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Prescriptions of analgesics during chronic cancer disease trajectories: A complete national cohort study

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Abstract

Purpose: Pain management principles vary considerably between chronic noncancer, acute and cancer pain. Cancer patients responding to oncological treatment may live with low tumor burden for years. Opioid treatment should reflect that the ratio between benefits and risks in these patients is different from patients with a rapidly progressive disease. Our study investigated the prescription patterns of analgesics in patients who died 6 to 9 years after cancer diagnosis.

Patients and methods: A pharmaco-epidemiological study based on the Norwegian Prescription Database and Cancer Registry of Norway. The 1-year periodic prevalence of receiving different analgesics and of persistent opioid use were analyzed. Persistent opioid use was defined as >365 Defined Daily Doses or >9000 mg Oral Morphine Equivalents during 365 days with prescriptions in all quarters of the 365 days period.

Data were reported for the first 7 years for patients who lived 8–9 years after cancer diagnosis ($N = 1502$), while for patients who lived 6–7 years ($N = 3817$) data was reported for the first 5 years after diagnosis.

Results: Compared to age- and gender adjusted general population, the 1-year periodic prevalence of opioid prescription was doubled the first year after diagnosis and remained raised with approximately 50%. The prevalence of persistent opioid use was threefold of the general population. Approximately 55% of patients with persistent opioid use 4 years after a cancer diagnosis were co-medicated with high doses of benzodiazepines and/or benzodiazepine-related hypnotics.

Conclusion: The findings of increased opioid use raise concerns regarding whether the benefits outweigh risks and side effects in this population.

KEYWORDS
cancer, opioids, pain, pharmcoepidemiology

Key Points

- The periodic prevalence of using opioids was doubled the first year after cancer diagnosis compared to the general population.
- The prevalence of persistent opioid use was threefold of the general population.
- Opioid dose before cancer diagnosis and the first year after has a strong association with persistent opioid use later in the disease trajectory.
- Approximately half of patients with persistent opioid use 4 years after a cancer diagnosis were co-medicated with high doses of benzodiazepines and/or benzodiazepine-related hypnotics.

1 | BACKGROUND

Pain can be classified in numerous ways, based on variables such as etiology, mechanism, duration, intensity, and localization. Traditionally, pain has often been categorized in three broad and clinically relevant categories, according to which analgesic treatments have differed in terms of drug selection and priority: chronic non-cancer pain (CNCP), acute/postoperative pain, or cancer pain.[1] However, the recent and disastrous opioid epidemic indicates that the principles for opioid use in cancer pain have also been applied in CNCP.[2,3] Treatment of cancer pain has been based on the WHO analgesic ladder with liberal prescriptions of opioids. In cancer patients with a limited life expectancy due to progressive disease, the analgesic effects of opioids have been considered to outweigh side effects and risks.[4] In CNCP on the other hand, there is an increasing evidence that the analgesic effect of long-term opioid treatment is limited or moderate, side effects are prevalent and the risk of problematic opioid use and addiction is high.[5–8]

The five-year overall survival has risen steadily for most common tumors.[9,10] This has resulted in increasing numbers of patients living with their cancers for several years even when curative treatment is not possible. Patients who live with cancer for several years can experience several types of pain including pain from the primary tumor or metastases, treatment-related pain from surgery, chemo-, hormone-, immune or radiotherapy, or chronic non-malignant pain, which is not related to disease or treatment.[11]

Cancer patients receiving noncurative treatments may enter long periods with a low or moderate tumor burden and quite stable disease. However, pain treatment can be challenging. These patients are neither cancer survivors nor have rapidly progressive cancer. For patients with longer life expectancy, treatment choices in pain management must consider that the ratio between benefits and risks of opioid treatment probably is different from patients with a rapidly progressive disease and short life expectancy. Prevalent side effects and consequences of long-term opioid treatment include addiction, tolerance development, physical dependence, cognitive dysfunction, hyperalgesia, and suppression of immune and endocrine systems.[12–15] Even though low or moderate opioid doses might be appropriate, these patients might benefit from applying many of the treatment principles for CNCP patients including screening, goal setting, monitoring, and exit programs.[16] Co-abuse of benzodiazepines is prevalent in CNCP patients with persistent opioid use.[17] Such co-medication with benzodiazepines is in conflict with guidelines for opioid use in CNCP[18,19] and has also been associated with too early opioid refills and increased risk of drug overdoses.[20,21] The prevalence of such co-medication is not known in patients with chronic cancer diseases receiving long-term opioid treatment. Drug use in the period from diagnosis until 1–2 years before death is of great interest in this patient population, because prescription patterns in this part of the disease trajectory may indicate whether patients have developed problematic opioid use.

Previous pharmaco-epidemiological studies have addressed first treatment episodes with opioids after a cancer diagnosis,[22] analgesic use in the last year of life in patients dying from cancer,[23] opioid use during the disease trajectory in patients dying within 5 years of cancer diagnosis[24] and opioid use in cancer survivors.[25] However, the prescriptions of analgesics during years of relatively stable cancer disease has not formerly been investigated in population-based studies.

The aim of this study was to investigate the prescription patterns of analgesics and benzodiazepines in patients living with cancer disease for a minimum of 6 years before death.

2 | MATERIAL AND METHODS

2.1 | Study design

A pharmaco-epidemiological study based on complete data from Norwegian national health registries. The study combines cross-sectional and cohort designs.

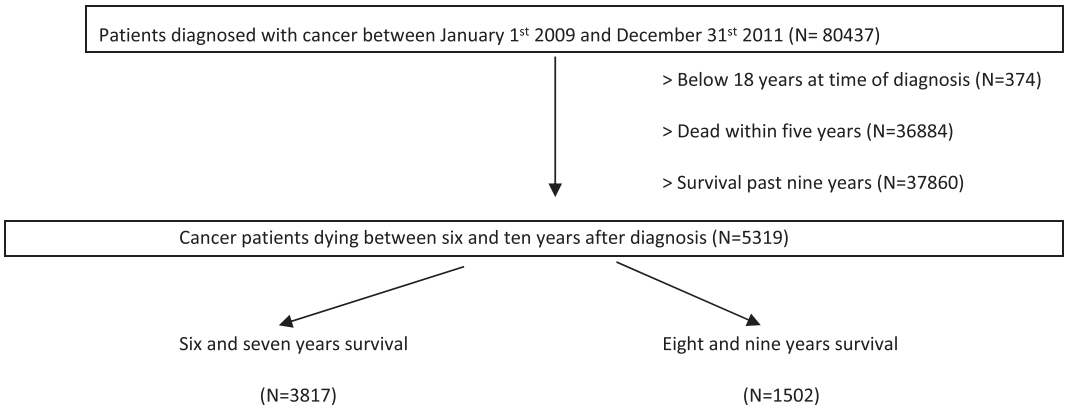

FIGURE 1 Study population. Flow sheet of included patients

2.2 | Study population

The study population consisted of all adult Norwegians, who died 6–9 years after being diagnosed with cancer disease between January 1st, 2009 and December 31st, 2011 (Figure 1). Patients were excluded if they had a second cancer diagnosis before 2015. Persons, who had been diagnosed with more than one cancer disease before December 31st, 2011, were included if the latest cancer diagnosis met the inclusion criteria.

2.3 | Data sources

The study was based on data from the complete national Cancer Registry of Norway, the complete national Norwegian Prescription Database (NorPD) and the Norwegian Population register. The individuals' unique personal identification number was used for linkage. The identification numbers were pseudonymized to ensure anonymity.

2.3.1 | Norwegian prescription database

Since January 1, 2004 NorPD contains information on all prescription drugs that are dispensed at pharmacies to individual patients outside institutions. Through a unique identifier dispensed drugs to each individual can be followed chronologically. Only prescriptions which are actually dispensed are captured.

2.3.2 | Cancer Registry of Norway

Since 1953, the Cancer Registry of Norway has collected population-based data on incidence, survival, and prevalence of cancer in Norway based on mandatory reporting of all cases of cancer. The registry contains information on tumor location, histology, month and year of diagnosis, and stage at time of diagnosis.

TABLE 1 ATC-codes of drugs included in the study

Drug	Anatomical therapeutic Chemical (ATC) codes
Opioids	N02A
Paracetamol	N02BE01 and N02BE51
NSAIDs	M01A
Gabapentinoids	N03AX16, N03AX12
Benzodiazepines	N03AE01, N05BA, N05CD
Benzodiazepine-related hypnotics	N05CF

2.3.3 | Norwegian population register

Data on time of death were obtained from the Norwegian population register, which contains complete national data.

2.4 | Drugs

All drugs sold in Norway are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (https://www.whocc.no/atc_ddd_index/). The ATC codes of included drug groups are presented in Table 1. Drug quantities are in this study measured as Defined Daily Doses (DDD) (https://www.whocc.no/atc_ddd_index/) and oral morphine equivalents (OMEQ). OMEQs are calculated based on previously published conversion ratios.[26]

In Norway, opioids are only available by prescription. The ATC codes of included drugs include all opioids marketed in Norway except for methadone, buprenorphine 8 mg, buprenorphine/naloxone combination, and opioids only used by anesthesiologists in hospitals (alfentanil, remifentanil, and sulfentanil). Methadone, buprenorphine 8 mg (Subutex, Reckitt Benckiser, Slough, Berkshire, and England), and buprenorphine/naloxone (Suboxone, Reckitt Benckiser, Slough, Berkshire, and England) were not included, because they are primarily used

in opioid maintenance therapy and are rarely used in pain management in Norway.

Benzodiazepines, benzodiazepine-related hypnotics and gabapentinoids are only available by prescription in Norway. Small quantities of paracetamol and nonsteroidal anti-inflammtaory drugs (NSAIDs) are available over the counter without prescription.

2.5 | Analysis strategy and statistics

The study population was stratified according to survival into two groups with survival of 6 and 7 years, and 8 and 9 years. Most analyses were performed for each stratum separately. The sixth year was defined as the sixth 365-day period after the 15th in the month of diagnosis, the seventh year as the seventh 365-day period after the month of diagnosis and so on. The study period was from the first to fifth year after diagnosis for patients with survival of 6 or 7 years, and from the first to seventh year after diagnosis for patients with survival of 8 or 9 years. Survival after the end of the study period ranged from 13 to 24 months.

Data on the prevalence of drug use are presented as 1-year periodic prevalence. The 1-year periodic prevalence for each drug class is the percentage of the study population receiving a prescription of the drug class during a 365-day period. Prescriptions dispensed in the month of diagnosis were excluded since the exact date of diagnosis is unknown. In this paper "prevalence" should be understood as the 1-year periodic prevalence.

Persistent opioid use was defined based on data from NorPD in accordance with previously published criteria.[27] The criteria are based on dispensed opioid volume and number of prescriptions for 365 days. The criteria for the applied definition of persistent opioid use were to use >365 DDDs or >9000 mg Oral Morphine Equivalents (OMEQs) during 365 days and to receive prescriptions in all quarters of the 365 days period. This definition clinically corresponds to using opioids daily, but not necessarily around the clock. Using criteria combining DDDs and OMEQs have previously been reported to reflect clinical dosing of opioids when data on several types of opioids are included, particularly, when weak and strong opioids are combined.[26] High-dose-use of opioids was defined as using more than 730 DDDs of opioids during a 365-days period and prescriptions all quarters of the year. High dose use of benzodiazepines and benzodiazepine-related hypnotics (separately) was defined as receiving more than 100 DDDs during one 365-days period.

The prevalence in the general population was adjusted for age and gender using the R-function "ageadjust.direct" in the R-package "epitools" (Tomas J. Aragon [2020]. epitools: Epidemiology Tools. R package version 0.5–10.1. https://CRAN.R-project.org/package=epitools), with the study population (1 year age groups) as reference population.

A multivariate analysis was performed with total opioid dose 365 to 180 days before cancer diagnosis and total opioid dose 365 days after cancer diagnosis as independent variables and persistent opioid use the fourth year after diagnosis as dependent variable. The relative risk of being a persistent opioid user 4-year after diagnosis was computed for four levels of opioid dose (mg OMEQ), with 0 as reference level: (0,q90], (q90, q95], (q95, q99], (q99, max] where q denotes quantile and (x,y] includes y but not x. The analysis was adjusted for age (four groups: ≤60, 61–70, 71–80, and >80) and gender. R version 4.0.2 was used for all analyses (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

2.6 | Ethics and approvals

The linkage of the data sources was approved by the Norwegian Data Inspectorate (10/00447-5) and by the Regional Committee for Medical Research Ethics (2010/131).

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

3 | RESULTS

3.1 | Study population

The study population of 5319 patients equals 6.6% of all patients diagnosed with cancer during the inclusion period (Figure 1). 1502 patients died 8 to 9 years after diagnosis and were followed for

TABLE 2 Study population

	Time from diagnosis to death	
	6–7 years	8–9 years
N	3817	1502
Age (mean, SD)	73.7 (11.5)	72.5 (11.1)
% females	44.5	42.5
Diagnostic groups		
Upper GI-tract (*N*,%)	45 (1.2)	15 (1.0)
Lower GI-tract (*N*,%)	646 (16.9)	207 (13.8)
Pancreas/liver/biliary (*N*,%)	32 (0.8)	6 (0.4)
Lung (*N*,%)	168 (4.4)	49 (3.3)
Melanoma (*N*,%)	178 (4.7)	78 (5.2)
Breast (*N*,%)	396 (10.4)	163 (10.9)
Female genitals (*N*,%)	184 (4.8)	67 (4.5)
Male genitals (*N*,%)	6 (0.2)	6 (0.4)
Prostate (*N*,%)	804 (21.1)	320 (21.3)
Kidneys+urinary tract (*N*,%)	325 (8.5)	146 (9.7)
Haematol. malign. (*N*,%)	349 (9.1)	144 (9.6)
Other malignancies (*N*,%)	684 (17.9)	301 (20.0)

7 years, and 3817 patients died between 6 and 7 years after diagnosis and were followed for 5 years (Table 2). The mean age was approximately 73 years in both groups, and the percentage of females 44.5 and 42.5, respectively. Cancers of the prostate, cancers in the lower gastrointestinal tract, breast cancer, hematological malignancies, and cancers of the kidney and urinary tract were the most common diseases. In 47% of the part of the study population where the cause of death was available ($N = 2818$), the recorded underlying cause of death was cancer, followed by cardiovascular diseases in 21% and respiratory diseases in 9%. An additional 8% had cancer as a contributory cause. For those dying from causes other than cancer, it is not known whether they had received curative treatment or still had active cancer disease.

3.2 | Opioid prescriptions

In both the groups with 6–7 and 8–9 years survival, the 1-year periodic prevalence of opioid prescription was highest the first year after diagnosis, with a 1-year periodic prevalence of 33% and 32%, respectively

TABLE 3 One-year periodic prevalence of prescriptions of different analgesics and benzodiazepines, and prevalence of high-dose prescription patterns years one to five after diagnosis in cancer patients dying 6 or 7 years after cancer diagnosis

Patients dying from cancer 6–7 years after diagnosis ($N = 3817$)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	% Study population (% age/gender-adjusted general population)				
One year periodic prevalence of opioid use	33.0 (16.6)	26.0 (17.2)	26.9 (17.6)	28.5 (18.3)	29.1 (18.7)
One year periodic prevalence of benzodiazepine use	22.2 (12.2)	18.4 (11.8)	18.0 (11.8)	17.4 (11.5)	16.9 (11.4)
One year periodic prevalence of benzo-related hypnotic use	30.0 (19.8)	26.3 (20.1)	26.4 (20.5)	26.5 (20.5)	27.0 (20.7)
One year periodic prevalence of paracetamol use*	28.2 (15.9)	22.4 (17.4)	25.1 (19.2)	28.2 (21.0)	31.6 (22.9)
One year periodic prevalence of NSAID use*	21.0 (20.3)	18.5 (18.6)	16.8 (17.3)	14.9 (16.2)	14.0 (14.7)
One year periodic prevalence of gabapentinoid use	2.5 (1.6)	2.9 (1.8)	3.2 (1.9)	3.7 (2.0)	4.5 (2.2)
Prevalence of persistent opioid use	2.3 (0.8)	2.9 (0.9)	3.3 (1.1)	3.7 (1.3)	4.7 (1.5)
Prevalence of high-dose opioid use	0.3 (0.1)	0.4 (0.1)	0.6 (0.1)	0.6 (0.1)	0.8 (0.1)
Prevalence of high-dose benzodiazepine use	7.0 (3.8)	7.0 (3.6)	6.6 (3.6)	6.4 (3.5)	6.2 (3.4)
Prevalence of high-dose benzo-related hypnotic use	17.3 (11.7)	17.1 (12.3)	18.1 (12.7)	17.8 (12.8)	18.7 (13.0)

TABLE 4 One-year periodic prevalence of prescriptions of different analgesics and benzodiazepines, and prevalence of high-dose prescription patterns years one to seven after diagnosis in cancer patients dying 8 or 9 years after cancer diagnosis

Patients dying from cancer 8–9 years after diagnosis ($N = 1502$)							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
	% Study population (% age/gender-adjusted general population)						
One year periodic prevalence of opioid use	32.2 (16.0)	24.0 (16.5)	24.4 (17.0)	24.4 (17.8)	25.1 (18.1)	28.0 (18.3)	30.3 (18.4)
One year periodic prevalence of benzodiazepine use	21.9 (11.7)	18.0 (11.4)	17.6 (11.4)	17.8 (11.2)	17.0 (11.1)	17.3 (10.8)	18.4 (10.6)
One year periodic prevalence of benzo-related hypnotic use	28.4 (19.2)	26.0 (19.6)	26.5 (20.2)	27.0 (20.4)	26.9 (20.7)	26.6 (20.5)	27.8 (20.3)
One year periodic prevalence of paracetamol use*	25.0 (14.8)	20.6 (16.3)	22.5 (18.1)	24.5 (20.0)	27.1 (22.0)	29.8 (24.2)	33.4 (25.9)
One year periodic prevalence of NSAID use*	22.7 (21.1)	20.3 (19.5)	19.0 (18.2)	17.1 (17.2)	15.8 (15.8)	13.7 (14.8)	12.5 (13.4)
One year periodic prevalence of gabapentinoid use	2.8 (1.6)	3.7 (1.7)	3.4 (1.8)	4.1 (2.0)	4.0 (2.2)	4.4 (2.4)	5.3 (2.5)
Prevalence of persistent opioid use	1.7 (0.6)	1.8 (0.8)	1.9 (0.9)	2.2 (1.1)	2.4 (1.3)	3.3 (1.5)	4.4 (1.7)
Prevalence of high-dose opioid use	0.3 (0.1)	<0.3 (0.1)	<0.3 (0.1)	<0.3 (0.1)	0.3 (0.1)	0.6 (0.1)	0.5 (0.1)
Prevalence of high-dose benzodiazepine use	7.9 (3.5)	6.9 (3.3)	7.6 (3.4)	6.8 (3.3)	6.9 (3.2)	6.9 (3.1)	6.9 (2.9)
Prevalence of high-dose benzo-related hypnotic use	16.2 (10.9)	15.7 (11.6)	16.6 (12.2)	17.7 (12.4)	18.6 (12.9)	18.4 (12.9)	19.4 (12.9)

Note: <0.3 (0.1) indicates a very low prevalence. Exact data could not be reported due to data protection/privacy regulations.
*Small quantities of paracetamol and NSAIDs are available over the counter.Drugs sold over the counter are not captured by Norwegian Prescription Database at an individual level and thus not included.

(Tables 3 and 4). The 1-year periodic prevalence was lowest in the second year, and subsequently increased during follow-up. The prevalence of persistent opioid use increased in both groups during follow-up, from approximately 2% to approximately 5%. Compared to the age- and gender adjusted general population the 1-year periodic prevalence of opioid prescription was doubled the first year after diagnosis and remained raised with 40%–60% throughout the study period. The level of persistent opioid use was approximately threefold of the general population throughout the study period in both groups.

The age profile of the study population differed from the general population, with the study population being older. While the 1-year periodic prevalence of opioid prescriptions increased with age in the general population, it decreased in the study population. Thus, the relative increase compared to the general population was higher in the younger subgroup compared to the older subgroup of the study population (Figure 2).

3.3 | Nonopioid analgesic prescriptions

The first year after diagnosis the 1-year periodic prevalence of prescriptions of paracetamol was approximately 70% higher in the study population than in the age-and gender adjusted general population in both study groups (Tables 3 and 4). The second year after diagnosis the 1-year periodic prevalence declined to levels approximately 25% above the age-and gender adjusted general population. During follow-

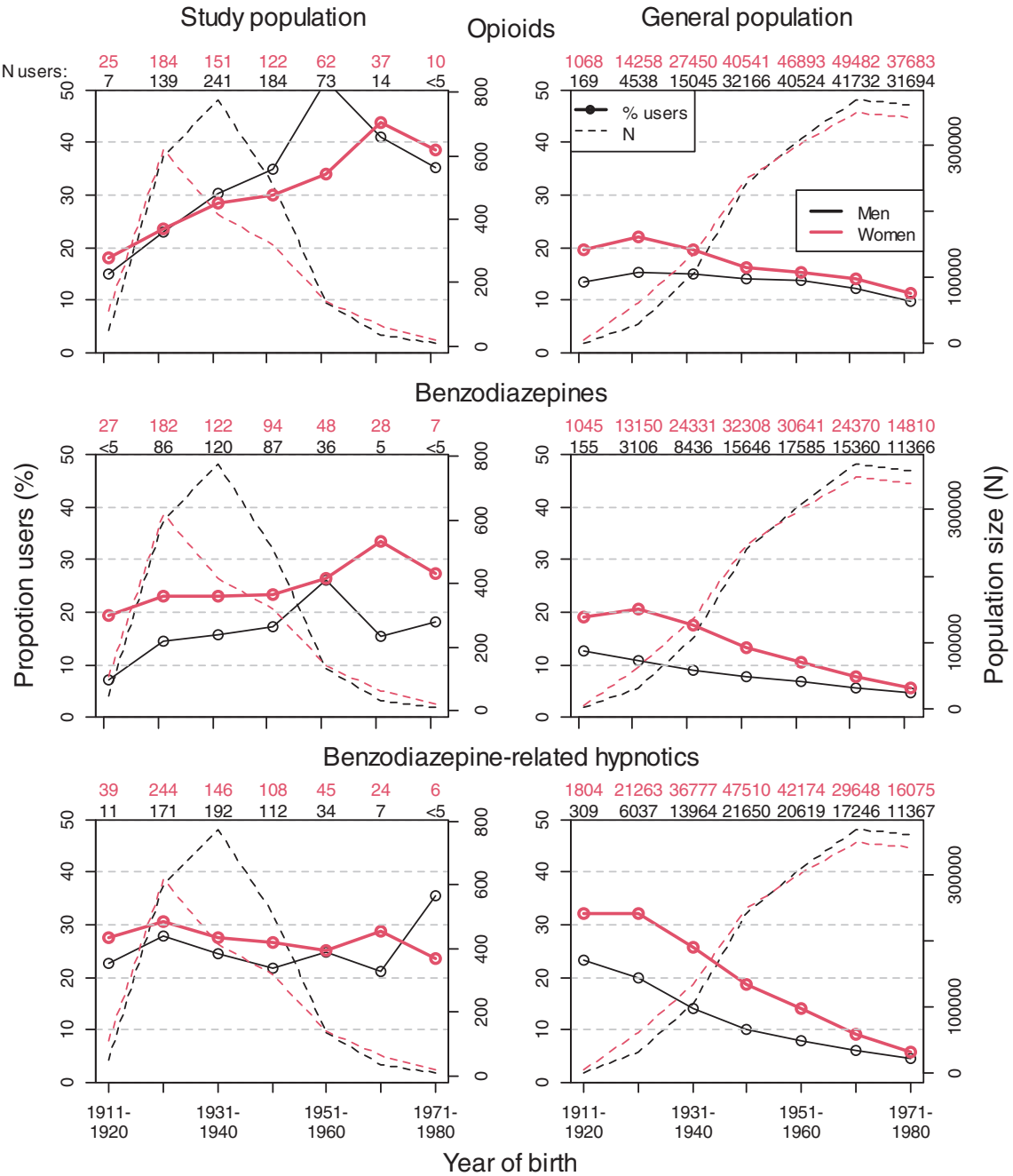

FIGURE 2 One-year periodic prevalence of prescriptions of opioids, benzodiazepines, and benzodiazepine-related hypnotics in different age groups in the study population the first year after diagnosis and the general population [Colour figure can be viewed at wileyonlinelibrary.com]

up the 1-year periodic prevalence of paracetamol increased steadily and reached the highest level at the end of follow-up.

The 1-year periodic prevalence of receiving NSAIDs was approximately similar to the age and gender adjusted general population in both groups throughout the study period. The 1-year periodic prevalence of receiving gabapentinoids was similar to the general population the first year after diagnosis. However, it increased during follow-up to approximately twice the level in the general population.

3.4 | Prescriptions of benzodiazepines and benzodiazepine-related hypnotics

For both benzodiazepines and benzodiazepine-related hypnotics the 1-year periodic prevalence was highest the first year after diagnosis (Table 3 and Table 4) with prevalences of 22% and 30%, respectively. These values were 80% and 50% above the prevalence in the age and gender adjusted general population. From the first to the second year after diagnosis, the 1-year periodic prevalence of receiving benzodiazepines and benzodiazepine-related hypnotics declined slightly and was relatively stable during the remaining part of the study period. During the study period the prevalence of high-dose use of benzodiazepines was stable at approximately 7% in both groups, approximately twice the prevalence in the age and gender adjusted general population. The prevalence of high dose use of benzodiazepine-related hypnotics increased gradually during the study period in both groups from approximately 17% to 19%. Approximately 70% of those receiving benzodiazepine-related hypnotics were high-dose users at the end of the study period.

When the 1-year periodic prevalence of prescriptions of benzodiazepines and benzodiazepine-related hypnotics was studied in different age groups it was observed that the 1-year periodic prevalence of prescriptions was quite stable across age groups in the study population (Figure 2). This is in contrast to the general population where the 1-year periodic prevalence increased with increasing age. Accordingly, the 1-year prevalence of prescriptions in the study population was higher compared to the general population in patients below 70 years of age.

3.5 | Multivariate analysis—persistent opioid use

Total opioid dose 365–180 days before and the first 365 days after diagnosis were strongly associated with persistent opioid use 4 years after diagnosis (Figure 3). In the multivariate analysis a high dose before diagnosis was still significantly associated with persistent opioid use 4-year after (relative risk (RR) = 2.3 (95% confidence interval 1.6–3.2) for the upper percentile) (Table 5), but much weaker so than a high dose the year after diagnosis (RR = 55.1 [33.2–91.5]).

3.6 | Co-medication

Approximately 55% of patients with persistent opioid use 4 years after cancer diagnosis were co-medicated with high doses of benzodiazepines and/or benzodiazepine-related hypnotics (Figure 4). Such co-medication was more prevalent in males. In patients on high doses of benzodiazepines co-medication with high doses of benzodiazepine-related hypnotics was common, whereas the vast majority of those receiving high doses of benzodiazepine-related hypnotics had no co-medication.

4 | DISCUSSION

The main finding in the present study was that the overall 1-year periodic prevalence of receiving opioids, benzodiazepines and benzodiazepine-related hypnotics was 50%–100% higher the first year after diagnosis in the study population compared to the age- and gender adjusted general population. The 1-year periodic prevalence declined the second year for all three classes of drugs but remained 30%–80% higher than the general population. Furthermore, co-medication with benzodiazepines and benzodiazepine-related hypnotics was common in patients with persistent opioid use, and opioid doses before the cancer diagnosis and the first year after diagnosis were associated with persistent opioid use 4 years after diagnosis.

The highest prevalence of receiving opioids the first year after diagnosis and the subsequent decrease could be explained either by opioids being prescribed for pain related to initial cancer treatment, or reduced pain after successful anti-cancer treatment. The trend of the rising 1-year periodic prevalence of opioid use from the second year and throughout the remaining study period could be interpreted as a consequence of either progression of the disease causing more pain, development of tolerance to opioids, development of treatment related pain or changes in coping mechanisms over time. When considering the increased 1-year periodic prevalence of opioid use the first year after diagnosis, it must also be taken into consideration that during the initial treatment it will often not always be possible to prognosticate which patient will respond to treatment and survive or have a prolonged disease trajectory, or which patient will have limited treatment effect and a rapid progression of disease. Thus, a more liberal prescription practice can be justified before it is known whether the patient will respond to the first lines of anti-cancer treatment.

The rise in the 1-year periodic prevalence of opioid prescriptions in patients below 70 years of age might have several explanations. Reasons may involve a variety of cancer diseases having different prevalences in different age-groups, cancer diseases having a variety of manifestations in different age groups, anti-cancer treatments causing pain depending on age, and age-related differences in pain sensitivity and coping strategies. Even though numerous causes for high pain intensity in the patients below 70 years of age can be hypothesized, this does not warrant a more liberal use of opioids in the patients below 70 years of age.

In the present study, the prevalence of persistent opioid use was threefold increased relative to age and gender adjusted general population. Previously it has been reported a 30% increased prevalence of persistent opioid use in long term survivors of cancer in Norway.[25] In the present study population the periodic prevalence of receiving opioids was substantially lower than the 80% periodic prevalence previously reported for the last year of life in Norwegian cancer patients.[23]

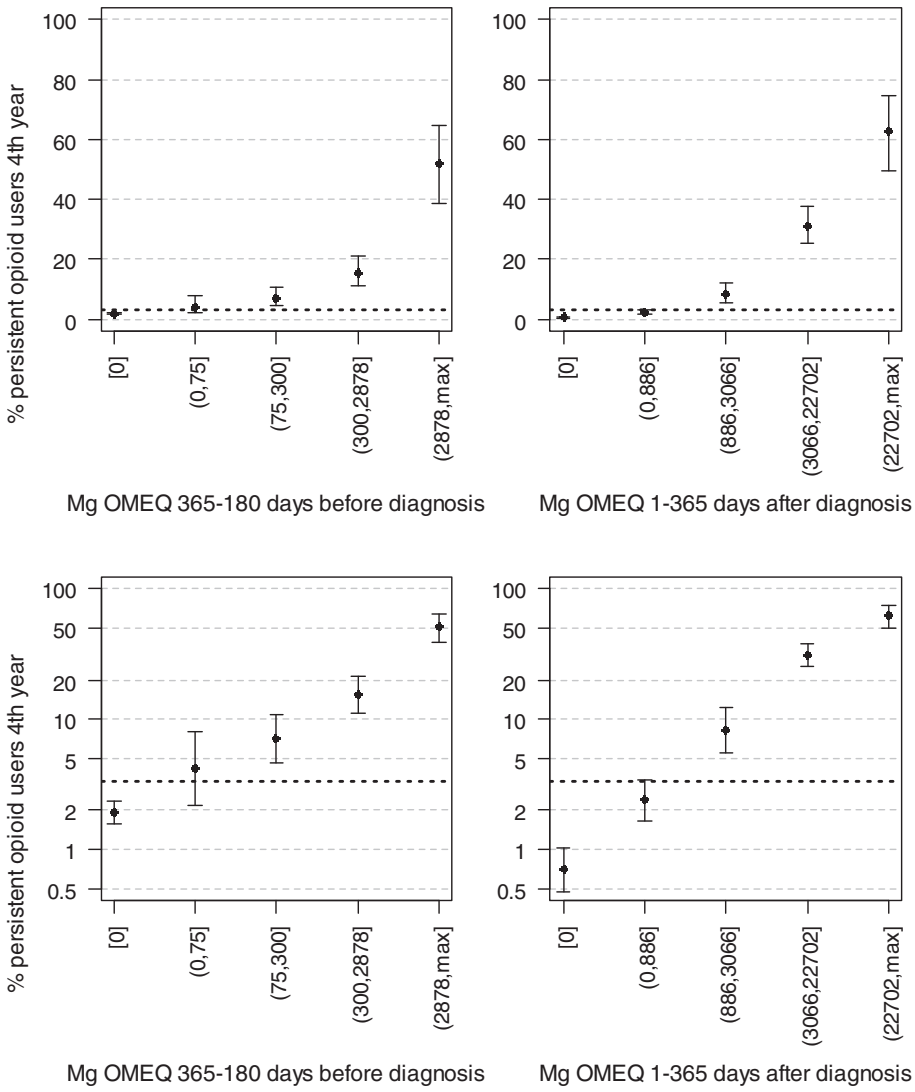

FIGURE 3 Proportion (%) persistent opioid users the 4th year after cancer diagnosis by opioid use 365–180 days before (left) and 1–365 days after (right) diagnosis. The five groups on the x-axes are defined as 0; (0,q90]; (q90,q95]; (q95,q99]; (q99,max] where q denotes quantile and (0,q90] means that 0 is not included and q90 is included. The dashed line is the proportion for the complete population. Drug quantities in oral morphine equivalents (OMEQ)

TABLE 5 Multivariate analysis of persistent opioid use 4 years after cancer diagnosis with total opioid dose 365 to 180 days before cancer diagnosis (iv1) and the first 365 days after diagnosis (iv2) as independent variables

	Relative risk	95% Confidence interval	*p*-value
Total opioid dose 365 to 180 days before diagnosis[a]			
First strata [0]	Reference		
Second strata (0, 75]	1.2	(0.68–2.11)	0.539
Third strata (75, 300]	1.63	(1.04–2.56)	0.034
Fourth strata (300, 2878]	1.79	(1.23–2.60)	0.002
Fifth strata (2878, Infinity]	2.27	(1.60–3.22)	<0.001
Total opioid dose 365 days after diagnosis[a]			
First strata [0]	Reference		
Second strata (0, 886]	3.00	(1.75–5.13)	<0.001
Third strata (886, 3066]	8.58	(4.80–15.32)	<0.001
Fourth strata (3066, 22 702]	31.39	(19.55–50.39)	<0.001
Fifth strata (22 702, Infinity]	55.08	(33.18–91.45)	<0.001

Note: Results for iv1 (or iv2) are adjusted for age, gender and iv2 (or iv1) and presented as relative risk. Each variable has 5 strata: 0; (0-q90]; (q90-q95]; (q95-q99]; (q99-max] where q denotes quantile and (0-q90] means that 0 is not included and q90 is included.

[a]Dose in oral morphine equivalents.

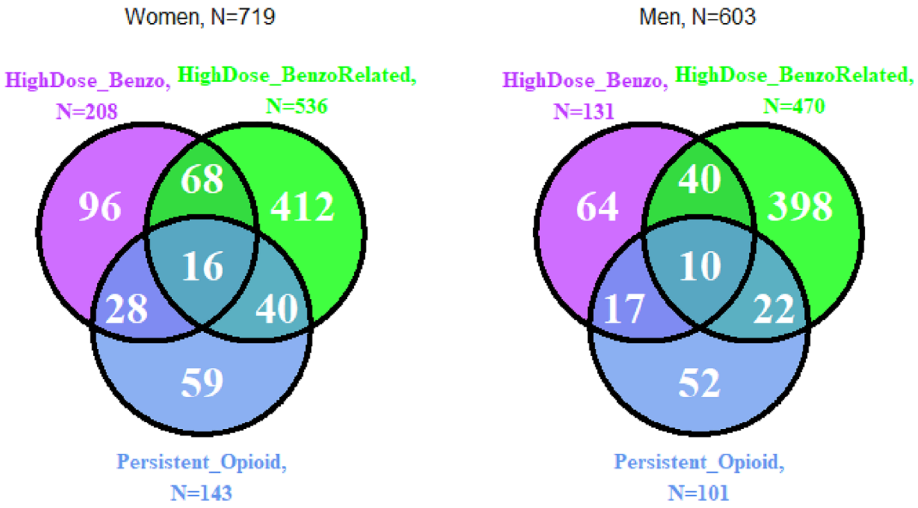

FIGURE 4 Venn diagrams illustrating co-medication with high doses (>100 DDD/year) with benzodiazepines and/or benzodiazepine-related hypnotics in patients with persistent opioid use 4 years after diagnosis [Colour figure can be viewed at wileyonlinelibrary.com]

These differences illustrate that the population in the present study differs markedly from populations previously investigated.

We advocate that in patients with pain during stable or very slowly progressive cancer, modified principles for treatment of CNCP should be considered.[16] This includes focusing on non-pharmacological treatments addressing coping strategies and functioning. When patients who have a fairly stable disease and low tumor burden are considered for long-term opioid treatment it is important to perform a thorough assessment of the pain condition in order to determine whether the pain is nociceptive pain from primary tumor or metastases, treatment-related pain after anti-cancer treatment, or a CNCP condition not related to the cancer disease. The first type of pain may often require a trial of opioid treatment, whereas second type of pain should be based on treatment with adjuvant drugs like gabapentinoids or tricyclic antidepressants. A trial of opioid therapy can be performed, but opioids only provide long lasting and clinically significant pain relief in a minority of patients with neuropathic pain type.[28,29] In the last category of pain, the treatment should be the same as in patients without cancer, i.e. primarily non-pharmacological if a clear nociceptive or neuropathic mechanism is not present. When opioid treatment is indicated in this patient group the core principles from opioid treatment of CNCP should be taken into consideration. A modification of the principles for opioid use in CNCP includes avoiding high doses low to moderate opioid doses fail to provide pain relief, not solely relying on on-demand opioids for exacerbations of pain, avoid the most rapid acting opioid formulations for on demand use, keeping opioid doses stable in the absence of clear disease progression and avoiding regular use of benzodiazepines.

The strength of the present study is that it is composed of complete national data from complete national registries. An inherent weakness of the study design is that it is not possible to know whether prescription drugs were ingested by the recipient. Interpretating the data from the end of the study period one must consider that survival after the end of the study period ranged from 13 to 24 months. Furthermore, it is a weakness that data on the cause of death was not available for the complete study population. In subjects where cancer was the cause of death it is not known whether these were radically treated/in remission or had active cancer disease. The inclusion of patients dying with causes of death other than cancer makes the study population more heterogenous. Because the prevalence of opioid use in long-term survivors of cancer is lower than in our study population,[25] inclusion of patients who did not die from cancer is likely to contribute to underestimation of the prevalence of analgesic use in those dying from cancer after 6–9 years long disease trajectories. This does not affect the main messages from the present study.

In conclusion, this study demonstrated that the 1-year periodic prevalence of receiving opioids, benzodiazepines and benzodiazepine-related hypnotics was substantially increased in patients living with chronic cancer diseases, particularly, in younger patients. Furthermore, co-medication with benzodiazepines and benzodiazepine-related hypnotics was prevalent in patients with persistent opioid use. These findings raise concerns regarding whether the benefits of treatment outweigh risks and side effects in this population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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