

## 1. Background

An increasing number of patients survive cancers in childhood and adolescence [16-18;32]. From cancers in adulthood, it is well documented that long-term survivors have higher prevalence of pain [21;40] and consumption of analgesics compared to the general population [15]. The increased prevalence of pain and analgesic use in long-term survivors of cancer is often a result of cancer treatment such as chemotherapy, surgery and radiotherapy, which can cause chronic pain, often with a substantial neuropathic component [30;41].

Chronic pain has also been an issue of concern in long-term survivors of cancer in the childhood and adolescence. However, it has not been well-established whether this group has increased prevalence of pain compared to the general population [1]. Findings have been inconsistent and had limitations regarding case definitions, pain assessment and age- and gender adjusted comparisons to the general population [1;31]. Even though the findings regarding pain in long term survivors of cancer in the childhood and adolescence have been conflicting, an odds ratio of 1.36 for self-reported use of opioids was found in a previous study from the United States [5].

Patients surviving cancer in early adulthood share the long-term expected survival after curative treatment with those being diagnosed with cancer in childhood and adolescence. Furthermore, they differ from other adult cancer survivors in terms of cancer diagnoses and psychosocial status. Thus, it is relevant and common to include long-term survivors of cancer in childhood, adolescence and early adulthood (CAEA) in the same study [34].

Chronic pain in cancer survivors due to previous cancer treatment should be treated as chronic non-malignant pain, and opioids should be prescribed with caution and according to guidelines [9;36]. Specifically, the use of short acting opioids and co-medication with benzodiazepines are in conflict with these guidelines due to risks of development of problematic opioid use and addictive behavior, and should thus be avoided [9;37;39].

Recently hazard ratios of 1.4 for receiving anxiolytics and hypnotics and of 1.2 for receiving antidepressants compared to age and sex matched controls from the general population have been reported [27;28]. Based on these findings we hypothesized that the use of prescription analgesics was also increased in this group. In populations of patients with chronic non-malignant pain and in long-term survivors of adulthood cancers, persistent users of opioids often co-medicate with benzodiazepines and/or benzodiazepine-related hypnotics [15;33]. If the hypothesis of increased use

of opioids in adult long-term survivors of CAEA is confirmed, an additional issue of concern is whether such co-medication is prevalent in this population.

The national Cancer Registry of Norway and the national Norwegian Prescription Database (NorPD) offer a unique possibility for investigating prescription patterns of drugs in a complete national cohort of long-term survivors after cancer in CAEA. In adult long-term survivors of cancer in CAEA we aimed at investigating the prevalence of analgesic drug use and associated benzodiazepine and benzodiazepine-related hypnotic use compared to the general population. Further, we aimed at investigating the prevalence of persistent use of opioids and combined use of opioids and benzodiazepines. Finally, we aimed at investigating the level of co-medication between persistent opioid users and use of high doses of benzodiazepines and/or benzodiazepine-related hypnotics.

## **2. Material and methods**

### 2.1 Study design

The study was a population-based retrospective descriptive study of analgesic and concomitant benzodiazepine use in adult long-term survivors of cancer in CAEA. The study was based on data from 2005 to 2012 from a complete national database on dispensed prescriptions.

### 2.2 Study population

In order to maximize the study population in accordance with the available data, the study population consisted of all Norwegian individuals, who were diagnosed with cancer in the years 1995 to 2002, 1985 to 1992 and 1975 to 1982, who were below 30 years of age at the time of diagnosis and alive 15, 25 and 35 years after diagnosis, respectively (figure 1 and figure 2). Data on drug use were collected 10, 20 and 30 years after diagnosis. The criterion of being alive 5 years after the time of data collection was applied in order to exclude persons, who at the time of data collection had a life limiting cancer disease in an advanced stage and received symptom-relieving drugs for this disease. Persons who had been diagnosed with a second cancer or emigrated were also excluded from the study population.

### 2.3 Data sources

The study was based on linkage of data from the national Cancer Registry of Norway and the national Norwegian Prescription Database (NorPD).

#### *2.3.1 Norwegian Prescription Database*

Since January 1, 2004, all pharmacies in Norway have monthly been obliged to submit data electronically to the Norwegian Institute of Public Health on all filled prescriptions. NorPD contains information on all prescription drugs, reimbursed or not, that are dispensed at pharmacies to individual patients outside institutions. Each person is assigned a unique identifier, which makes it possible individually to monitor all dispensed drugs chronologically. Because prescription data are collected from pharmacies, only filled prescriptions are actually captured.

#### *2.3.2 Cancer Registry of Norway*

Since 1953, the nationwide Cancer Registry of Norway has collected population-based data on incidence, survival, and prevalence of cancers in Norway based on mandatory reporting of all cases of cancer. The registry contains information on tumor location, histology, and stage at time of diagnosis. Data on diagnosis were used in this study. Month of diagnosis was available, not the exact date.

### 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/](https://www.whocc.no/atc_ddd_index/)). Drug quantities were in this study measured as Defined Daily Doses (DDD) ([https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/)). One DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. As examples, one DDD of oral codeine/paracetamol equals 120 mg codeine and one DDD of oral morphine equals 100 mg.

In Norway, opioids are only available by prescription. The included opioids are covered by ATC group N02A. This ATC code covers all opioids marketed in Norway with the exception of methadone, buprenorphine 8 mg, buprenorphine/naloxone combination, and opioids only used by anesthesiologists in hospitals (alfentanil, remifentanil, and sufentanil). Methadone, buprenorphine 8 mg (Subutex, Reckitt Benckiser, Slough, Berkshire, England), and buprenorphine/naloxone (Suboxone, Reckitt Benckiser, Slough, Berkshire, England) were not included, because they are mainly used in addiction medicine as opioid maintenance therapy and are rarely used in pain management in Norway.

Benzodiazepines (ATC codes N03AE01, N05BA and N05CD), the benzodiazepine-related hypnotics zopiclone and zolpidem (ATC code N05CF), and the gabapentinoids, gabapentin and prebalignin (ATC code N03AX16, N03AX12), are only available by prescription in Norway. Small quantities of paracetamol (ATC code N02BE01, N02BE51) and NSAIDs (ATC code M01A) are available over the counter in Norway.

## 2.5 Analysis strategy and statistics

The analyses of drug consumption were based on prescriptions from 2005 to 2012. Some results were presented separately for those being alive 10, 20 and 30 years after diagnosis, because 1) these patients had received oncological treatment in different decades, and 2) the large difference in time since cancer diagnosis/treatment. The study population was further stratified into persons, who were diagnosed with cancer, when they were from 0 to 9 years of age, from 10 to 19 years of age and from 20 to 29 years of age. This stratification was motivated by differences in developmental stage at time of diagnosis/treatment and differences in cancer diagnoses and treatment. Only persons who were from 10 to 19 and from 20 to 29 years of age were included in the group with data 10 years after diagnosis, because children below 8 years of age would not have reached adult age 10 years after diagnosis.

Each year after diagnosis was defined as a 365-day period from the first day of the month of diagnosis. Consequently, the tenth year after diagnosis was not a calendar year, but the 365-day period starting

the first day of the month of diagnosis, 10 years after diagnosis. For each patient data on dispensed drugs from one 365-day period were used. This was the 10<sup>th</sup>, 20<sup>th</sup> and 30<sup>th</sup> 365-day period after diagnosis, respectively (figure 2).

Persistent opioid use was defined based on data from NorPD in accordance with previously published criteria [44]. The criteria are based on dispensed opioid volume and number of prescriptions in a 365 days period. In contrast to the original method developed by Svendsen et al, the present study only applied DDD for measurement of drug quantities, not the original combination of DDD and morphine equivalents [44]. The criteria for the applied definition of persistent opioid use were to use >365 DDD during 365 days and to receive prescriptions in all quarters of the year. This definition clinically corresponds to use of opioids on a daily basis, but not necessarily around the clock. High-dose-use of opioids was defined as using more than 730 DDD of opioids during the tenth year after diagnosis 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 in one year. Co-medication was investigated by constructing Venn-diagrams.

To compare with the general population, the prevalence ratios were age and gender adjusted using the function *ageadjust.indirect* in the R-package *epitools* with the total Norwegian population in the relevant age group as reference population. The relevant age group was 20-59 years when considering the complete study-population, and 20-29 when considering the subgroup, who were 20-29 ten years after diagnosis, and so forth. Those who died before 2015 were subtracted from the reference population to make it more comparable to the study population. Details on the methods have been published in a previous paper by our group [15]. For the general population data from 2010 were used for prevalence calculations.

## 2.6 Research ethics and approvals

The linkage of the data sources was approved by the Norwegian Data Inspectorate (10/00447-5 and 13/00577-4) 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 endorsement by the Cancer Registry of Norway neither is intended nor should be inferred.

### **3. Results**

#### *3.1 Study population*

The study population consisted of 5585 persons, 2893 (52%) males with mean age 20.3 years at the time of diagnosis (SD=7.9) and 2692 (48%) females with mean age 21.0 years at diagnosis (SD=7.8). The most prevalent diagnostic groups were cancer of male genitals, cancer of female genitals, hematological malignancies, cancers of the central nervous system and malignant melanoma (table 1).

#### *3.2 Analgesic use*

In the complete study population neither stratified for time since cancer diagnosis nor cancer type, the overall finding was that the age adjusted one-year period prevalence of prescriptions of opioids, benzodiazepines and benzodiazepine-related hypnotics was 20-50% increased and the one-year period prevalence of prescriptions of gabapentinoids was increased two-fold compared to the general population in both males and females (figure 3). However, the one-year period prevalence of prescriptions of paracetamol and NSAIDs was not increased compared to the general population. In females the age adjusted prevalence of high-dose use of benzodiazepines, benzodiazepine-related hypnotics, persistent opioid use and high-dose opioid use were increased compared to the general population, whereas in males only the prevalence of high-dose benzodiazepine use was increased. When the study population was stratified according to cancer type there was no clear pattern, and the confidence intervals were wide and overlapping (figure 3). When the study population was stratified according to age at diagnosis and time since cancer diagnosis the one-year period prevalence of opioid use and the prevalence of persistent opioid use were with only two exceptions higher in the study population compared to the general population (table 2). Overall, the one-year period prevalence of opioid use was higher in the highest age groups both in the study population and in the general population (table 2).

The median annual dose of gabapentinoids measured in DDDs was approximately twice as high in the cancer survivors compared to the general population.

#### *3.3 Persistent opioid use and co-medication*

The percentage of persistent and/or high-dose opioid users with co-medication with high doses of benzodiazepines and/or benzodiazepine-related hypnotics was higher in cancer survivors compared to the general population (figure 4). All high-dose opioid users in the study population were co-medicated with high doses of benzodiazepines and/or benzodiazepine-related hypnotics, whereas in the general population two thirds of high-dose opioid users had such co-medication. In the study population 79% of persistent opioid users were co-medicated with benzodiazepines and/or benzodiazepine-related hypnotics compared to 62% in the general population.

#### 4. Discussion

The main findings in the present study was that survivors of cancer in CAEA only had a slightly higher one-year period prevalence of opioid use and of persistent and high-dose opioid use compared with the general population. However, a finding of major concern was that co-medication with high doses of benzodiazepines and benzodiazepine-related hypnotics was far more frequent in cancer survivors with persistent or high-dose opioid use compared to individuals in the general population with persistent or high-dose opioid use.

The slightly higher prevalence of opioid use including persistent and high-dose opioid use is in line with the previous findings based on self-reported drug use [5]. There are three possible explanations for this finding. The first and most obvious explanation is that this population of adult survivors of cancer in CAEA may have higher prevalence of severe chronic pain due to previous cancer treatment. This explanation is in accordance with previous studies reporting a higher prevalence of pain in survivors of cancer in CAEA, but the literature has, however, not been unanimous with regard to findings of such a high pain prevalence [1;31]. The second possible explanation is that this group may have adopted more passive and drug-focused coping strategies for managing chronic pain compared to the general population. The third possible explanation is that physicians generally might be more prone to offer analgesics to chronic non-malignant pain in cancer survivors. Although this study did not include data on causes of chronic pain, the increased consumption of gabapentinoids may indicate a higher prevalence of neuropathic pain compared to the general population. In turn, higher prevalence of neuropathic pain may certainly also be the reason for the higher prevalence of persistent opioid use. Because 12% of the study population were survivors after tumors of the central nervous system which has epilepsy as a known complication [45], it is possible that some patients received gabapentinoids as an antiepileptic and not as an analgesic. However, reimbursement codes (data not presented) indicated that only two patients in the study population received gabapentinoids for treatment of epilepsy.

Our research group has recently studied analgesic consumption in adult cancer survivors in a population-based study in Norway using the same registers as in the present study [15]. Although consumption of analgesics in adult long-term survivors of cancer in CAEA is moderately increased compared to the general population, the consumption is substantially lower than in survivors of adult cancers. Chronic pain due to either cancer surgery, radiotherapy or chemotherapy may be more severe and prevalent in long-term survivors of cancer in adult life compared to adult survivors of cancer in CAEA. It can be speculated that reasons may include different anti-cancer therapies and time since therapies, pronounced neuroplasticity in children, and psychological, social and existential issues

related to age and maturity. The difference in opioid use between long-term survivors of cancer in CAEA and adulthood indicates that the latter group either has a higher prevalence of sequelae including chronic pain, or is more prone to use opioids for pain irrespective of pain mechanisms, or has an increased prevalence of problematic opioid use and/or addictive behavior.

The findings in the present study should be interpreted in light of the overall prescription pattern of opioids in Norway, where the one-year period prevalence of receiving opioids is 13 % in the adult population and 1% are persistent opioid users according to a wide definition [14;44]. The rate of opioid-related deaths has the last ten years been stable at 8 to 9 per 100 000 in the age group 15 to 64 years (<https://www.fhi.no/nyheter/2018/nakotikautlostet-dodsfall-2017/>). Both these prevalences and death rates are substantially lower than in North-America [25].

In chronic non-malignant pain the use of opioids has been associated with higher levels of pain, poor functional status and reduced quality of life [10]. Furthermore, persistent and high dose opioid use for non-malignant pain has in several population-based studies been associated with problematic opioid use, and recent data have estimated that the risk of addiction seems to be much higher than previously expected (>20%) [24;25]. The combination of the disappointing efficacy of persistent opioid treatment and the over-all harm data have increasingly questioned whether opioids should be prescribed for chronic non-malignant pain [8;9;10]. In this respect chronic pain in adult long-term survivors of cancer in CAEA may be considered as one subgroup imbedded in the wide variety of patients suffering from chronic non-malignant pain. Thus, in our study it is a worrying finding that the prevalence of high-dose use of benzodiazepines, benzodiazepine-related hypnotics, persistent opioid use and high-dose opioid use were increased in females compared to the general population. Interestingly, this finding is in line with several other studies in chronic non-malignant pain patients, where a higher consumption of analgesics including opioids have been found in females compared to males [2;7]. This may be explained by the fact that females have demonstrated higher biological sensitivity and a lower threshold for pain stimuli than men, possibly mediated and modulated by gonadal hormonal factors, as well as by the fact that females generally tend to seek medical support more frequently than males [4;11;19;38;42].

The pronounced degree of co-medication with benzodiazepines and benzodiazepine-related hypnotics in persistent and high-dose opioid users could be expected due to previous reports of higher prevalence of use of benzodiazepines and benzodiazepine-related hypnotics in survivors of cancer in CAEA compared to the general population [28]. This finding is also in line with findings from other chronic non-malignant pain populations [43]. Preclinical evidence has suggested that benzodiazepines



increase the rewarding and reinforcing effects of opioids, which can explain the mechanisms of the risk of co-medication with benzodiazepines turning into addictive behavior towards both substances [23;46]. This co-medication is also in conflict with existing guidelines in Norway and elsewhere [9;36]. The level of anxiety is raised in cancer survivors compared to healthy controls and this also pertains to survivors of childhood cancer [35]. Anxiety and pain commonly co-occur and this might explain the higher prevalence of high-dose opioids and benzodiazepines and benzodiazepine-related hypnotics.

A finding, which seems to be of high relevance for pain management of cancer survivors in general, is the high consumption of gabapentinoids [30;41]. Although there is sparse evidence for the prevalence and severity of neuropathic pain in long-term childhood and adolescence survivors, it is well known that the prevalence of neuropathic pain in adult cancer survivors are generally high. Thus, up to 50 % of cancer survivors experience some degree of chronic neuropathic pain [30], and the severity of neuropathic pain in cancer survivors is associated with impairments in physical functioning, emotional well-being, sleep, and work [29]. Further, the long-term reversibility of these chronic neuropathic pain conditions remains questionable, notably in chemotherapy-induced peripheral neuropathies (CIPN) which may persist or last several years after the end of anticancer chemotherapies. CIPNs are also known to be problematic in young patients (children, adolescents, and young adults), where they may interfere with development and social life and be associated with comorbidities such as depression, insomnia and reduced health related quality of life [20;26]. However, it is noteworthy that these long-term effects remain poorly studied. In a Danish study of breast cancer survivors gabapentinoids and antidepressants were the most frequently used analgesics for treatment of neuropathic pain [40]. The effects of gabapentin and pregabalin are well documented in different non-malignant neuropathic pain conditions (NNTs ranging from 4.2 to 6.4) [12;13], whereas the evidence for their use for neuropathic pain in cancer and cancer survivors is weak. Of specific note, is the fact that the criteria from the International Association for the Study of Pain (IASP) have not been developed to address neuropathic pain due to cancer or cancer treatment [22]. At the moment, there exist no other criteria with a defined clinical consensus or empirical evidence, although an alternative approach developing different diagnostic criteria for cancer-related neuropathic pain may be underway [6]. However, the increased prevalence of use of gabapentinoids also raises the issue of addictive behaviour, as there is increasing evidence for the addictive properties of these drugs [3].

The major strengths of the present study are that data are derived from complete national registries and comparisons are made with the age- and gender adjusted general population, thus recall bias and selection bias are avoided. The major limitation of the study is inherent to pharmaco-epidemiological studies based on data on dispensed drugs; it is not known whether all drugs are used by the recipient

at a time point close to the filling of the prescription. If not all drugs are used by the recipient, but either stored for future use or sold/given to third parties, the data will overestimate both quantities of drugs and possibly the period prevalences of drug use in the study population. However, this is probably less relevant in studies of repeated prescriptions and persistent use. Due to over the counter sales of paracetamol and NSAIDs, these drugs were not captured by NorPD and the consumption of these drugs is underestimated in both the study population and the general population. The descriptive nature of the study does not allow conclusions about causality in the relationship between the cancer disease, pain and drug use. Furthermore, the lack of background variables related to details about the cancer treatment and socioeconomic status does not allow detailed investigation of risk factors for opioid use in the study population. The age-span in the study population makes the study population more heterogeneous than if it was narrowed down to a smaller age-span, which certainly is a potential weakness. Thus, the stratification of the study population according to disease (figure 3) and age at both diagnosis and follow-up (table 2) are crucial as these analyses showed a consistent pattern across age groups. Therefore, the large age-span in the study population is unlikely to have major impact on the overall findings and conclusions of the study.

In conclusion, this study has demonstrated a moderately increased use of analgesics in adult long-term survivors of cancer in CAEA compared to the general population. A finding of major concern is that even though only small minority are persistent or high-dose users of opioids, the vast majority of these individuals co-medicate with high doses of benzodiazepines and/or benzodiazepine-related hypnotics. The high degree of co-medication with benzodiazepines and/or benzodiazepine-related hypnotics in survivors on persistent and high-dose opioids might be an indication of problematic opioid use or addictive behavior.

Conflict of Interest: The authors have no conflicts of interest.

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### **Figure Legends**

**Figure 1:** Flow-sheet of inclusion of patients. Results are presented separately for the eight groups in the study population.

**Figure 2:** Stratification of study population according to time of diagnosis (1975-1982, 1985-1992 and 1995-2002) and age at diagnosis (0-10, 11-20 and 21-30). The number of individuals in each stratum is also shown. Examples are shown in the blue/red lines: Persons who had a first cancer diagnosis in June 1981, 1991, or 2001 (blue lines), were alive by 01.06.2016 (35, 25 or 15 years after the diagnosis)(red line), and had no second cancer before 01.01.2015 (end of cancer registry data)(red line), were followed with respect to drug use in 365 days from 01.06.2011. The number of individuals in the different age groups in the period where drug use is captured (2005-2013) is the sum of relevant individuals from the different periods of cancer diagnosis (illustrated by the grey arrows).

**Figure 3:** Age adjusted prevalence ratios (N/1000) with 95 % confidence intervals of study drugs and prescription patterns for the complete study population (aged 20-59 years) and stratified by cancer type. Males in blue, females in red. If 95 % confidence interval does not include the horizontal line, there is statistically significant difference between study population and general population. The horizontal lines indicate the prevalence of the general population aged 20-59 yrs. Number of drug users are given at bottom.

**Figure 4:** Venn diagrams of co-medication with high doses of benzodiazepines (Benzo) and benzodiazepine-related hypnotics (BenzoLike) in patients with persistent or high-dose opioid (Opio) use in the study population of cancer survivors and the general population.