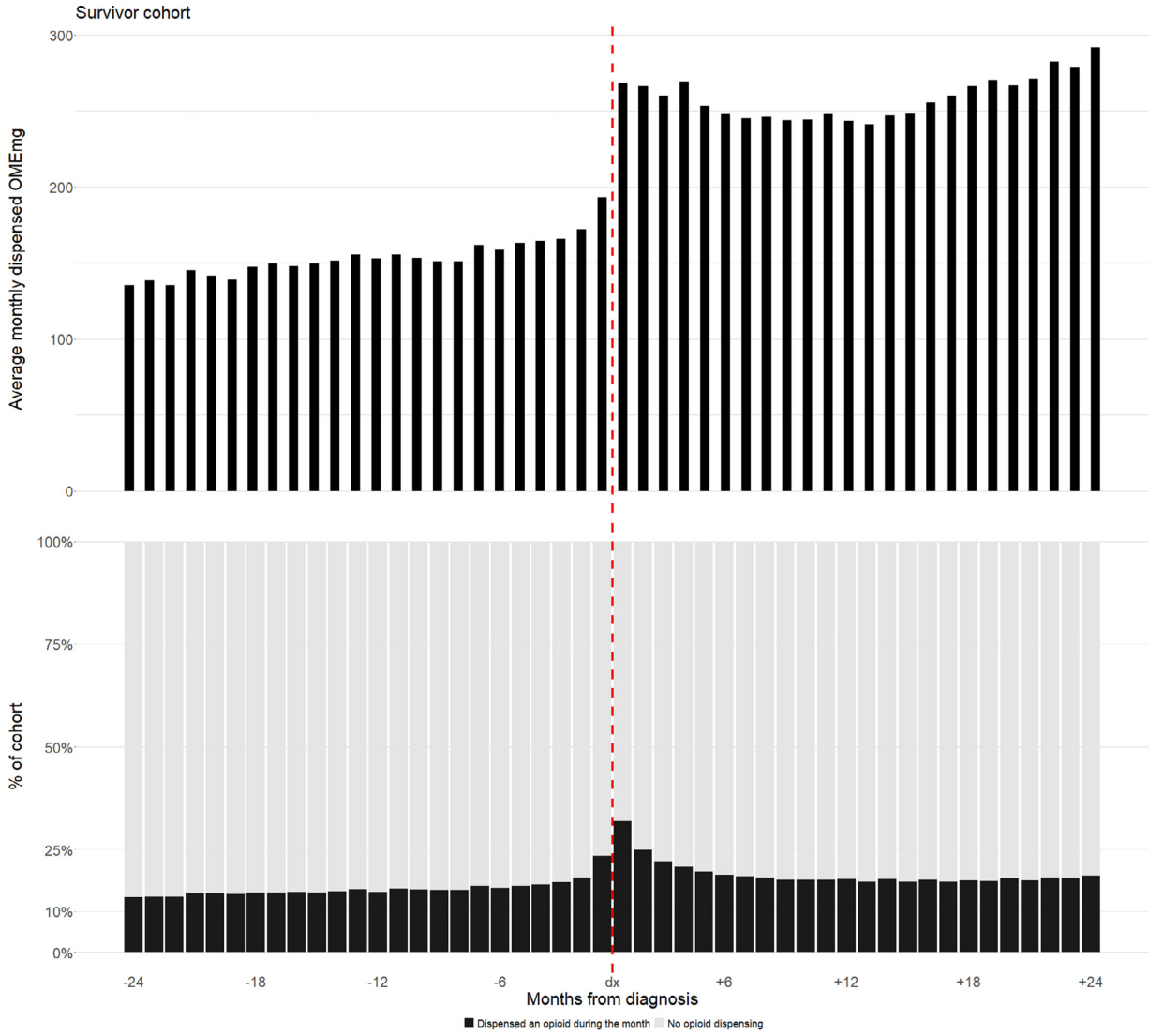

Fig. 1. Average monthly dispensed oral morphine equivalent milligrams (top) and proportion of the survivor cohort dispensed an opioid in each month (bottom).

Table 2

Average Monthly Dispensed Oral Morphine Milligrams (OMEmg) and Estimated Change in Monthly Dispensed OMEmg at Cancer Diagnosis, Stratified by Prediagnosis Opioid Use Trajectory Group; Survivor Cohort

	Average dispensed OMEmg (SD)		
	Prediagnosis	Postdiagnosis	Change at diagnosis (95% CI)
Survivor cohort	153 (916)	259 (1191)	83.3 (75.7; 91.0)
Trajectory 1: infrequent use	18 (127)	69 (540)	50.8 (48.5; 53.2)
Trajectory 2: late increasing use	24 (202)	247 (1327)	221.3 (214.3; 228.3)
Trajectory 3: moderate use	295 (781)	527 (1472)	117.4 (87.0; 147.8)
Trajectory 4: sustained use	1797 (3087)	1719 (2642)	13.0 (−91.8; 117.8)

49–53]). Prior to diagnosis, opioid treatment was predominantly comprised of other opioids for all trajectory groups except the Sustained use trajectory group; following diagnosis, strong opioids made up the majority of treatment for all trajectory groups (Fig. 2).

Within each prediagnosis trajectory group, we identified five to six postdiagnosis opioid dispensing trajectory groups, including a trajectory for no opioid dispensing (Fig. 3). The types of postdiagnosis trajectories we identified were broadly similar across prediagnosis groups, but the proportions of people in each postdiagnosis trajectory group varied – often reflecting prediagnosis patterns of use. For example, in prediagnosis groups with more regular dispensing we observed the majority of people (> 50%) continuing into postdiagnosis trajectories with high or ongoing use. Similarly, in prediagnosis groups with low use we found the vast majority (> 75%) of people were in in postdiagnosis groups with no or infrequent opioid use.

Decedent Cohort

We observed 9802 people dispensed an opioid prior to cancer diagnosis who died during the 24 months following diagnosis. Overall, 56% of the cohort was male; median age at diagnosis was 74 years (IQR: 64; 82); and the most common cancers were lung (26%), liver (24%), and blood and connective/soft tissue cancers (13%; Supplementary Table c). Median time to death was 5.7 months (interquartile range: 1.9, 11.9 months). Prior to diagnosis an average of 21% of the decedent cohort was dispensed an opioid during each month with an average of 247 OMEmg (SD: 1143) per dispensing (Supplementary Fig. d, Supplementary Table d). Following diagnosis, an average of 48% of the decedent cohort

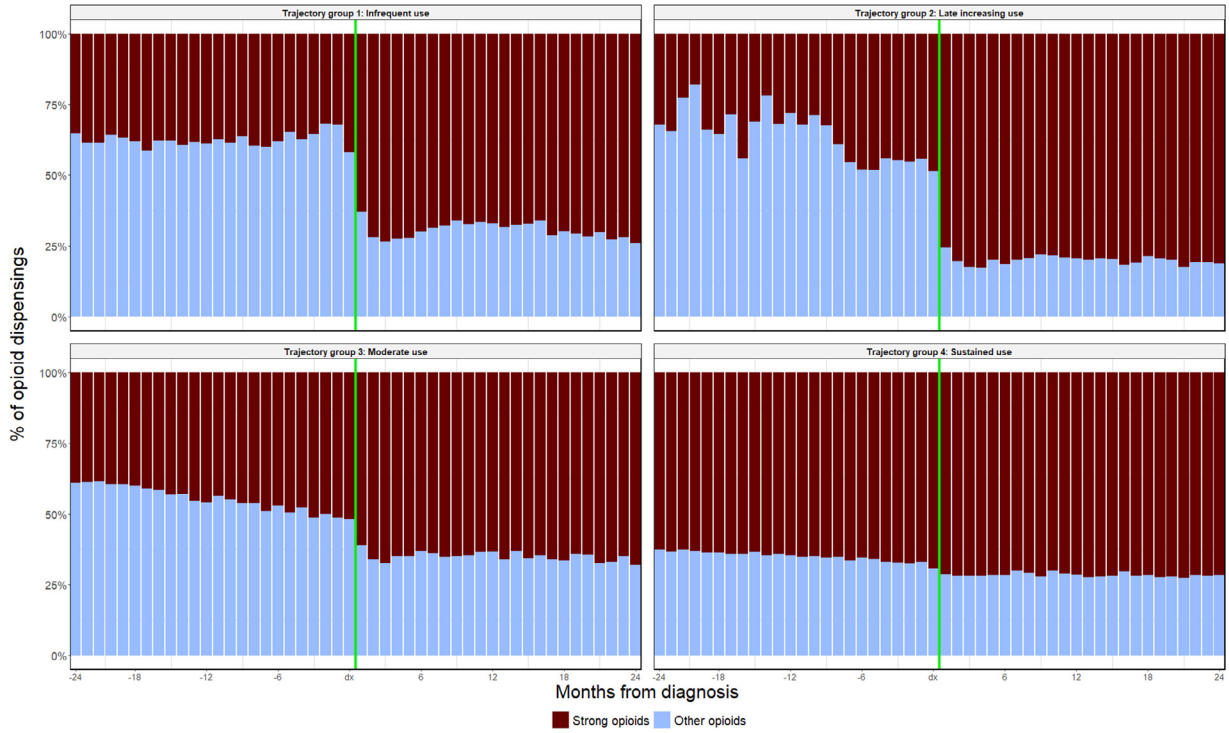

Fig. 2. Proportion of opioid dispensings in each month stratified by type of opioids (strong or other) and prediagnosis opioid use trajectory; survivor cohort. Green vertical line indicates month of diagnosis.

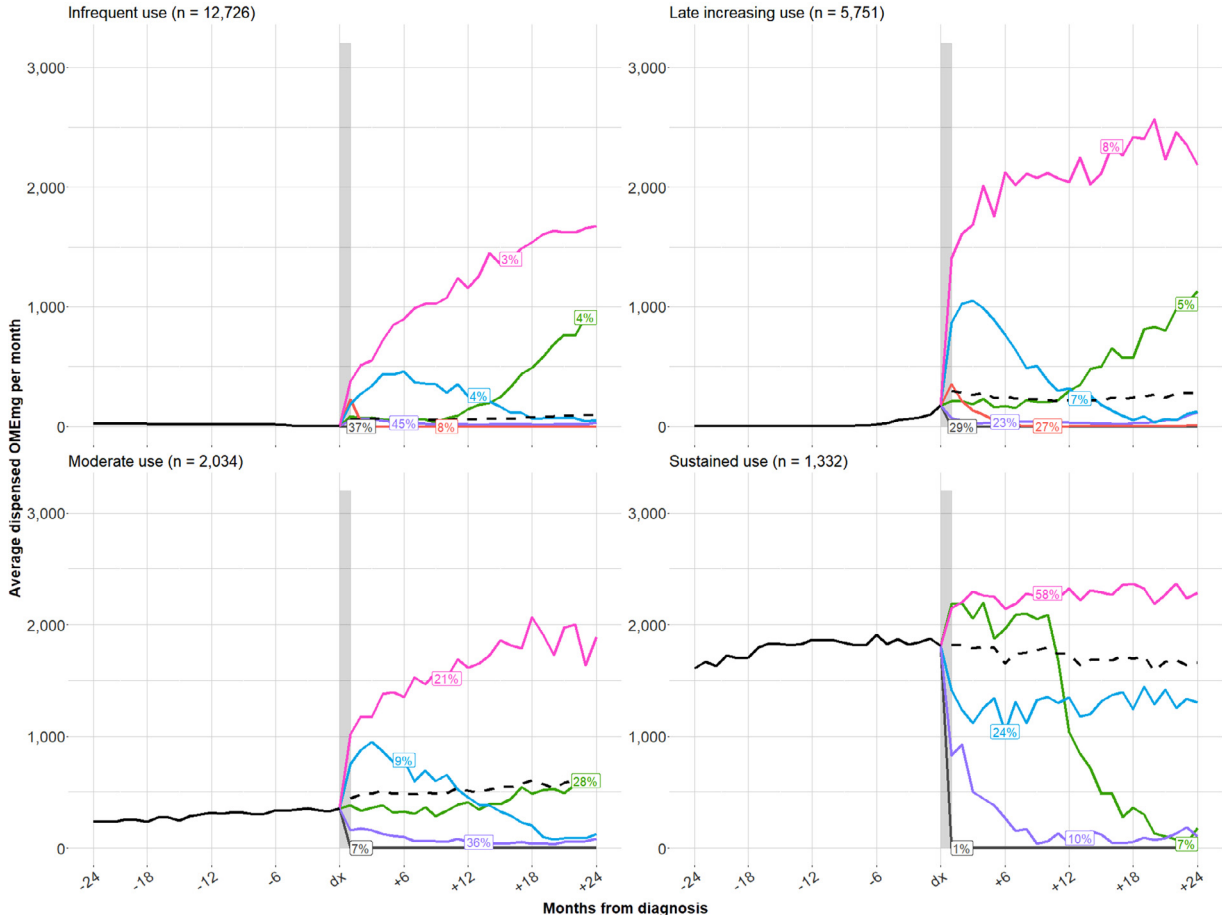

Fig. 3. Average monthly dispensed oral morphine equivalent milligrams overall (dashed black line) and in postdiagnosis opioid use trajectory groups, stratified by prediagnosis opioid trajectory group; survivor cohort. Percentages show the proportion of each prediagnosis trajectory group assigned to each postdiagnosis trajectory group.

alive during each month was dispensed an opioid with an average of 1210 OMEmg (SD: 3228) per dispensing.

We identified four prediagnosis trajectories: (1) Infrequent use (less than monthly dispensing, small amounts of OMEs dispensed; 41% of the decedent cohort); (2) Late increasing use (less than monthly dispensing, small amounts of OMEs dispensed until the six months preceding diagnosis; 36%); (3) Moderate increasing use (monthly dispensings, larger quantities of OMEs dispensed that increase 12 months preceding diagnosis; 12%); and (4) Sustained use (monthly dispensings, large quantities of OMEs dispensed; 11%; Supplementary Table c, Supplementary Fig. e). There were large proportions of lung cancers in the Late and Moderate increasing use trajectory groups and large proportions of blood and connective/soft tissue cancer in the Moderate increasing and Sustained use trajectory groups (Supplementary Fig. f, Supplementary Table c). The Late increasing trajectory group had a lower proportion of colorectal cancers than the other groups. Males comprised the majority of all trajectory groups except for the Moderate increasing (50% female) and Sustained use (56% female) trajectory groups (Supplementary Fig. f, Supplementary Table c). The Moderate increasing and Sustained use groups had larger proportions of nonopioid analgesic and psychotropic use both before and after diagnosis, as well as higher comorbidity burdens (Supplementary Fig. g, Supplementary Table c).

During the month of diagnosis, we observed an overall increase in dispensed OMEmg of 451 OMEmg (95% CI: 434−468; Supplementary Table d). Each prediagnosis trajectory group, except the Sustained use trajectory group, experienced an increase in dispensed OMEmg during the month of diagnosis, with the largest occurring in the Late increasing use trajectory group (1102 OMEmg [95% CI: 1080−1123]) and smallest in the Infrequent use trajectory group (251 OMEmg [95% CI: 241−261]). Prior to diagnosis, opioid treatment was predominantly comprised of other opioids for the Infrequent and Late increasing use trajectory groups; following diagnosis strong opioids made up the majority of treatment for all trajectory groups (Supplementary Fig. h).

Within each prediagnosis opioid trajectory group, we observed three to four postdiagnosis opioid dispensing trajectory groups (Supplementary Fig. i). The proportions of patients in each of these postdiagnosis trajectory groups, including no opioid dispensing, was similar between prediagnosis trajectory groups and, overall, opioid use increased for all groups during the postdiagnosis period.

Discussion

To our knowledge, this is the first study to examine detailed opioid dispensing trajectories among people receiving opioids during the 48 months before and after a cancer diagnosis. Average opioid use increased for both the survivor and decedent cohorts following diagnosis and never returned to prediagnosis levels. Moreover, while the proportion of the survivor cohort dispensed an opioid during a given month following diagnosis quickly returned to levels similar to those in the prediagnosis period, those dispensed opioids after diagnosis were dispensed higher average quantities of OMEmg than at any point during the preceding 48 months.

Our findings align with those from previous studies suggesting opioid use before cancer diagnosis is associated with continuing use following diagnosis, but further highlight that the heterogeneity of prior use is associated with different patterns of use after diagnosis.[9] In our study, groups with higher average monthly OMEmg preceding diagnosis generally continued this pattern postdiagnosis, with smaller proportions of people stopping opioid treatment after diagnosis. These groups also had larger proportions of older patients as well as those dispensed medicines to treat noncancer comorbidities, nonopioid analgesics, and psychotropics, than other trajectory groups. These patterns suggest that postdiagnosis use of opioids in these trajectory groups may have been driven by noncancer pain, consistent with the finding that the Sustained use trajectory groups in both cohorts were the only groups that did not experience a significant increase in opioid use during the month of diagnosis.

In our study, roughly 70% of the survivor cohort and 80% of the decedent cohort received opioid treatment following diagnosis. These proportions are higher than recent estimates of cancer-related pain prevalence in Australia and internationally,[1,25] and CNCP prevalence.[26–29] This may be due to the nature of the cohorts, comprised of people initiating opioid treatment prior to cancer diagnosis, and reinforces the role that noncancer factors, such as pre-existing, noncancer comorbidities, may have played in driving postdiagnosis opioid treatment. Additional support for the role of noncancer factors comes from previous research using GBTMs to analyse self-reported opioid use data from people with HIV that found cancer diagnosis was not significantly associated with assignment to opioid use trajectory group.[30]

Most studies employing GBTMs to examine patterns of opioid use have either excluded people with cancer or lacked the ability to identify them.[12–15] Nonetheless, several studies have modelled patterns of use starting from a person's first opioid dispensing and reported trajectories broadly matching those we observed in our postdiagnosis opioid use trajectory groups.[12–14] There is typically a higher, steady use group; a group whose use quickly declines to zero; a group whose use increases shortly after initiation but declines with time; and a group with low use immediately following initiation that increases with time. All of our prediagnosis trajectory groups—excluding the Sustained use groups—were generally dispensed low levels of opioids. The use of opioids following diagnosis for most of these patients likely represented treatment initiation, so it is perhaps not surprising our postdiagnosis trajectory groups largely resemble those reported from these noncancer cohorts.

Consistent with another, non-GBTM study of people with colon cancer, we observed that a cancer diagnosis was also associated with significant increases in dispensed OMEmg during the month of diagnosis.[31] Even more noteworthy are the changes in proportions of dispensed opioids represented by strong versus other opioids from the month of cancer diagnosis in all but the Sustained use group. In these groups, strong opioids comprised the minority of analgesia treatment prior to diagnosis but the majority thereafter. This change may reflect higher needs for analgesia following cancer-related surgeries or other cancer-related events, or a desire by some clinicians to transition patients from products containing paracetamol (e.g., codeine and paracetamol), which may mask neutropenic fever or aggravate liver toxicities during cancer treatment. It is also consistent with qualitative research suggesting that prescribers are more comfortable using strong opioids when someone has a cancer diagnosis.[32]

Strengths and Limitations

Our study used a large, population-based dataset to describe trajectories of opioid dispensing before and after a cancer diagnosis. These data do not include clinical measures, such as pain severity, disease stage or performance status, and our findings should be interpreted with these limitations in mind. While we have suggested that noncancer factors, such as comorbidities, may be an important driver of postdiagnosis opioid treatment in our cohort, other factors we cannot observe, such as patients living with active disease and receiving on-going cancer treatments, also likely drive postdiagnosis opioid treatment. We have applied the descriptor, "survivor" to distinguish people who remained alive 24 months after

diagnosis, but a number of people in our survivor cohort are likely to have been receiving active cancer treatment, including some who went on to die from their disease beyond this observation window. Similarly, we used a proxy measure to ascertain comorbidity burden and it is not possible to interpret this measure in terms of its contribution to pain. Low-dose formulations of codeine were available without a prescription during the study period, so this treatment, as well as any opioid medicines accessed outside of the PBS (i.e., through private prescription) were not captured in our data. Private prescribing of opioids is not common in Australia and we expect its impact on our findings to be minimal.[33] However, PBS data do not contain records of opioid medicines dispensed to hospital inpatients and our results likely under-estimate the amount of opioids dispensed in our study, particularly around the time of cancer diagnosis when cancer-related surgery is likely to have driven opioid use. PBS data contain records of dispensed medicines and we do not know if the dispensed medicines, including opioids, were ultimately used by the people to whom they were dispensed. Our OMEmg results may over estimate the true quantity of opioids used by our cohorts. Finally, PBS records do not contain data on prescribed dose, indication, or intended duration of treatment and do not provide information on whether dispensed quantities were consumed.

Conclusions

Our population-based study found considerable heterogeneity in the use of opioids before a diagnosis of cancer. Opioid use for most people increased significantly from the month of cancer diagnosis and, for those who continued to be dispensed opioids up to 24 months postdiagnosis, never returned to prediagnosis levels. Our findings suggest noncancer factors (e.g. pre-existing, noncancer comorbidities) may drive a significant proportion of postdiagnosis opioid use. In our study, opioid dispensing is an indicator for pain that does not specifically provide information about pain severity, pain type (e.g., neuropathic), or location of pain. These factors in turn would be influenced by cancer type, stage at diagnosis and then subsequent clinical course. Such information might be determined from free text clinical annotation and or patient reported measures, the latter of which are currently being implemented into routine clinical practice in some jurisdictions such as cancer centres. Understanding the natural history of specific cancer subtypes might explain the variation in the opioid use trajectories. Studies with access to such detailed clinical data would facilitate research examining whether changes in dispensing are commensurate with analgesic need or due to other factors that may increase risks of opioid-related harm disproportionately to the benefits of opioids. Any such investigations should seek to balance risk of harm against the clinical benefit to ensure access to opioid medicines for those patients who need them.

Disclosures

SAP is a member of the Drug Utilisation Sub Committee of the Pharmaceutical Benefits Advisory Committee. The views expressed in this paper do not represent those of the Committee. The remaining authors have no competing interests to declare.

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Supplementary Table a)

Opioid Medicines Included in the Study

Opioid	ATC code	PBS item code
Buprenorphine	N02AE01	08865N, 08866P, 08867Q, 10746N, 10755C, 10756D, 10770W, 10948F, 10949G, 10953L, 10957Q, 10959T, 10964C, 10970J
Codeine	N02AA, N02AA59, N02AJ06, N02AJ07, N02BA51, N02BE51, R05DA04	04061R, 01214X, 05063L, 04286N, 01215Y, 03316M, 04170L, 04171M, 04275B, 08785J, 10186D, 07375E, 07530H, 06031K, 06032L
Fentanyl	N02AB03	05265D, 05277R, 05278T, 05279W, 05280X, 05401G, 05402H, 05403J, 05406M, 05407N, 05408P, 05409Q, 05410R, 05411T, 05412W, 05437E, 05438F, 05439G, 05440H, 05441J, 08878G, 08891Y, 08892B, 08893C, 08894D, 10600X, 10601Y, 10602B, 10603C, 10604D, 10607G, 10608H, 10610K, 10611L, 10612M, 10613N, 10684H, 10697B, 10698C, 10713W, 10729Q, 10737D, 10738E, 10739F
hydromorphone	N02AA03	08420E, 08421F, 08422G, 08423H, 08424J, 08541M, 08542N, 08543P, 09299K, 09406C, 09407D, 09408E, 09409F
Methadone	N02AC, N02AC52	01606M, 01609Q, 05399E, 05400F, 06035P, 06036Q, 06037R
Morphine	N02AA01	01607N, 01644M, 01645N, 01646P, 01647Q, 01653B, 01654C, 01655D, 01656E, 02122Q, 02123R, 02124T, 02332R, 02839K, 02840L, 02841M, 04349X, 05391R, 05392T, 05393W, 05394X, 05395Y, 05396B, 08035X, 08146R, 08305D, 08306E, 08349K, 08453X, 08454Y, 08489T, 08490W, 08491X, 08492Y, 08493B, 08494C, 08669G, 08670H, 10864T, 10869C, 10874H, 10878M
Oxycodone	N02AA05	02481N, 02622B, 05195K, 08385H, 08386J, 08387K, 08388L, 08464L, 08501K, 08502L, 08644Y, 08681X, 09399Q, 09400R
Oxycodone & naloxone	N02AA55	08000C, 08934F, 08935G, 08936H, 10757E, 10758F, 10776E, 11102H, 11111T
Tapentadol	N02AX06	10091D, 10092E, 10094G, 10096J, 10100N
Tramadol	N02AX02	02527B, 05232J, 08455B, 08523N, 08524P, 08525Q, 08582Q, 08611F, 08843K, 09199E, 09200F, 09201G

Abbreviations: ATC = Anatomical Therapeutic Chemical; PBS = Pharmaceutical Benefits Scheme.

Supplementary Table b)

International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), Topography Codes Included in the Study

Cancer Grouping	ICD-O-3 Topography Code
Blood/connective/soft tissue cancers	C42, C44, C47 − C49
Bone cancers	C40, C41
Brain and central nervous system (CNS) cancers	C70 − C72
Breast cancers	C50
Colorectal cancers (CRC)	C18 − C21
Eye cancers	C69
Female reproductive system cancers	C51 − C58
Head/face/neck cancers	C76
Liver/digestive system other cancers	C15 − C17, C22 − C26
Lung cancers	C34
Male reproductive system cancers	C60 − C63
Oral cancers	C01 − C14
Renal cancers	C64 − C68
Respiratory/intrathoracic cancers	C30 − C33, C37 − C39
Thyroid/adrenal/endocrine system cancers	C73 − C75, C77

Supplementary Table c)

Secondary Cohort Patient and Treatment Characteristics at, Before, and After Cancer Diagnosis

	Secondary Cohort	Trajectory 1: Infrequent Use	Trajectory 2: Late Increasing Use	Trajectory 3: Moderate Increasing Use	Trajectory 4: Sustained Use
n (%)	9802 (100)	4003 (41)	3561 (36)	1171 (12)	1067 (11)
median age (IQR)	74 (64; 82)	75 (66; 83)	71 (61; 80)	76 (67; 83)	78 (68; 85)
Age group, n (%):					
< 35	58 (<1)	[a]	[a]	[a]	[a]
35–54	829 (9)	280 (7)	432 (12)	[a]	[a]
55–74	4171 (43)	1630 (41)	1719 (48)	443 (38)	379 (36)
75 +	4744 (48)	2072 (52)	1377 (39)	652 (56)	643 (60)
Sex, n (%)					
Males	5452 (56)	2305 (58)	2084 (59)	586 (50)	477 (45)
Dispensed an analgesic medicine, n (%):					
Prediagnosis	5356 (55)	2165 (54)	1501 (42)	863 (74)	827 (78)
Postdiagnosis	4489 (46)	1644 (41)	1622 (46)	621 (53)	602 (56)
Dispensed paracetamol, n (%):					
Prediagnosis	4792 (49)	1964 (49)	1293 (36)	793 (68)	742 (70)
Postdiagnosis	3179 (32)	1215 (30)	1023 (29)	485 (41)	456 (43)
Dispensed pregabalin, n (%):					
Prediagnosis	1478 (15)	486 (12)	389 (11)	282 (24)	321 (30)
Postdiagnosis	2234 (23)	698 (17)	939 (26)	290 (25)	307 (29)
Dispensed gabapentin, n (%):					
Prediagnosis	87 (1)	23 (1)	14 (< 1)	22 (2)	28 (3)
Postdiagnosis	105 (1)	30 (1)	27 (1)	23 (2)	25 (2)
Dispensed pizotifen, n (%):					
Prediagnosis	41 (< 1)	14 (< 1)	11 (< 1)	8 (1)	8 (1)
Postdiagnosis	20 (< 1)	[a]	[a]	[a]	[a]
Dispensed a psychotropic medicine, n (%):					
Prediagnosis	5004 (51)	1910 (48)	1515 (43)	799 (68)	780 (73)
Postdiagnosis	5703 (58)	2256 (56)	1976 (55)	767 (65)	704 (66)
Dispensed an antidepressant, n (%):					
Prediagnosis	3167 (32)	1183 (30)	864 (24)	559 (48)	561 (53)
Postdiagnosis	3109 (32)	1183 (30)	1004 (28)	473 (40)	449 (42)
Dispensed an antiepileptic, n (%):					
Prediagnosis	524 (5)	227 (6)	138 (4)	82 (7)	77 (7)
Postdiagnosis	898 (9)	387 (10)	306 (9)	100 (9)	105 (10)
Dispensed an antipsychotic, n (%):					
Prediagnosis	527 (5)	182 (5)	155 (4)	86 (7)	104 (10)
Postdiagnosis	1989 (20)	749 (19)	746 (21)	237 (20)	257 (24)
Dispensed an anxiolytic, n (%):					
Prediagnosis	1594 (16)	569 (14)	465 (13)	274 (23)	286 (27)
Postdiagnosis	1418 (14)	501 (13)	488 (14)	227 (19)	202 (19)
Dispensed an hypnotic and/or sedative, n (%):					
Prediagnosis	1868 (19)	694 (17)	567 (16)	311 (27)	296 (28)
Postdiagnosis	2251 (23)	905 (23)	793 (22)	307 (26)	246 (23)
Dispensed an NSAID, n (%):					
Prediagnosis	3429 (35)	1371 (34)	1197 (34)	492 (42)	369 (35)
Postdiagnosis	1267 (13)	463 (12)	481 (14)	179 (15)	144 (13)

(*Continued*)

Supplementary Table c)
Continued

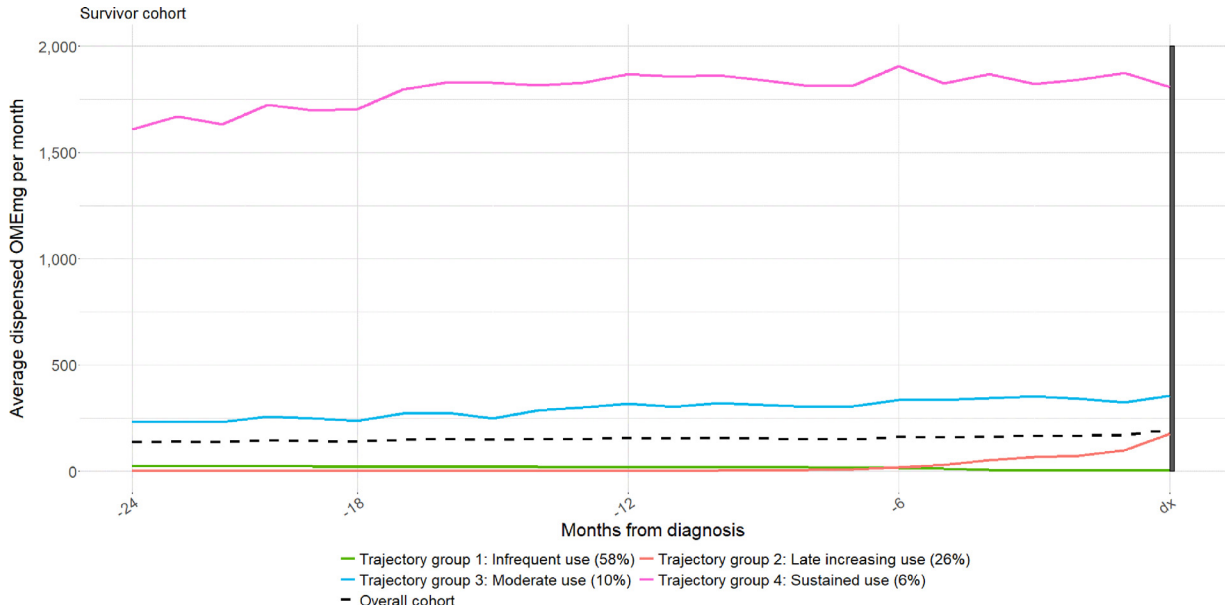
	Secondary Cohort	Trajectory 1: Infrequent Use	Trajectory 2: Late Increasing Use	Trajectory 3: Moderate Increasing Use	Trajectory 4: Sustained Use
Dispensed nonselective NSAIDs, n (%)					
Prediagnosis	1581 (16)	619 (15)	586 (16)	221 (19)	155 (15)
Postdiagnosis	628 (6)	232 (6)	261 (7)	75 (6)	60 (6)
Dispensed selective COX-2 inhibitors, n (%)					
Prediagnosis	2289 (23)	937 (23)	753 (21)	348 (30)	251 (24)
Postdiagnosis	722 (7)	261 (7)	259 (7)	115 (10)	87 (8)
First cancer diagnosis, n (%)					
Blood/connective/soft tissue	1247 (13)	534 (13)	342 (10)	184 (16)	187 (18)
Bone	25 (< 1)	[a]	[a]	[a]	[a]
Brain & CNS	233 (2)	146 (4)	55 (2)	20 (2)	12 (1)
Breast	282 (3)	114 (3)	86 (2)	34 (3)	48 (4)
Colorectal	1013 (10)	474 (12)	294 (8)	125 (11)	120 (11)
Eye	6 (< 1)	[a]	[a]	[a]	[a]
Female reproductive	343 (3)	137 (3)	126 (4)	38 (3)	42 (4)
Head, face, and/or neck	11 (< 1)	[a]	[a]	[a]	[a]
Liver/digestive other	2305 (24)	941 (24)	901 (25)	246 (21)	217 (20)
Lung	2593 (26)	941 (24)	1066 (30)	324 (28)	262 (25)
Male reproductive	414 (4)	179 (4)	151 (4)	47 (4)	37 (3)
Oral	241 (2)	88 (2)	102 (3)	19 (2)	32 (3)
Renal	502 (5)	205 (5)	186 (5)	54 (5)	57 (5)
Respiratory/intrathoracic	235 (2)	80 (2)	99 (3)	32 (3)	24 (2)
Thyroid/adrenal/endocrine	352 (4)	156 (4)	131 (4)	43 (4)	22 (2)
Prediagnosis RxRisk conditions/dispensings, n (%): (excluding opioid and cancer medicines)					
0	354 (4)	[a]	[a]	[a]	[a]
1–5	4661 (48)	[a]	[a]	[a]	[a]
5 +	4787 (49)	2009 (50)	1274 (36)	782 (67)	722 (68)
Postdiagnosis RxRisk conditions/dispensings, n (%): (excluding opioid and cancer medicines)					
0	1168 (12)	414 (10)	485 (14)	146 (12)	123 (12)
1–5	4666 (48)	1915 (48)	1857 (52)	460 (39)	434 (41)
5 +	3968 (40)	1674 (42)	1219 (34)	565 (48)	510 (48)

[a]Cells with counts < 6 and those that may allow counts of <6 to be inferred have been suppressed per ethical conditions of the study.

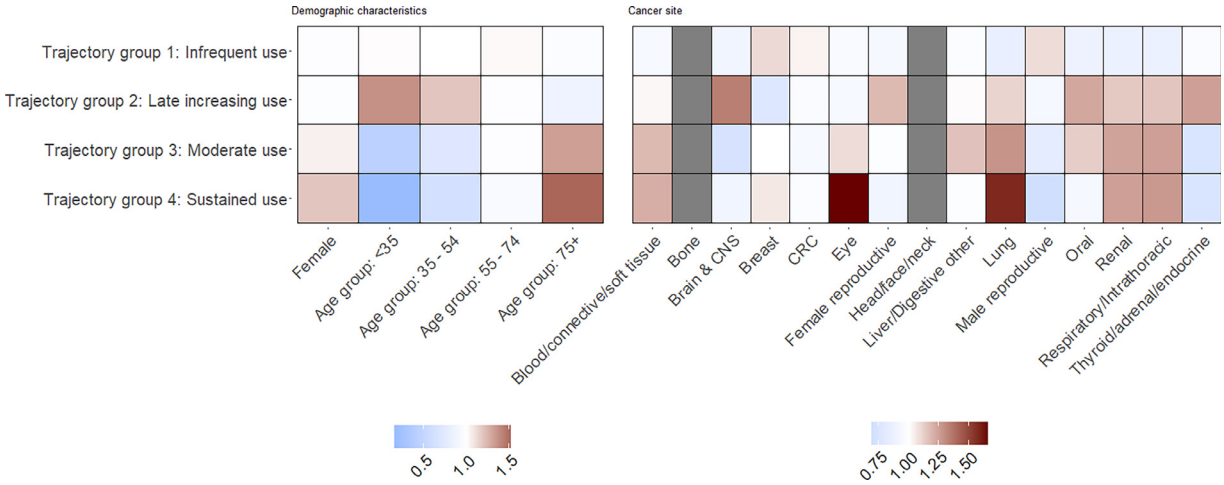
Supplementary Table d)

Average Monthly Dispensed Oral Morphine Milligrams (OMEmg) and Estimated Change in Monthly Dispensed OMEmg at Cancer Diagnosis, Stratified by Prediagnosis Opioid Use Trajectory Group; Secondary Cohort Cohort

	Average Dispensed OMEmg (SD)		
	Prediagnosis	Postdiagnosis	Change at Diagnosis (95% CI)
Secondary cohort	247 (1143)	1210 (3228)	450.9 (434.2; 467.5)
Trajectory 1: infrequent use	27 (244)	621 (2166)	251.1 (241.4; 260.7)
Trajectory 2: late increasing use	37 (388)	1641 (4026)	1101.7 (1080.3; 1123.1)
Trajectory 3: moderate increasing use	332 (928)	1381 (3087)	458.6 (406.5; 510.8)
Trajectory 4: sustained use	1679 (2780)	2216 (3823)	−68.8 (-175.0; 37.4)

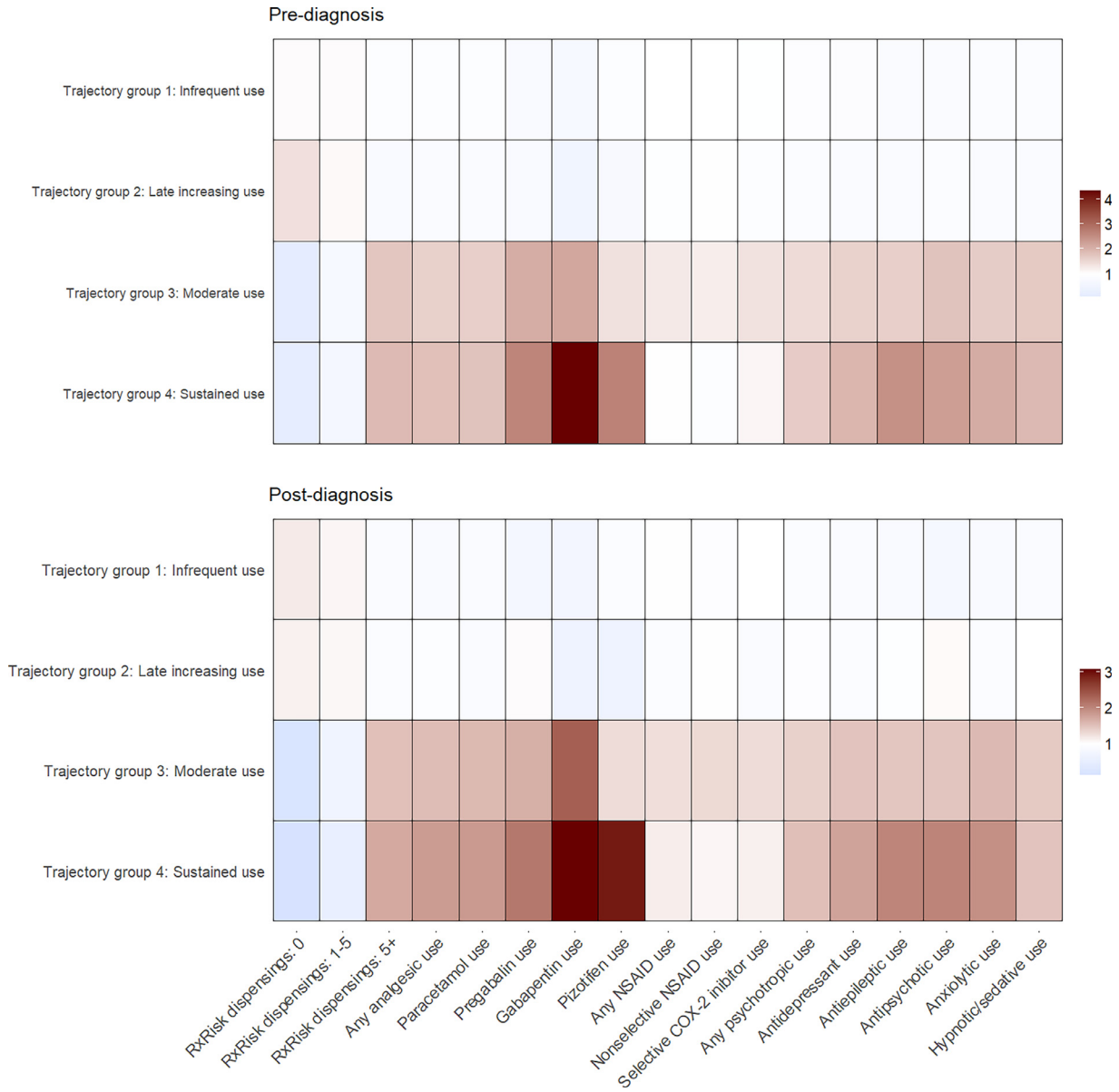


Supplementary Fig. a). Average dispensed oral morphine equivalent milligrams per month from 24 months prior to cancer diagnosis to diagnosis; stratified by opioid use trajectory group; survivor cohort. Percentages denote the proportion of the survivor cohort assigned to each trajectory group. Shaded vertical area denotes month of cancer diagnosis.

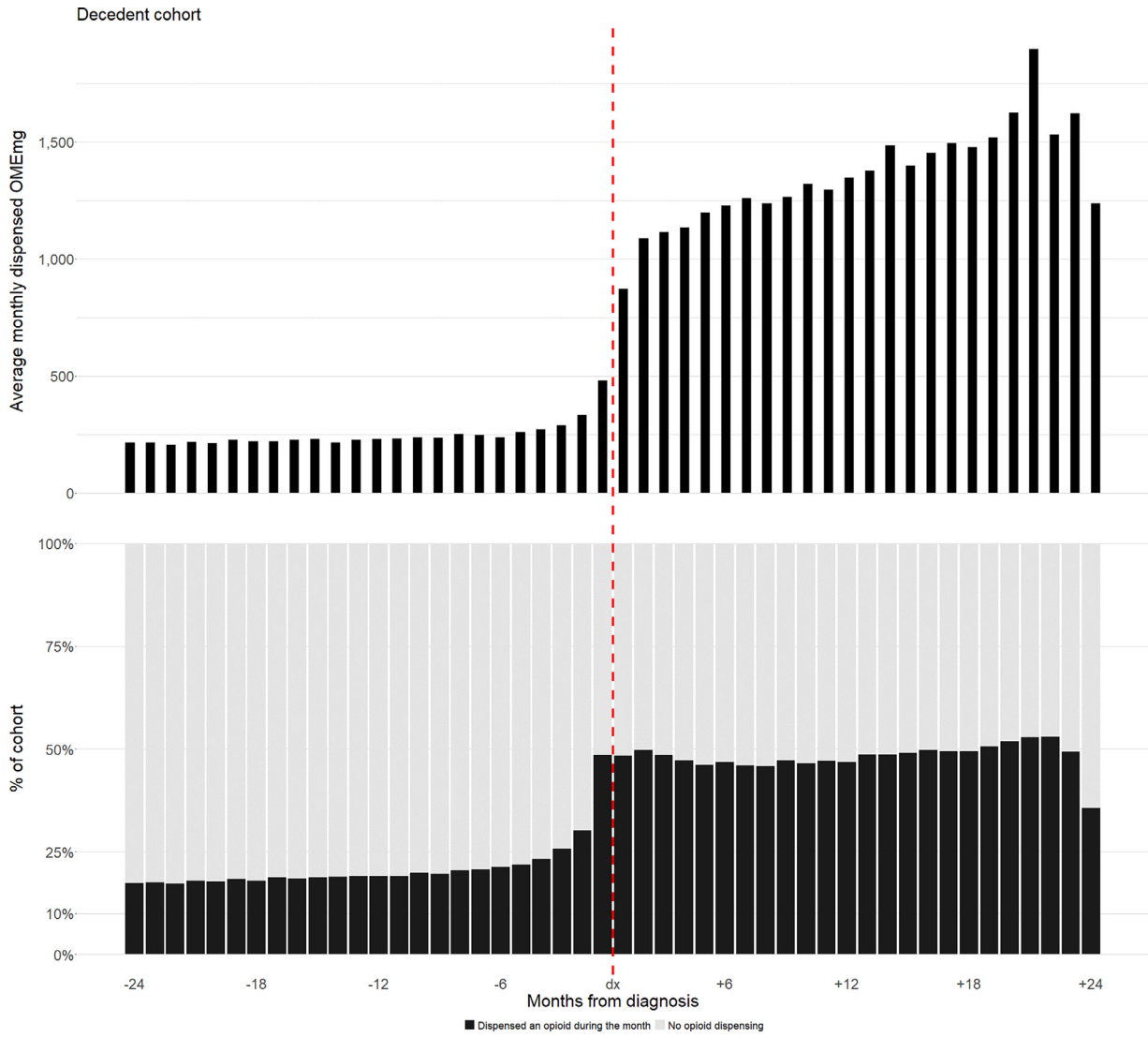


Supplementary Fig. b). Prevalence of demographic characteristics and cancer diagnoses, relative to the entire survivor cohort. White coloured cells indicate the prevalence within the trajectory group was equivalent to that in the entire survivor cohort; red indicates prevalence within the trajectory group is higher than the overall cohort prevalence; blue indicates prevalence within the trajectory group is lower than the overall cohort prevalence; grey indicates values suppressed due to low cell counts.

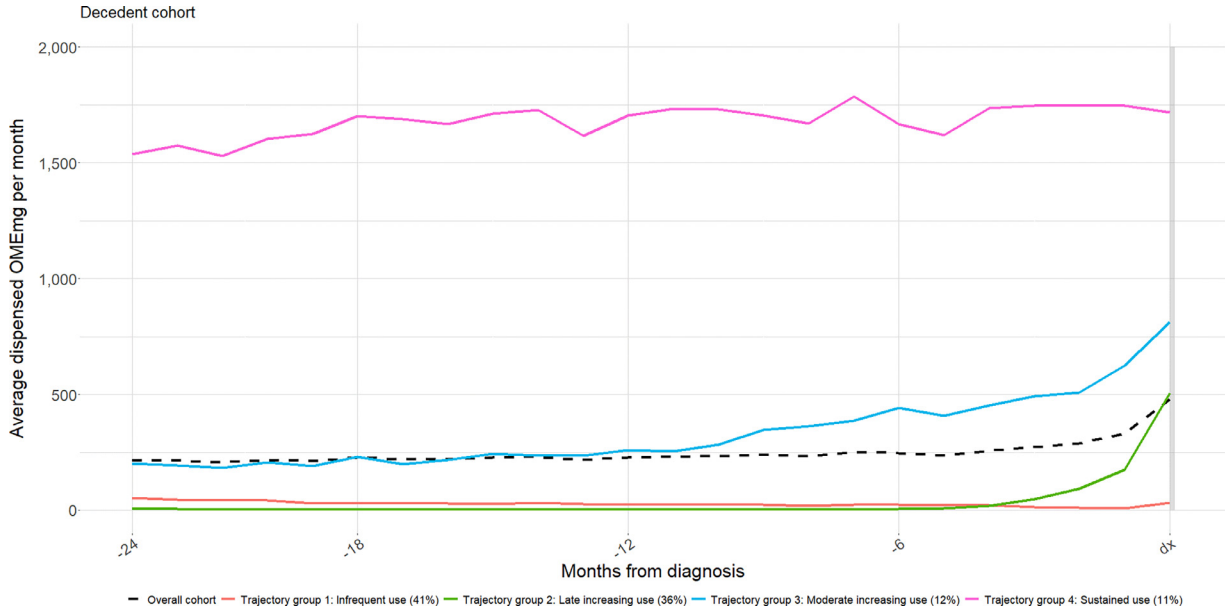
Blood/connective/soft tissue cancers (ICD-O-3 codes: C42, C44, C47 – C49); Bone cancers (C40, C41); Brain and central nervous system (CNS) cancers (C70 – C72); Breast cancers (C50); Colorectal cancers (CRC; C18 – C21); Eye cancers (C69) Female reproductive system cancers (C51 – C58); Head/face/neck cancers (C76); Liver/digestive system other cancers (C15 – C17, C22 – C26); Lung cancers (C34); Male reproductive system cancers (C60 – C63); Oral cancers (C01 – C14); Renal cancers (C64 – C68); Respiratory/intrathoracic cancers (C30 – C33, C37 – C39); Thyroid/adrenal/endocrine system cancers (C73 – C75, C77).



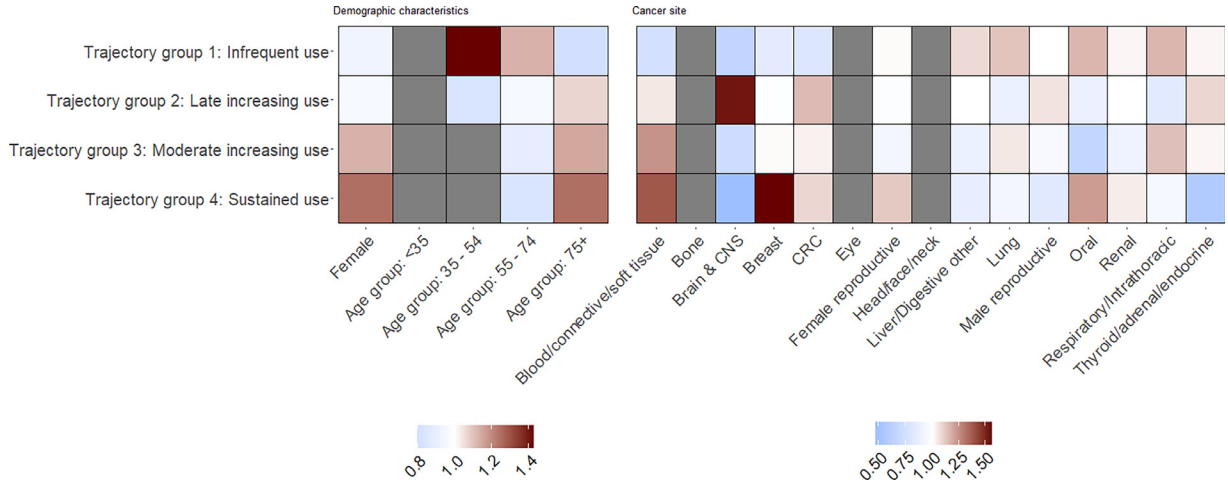
Supplementary Fig. c). Prevalence of medicine use characteristics, relative to the entire survivor cohort. White coloured cells indicate the prevalence within the trajectory group was equivalent to that in the entire survivor cohort; red indicates prevalence within the trajectory group is higher than the overall cohort prevalence; blue indicates prevalence within the trajectory group is lower than the overall cohort prevalence; grey indicates values suppressed due to low cell counts.



Supplementary Fig. d). Average monthly dispensed oral morphine equivalent milligrams (top) and proportion of the cohort alive and dispensed an opioid in each month (bottom); decedent cohort. Red dashed line indicate month of diagnosis.

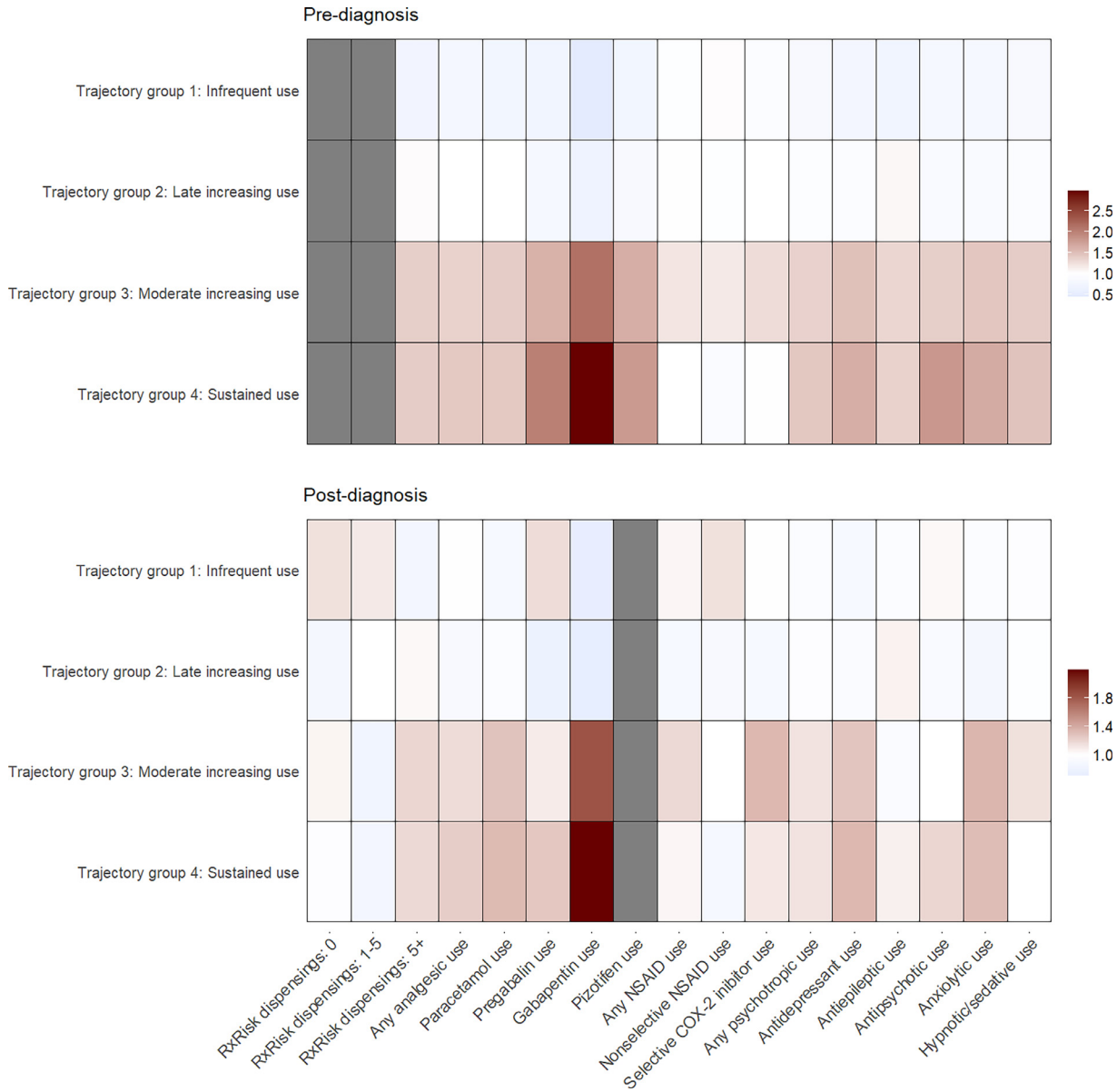


Supplementary Fig. e). Average dispensed oral morphine equivalent milligrams per month from 24 months prior to cancer diagnosis to diagnosis; stratified by opioid use trajectory group. Percentages denote the proportion of the decedent cohort assigned to each trajectory group. Shaded vertical area denotes month of cancer diagnosis.

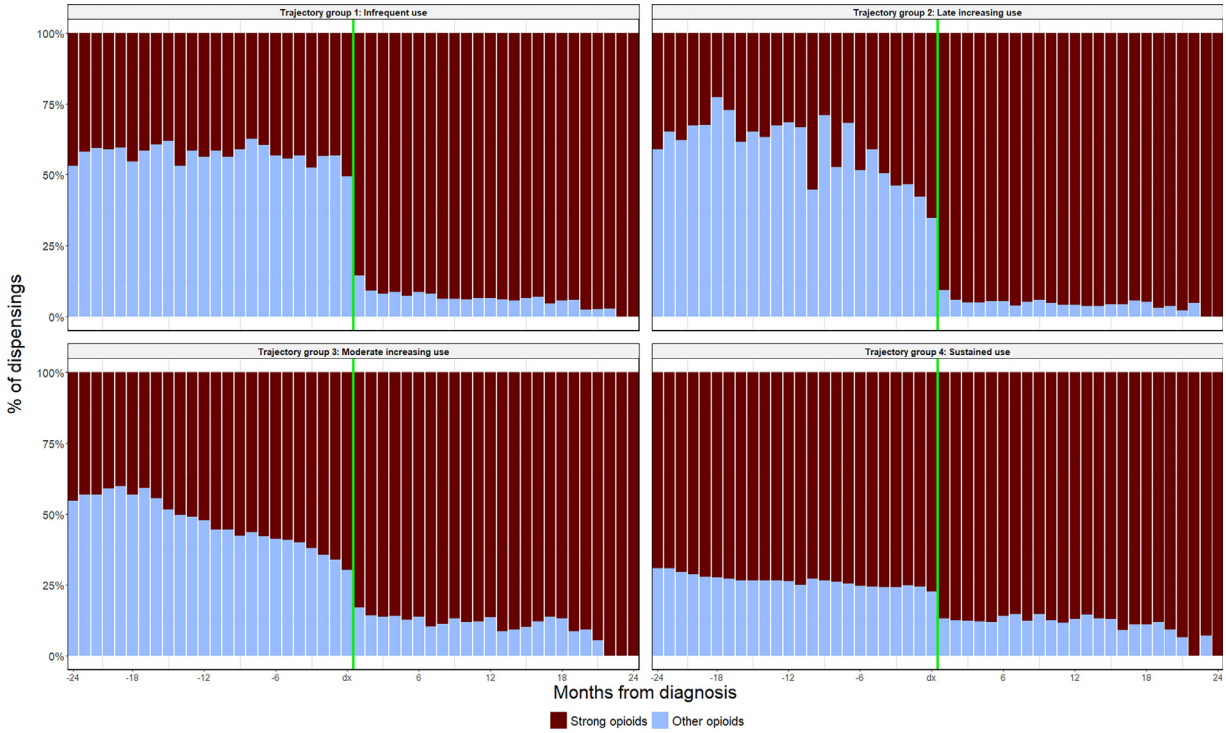


Supplementary Fig. f). Prevalence of demographic characteristics and cancer diagnoses, relative to the entire decedent cohort. White coloured cells indicate the prevalence within the trajectory group was equivalent to that in the entire decedent cohort; red indicates prevalence within the trajectory group is higher than the overall cohort prevalence; blue indicates prevalence within the trajectory group is lower than the overall cohort prevalence; grey indicates values suppressed due to low cell counts.

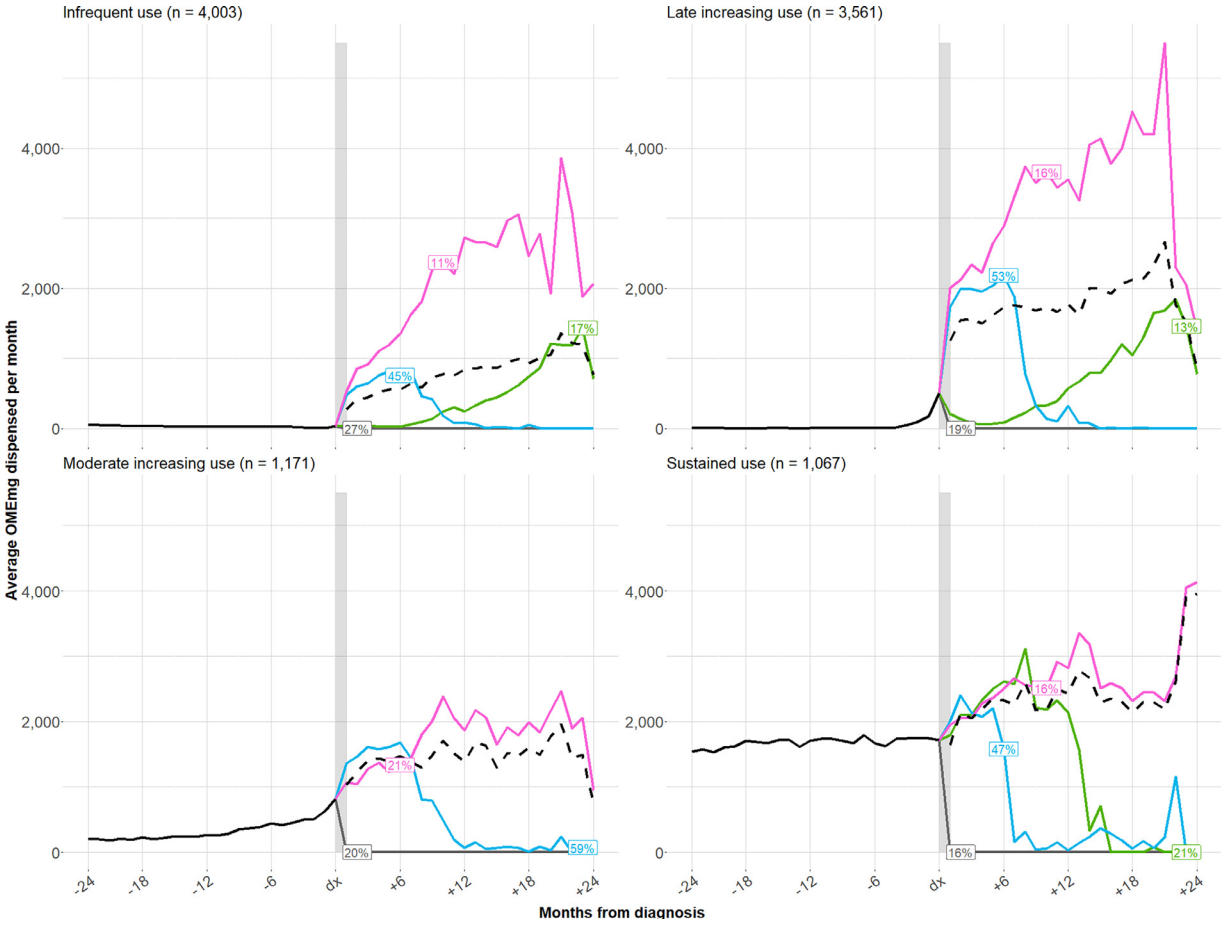
Blood/connective/soft tissue cancers (ICD-O-3 codes: C42, C44, C47 – C49); Bone cancers (C40, C41); Brain and central nervous system (CNS) cancers (C70 – C72); Breast cancers (C50); Colorectal cancers (CRC; C18 – C21); Eye cancers (C69) Female reproductive system cancers (C51 – C58); Head/face/neck cancers (C76); Liver/digestive system other cancers (C15 – C17, C22 – C26); Lung cancers (C34); Male reproductive system cancers (C60 – C63); Oral cancers (C01 – C14); Renal cancers (C64 – C68); Respiratory/intrathoracic cancers (C30 – C33, C37 – C39); Thyroid/adrenal/endocrine system cancers (C73 – C75, C77).



Supplementary Fig. g). Prevalence of medicine use characteristics, relative to the entire decedent cohort. White coloured cells indicate the prevalence within the trajectory group was equivalent to that in the entire decedent cohort; red indicates prevalence within the trajectory group is higher than the overall cohort prevalence; blue indicates prevalence within the trajectory group is lower than the overall cohort prevalence; grey indicates values suppressed due to low cell counts.



Supplementary Fig. h). Proportion of opioid dispensings in each month stratified by type of opioids (strong or other) and pre-diagnosis opioid use trajectory; decedent cohort. Green vertical line indicates month of diagnosis.



Supplementary Fig. i). Average monthly dispensed oral morphine equivalent milligrams overall (dashed black line) and in post-diagnosis opioid use trajectory groups, stratified by prediagnosis opioid trajectory group; decedent cohort. Percentages show the proportion of each prediagnosis trajectory group assigned to each postdiagnosis trajectory group.