1. Background

Due to advances in oncological treatment, the prognosis of several cancer forms have improved and the numbers of long-term cancer survivors are increasing [12]. Patients who become long-time survivors or enter long-term remission after curative cancer treatment often have chronic pain due to either surgery, chemotherapy or radiotherapy [6;10]. Furthermore, there is no reason to believe that this population has lower prevalence of other chronic non-malignant pain conditions compared to the general population. From several studies, a prevalence of chronic non-malignant pain of approximately 30% has been reported in the adult Norwegian population [3;13], with higher prevalence in higher age groups.

The principles for treatment of cancer pain and chronic non-malignant pain are very different, and wrongful application of principles for treatment of cancer pain in other patient groups is associated with serious adverse consequences including problematic opioid use and addiction [2]. Whereas treatment of cancer pain is based on the WHO analgesic ladder with opioid therapy as a key element, the treatment of chronic non-malignant pain is based on non-pharmacological treatment and opioids should only be prescribed to highly selected patients with a well-defined nociceptive cause of their pain [1;7]. Major differences between the principles for treatment of cancer pain in a palliative care setting and treatment of chronic non-malignant pain are that in chronic pain combinations of long and short acting opioids as well as co-medication with benzodiazepines should be avoided [7;8].

Guidelines for treatment of chronic pain in cancer survivors have been developed, and emphasize that opioids should be prescribed with caution and only to selected patients in this group [16]. Little is known about the actual use of analgesics in this patient population. However, a clinical impression is that in many cancer survivors principles for treatment of cancer pain are applied even though the patients have responded to cancer treatment and do not have progressive cancer disease.

Linkage of the Cancer Registry of Norway and the Norwegian Prescription Database (NorPD) allows a unique possibility for investigation of actual drug consumption in a complete national cohort of cancer survivors. The overall aim of this study was to investigate the prescription patterns of analgesics and benzodiazepines in a population of cancer patients ten years after diagnosis of cancer. The following specific research questions were addressed:

- What was the one-year periodic prevalence of use of opioids, paracetamol, Non-steroidal Anti-Inflammatory Drugs (NSAIDs), gabapentinoids, benzodiazepines and benzodiazepine-related hypnotics 10 years after cancer diagnosis compared to the age and gender adjusted general population?
- What was the prevalence of persistent and high-dose opioid use 10 years after cancer diagnosis compared to the age and gender adjusted general population?
- What was the prevalence of co-medication with high doses of benzodiazepines and benzodiazepine-related hypnotics in patients who were persistent opioid users 10 years after cancer diagnosis?

- Were any specific types of cancer disease associated with a higher prevalence of opioid use, persistent opioid use, high-dose opioid use or use of benzodiazepines?

2. Material and methods

2.1 Study design

The study was a cross sectional study of analgesic and benzodiazepine use in long-term survivors of cancer ten years after cancer diagnosis.

2.2 Study population

The study population was patients who were diagnosed with cancer at age 18 or above in the years 1998 to 2002 who were alive 15 years after cancer diagnosis. The population was studied ten years after diagnosis. The criterion of being alive 15 years after diagnosis was applied in order to exclude patients who were terminally ill or had rapidly progressing disease ten years after diagnosis. If patients had several cancer diagnoses, they had to be alive 15 years after the most recent cancer diagnosis.

2.3 Data sources

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

2.3.1 Norwegian prescription database

Since January 1, 2004, all pharmacies in Norway have been obliged to submit data electronically to the Norwegian Institute of Public Health on all dispensed prescriptions on a monthly basis. 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 to follow chronologically all dispensed drugs to each individual. Because prescription data are collected from pharmacies, only prescriptions that 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, and stage at time of diagnosis. Data on diagnosis were used in this study.

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/). Drug quantities are in this study measured as Defined Daily Doses (DDD) (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 sulfentanil). 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 primarily used in 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 prebagalin (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 without prescription in Norway.

2.5 Analyses strategy and statistics

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 some analyses the study population was stratified according to type of cancer.
The one year periodic prevalence of drug use is defined as receiving at least one prescription of the drug during the defined 365-day period.
Persistent opioid use was defined based on data from NorPD in accordance with previously published criteria [18]. The criteria are based on dispensed opioid volume and number of prescriptions during 365 days. 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. 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 using opioids daily 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 during one year.

Age and gender adjusted prevalence ratios were computed using the function *ageadjust.indirect* in the R-package *epitools* with the total Norwegian population aged 28 and over in 2010, obtained from Statistics Norway, as reference population. Those who died before 2015 were subtracted from the reference population to make it more comparable to the study population. In each one-year age- and gender group A, the expected number of drug users in the study population was computed as the number of cancer survivors times the proportion of drug users in the general population, $U_{S,A}^{E} = N_{S,A}U_{G,A}/N_{G,A}$. Here *S* and *G* denote study- and general population, respectively, and *U* and *N* denote the number of drug users and the number of individuals in the population, respectively. The age- and gender adjusted ratio was then computed as $R_S^{adj} = R_G\ U_S\ /U_S^E$ where R_G is the prevalence ratio in the general population, U_S is the total number of users in the study population, and U_S^E is the

expected total number of users in the studypopulation, i.e. $R_G = \sum_A U_{G,A} / \sum_A N_{G,A}$, $U_S = \sum_A U_{S,A}$ and $U_S^E = \sum_A U_{S,A}^E$.

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

A total of 21426 persons were included in the study population (Figure 1). Mean age ten years after diagnosis was 65.1 years (SD=13.6) and 59% were females. Cancers of the breast, prostate, lower gastrointestinal tract and female genitals were the most common (table 1). Patients who survived cancers of the prostate, lower gastrointestinal tract and kidney and urinary tract were the oldest at time of diagnosis whereas persons who survived cancers of the male genitals, hematological malignancies and melanoma were the youngest (table 1 and figure 2).

3.2 Prevalence of analgesic use

When data from the age and gender adjusted study population were compared with the general population, the one-year periodic prevalence of use of all the analgesics studied (opioids (143.5 vs 129.6/1000), paracetamol, NSAIDs and gabapentinoids) were higher in the study population compared to the general population (table 2) ten years after cancer diagnosis. When the age adjusted study population was stratified by gender and diagnostic groups the prevalence of opioid use, persistent opioid use, high-dose opioid use and use of benzodiazepines was higher in long-term survivors of cancers of the lungs (N=255) and upper gastrointestinal tract (N=172) than in the general population for both males and females (Fig 3). In the other diagnostic groups, no major differences or clear patterns were observed.

3.3 Prevalence of benzodiazepine use

The one-year periodic prevalence of use of benzodiazepines (88.3 vs. 77.9/1000) and benzodiazepine-like hypnotics (118.1 vs. 97.4/1000) was higher in the age and gender adjusted study population ten years after diagnosis compared to the general population (table 2). Furthermore, the prevalence of high-dose use of both benzodiazepine-like hypnotics (56.4vs. 44.8/1000) and benzodiazepines (27.4 vs. 23.9/1000) were higher in the age and gender adjusted study population compared to the general population.

3.4 Persistent and high-dose opioid use

Both the prevalence of persistent (6.5 vs. 4.8/1000) and high dose (2.7 vs. 1.3/1000) opioid use was higher in the age and gender adjusted study population compared to the general population (table 2). The vast majority of patients with persistent or high-dose opioid use received treatment with either short acting opioids alone or a combination of short and long acting opioids (table 3). Less than 10% of persistent and high-dose users received only long acting opioid formulations.

3.5 Co medication with benzodiazepines and hypnotics

The majority of patients with persistent or high-dose opioid use were also high-dose users of either benzodiazepines or benzodiazepine-like hypnotics (figure 4). Twenty-two and 24 percent (eller %? – eller “twenty-four percent”? – eller “22% and 24%”?) of persistent and high-dose opioid users, respectively, received high doses of both benzodiazepines and benzodiazepine-related hypnotics.

4. Discussion

The main findings in the present study were that long time cancer survivors in Norway had a moderately higher prevalence of analgesic use, persistent opioid use and high-dose opioid use compared to the general population. Because of chronic treatment-related pain after surgery, chemotherapy or radiotherapy the prevalence of chronic pain is probably higher in long-term cancer survivors compared to the age and gender adjusted general population. Thus, a higher prevalence of analgesic use was expected in long time cancer survivors. The finding that the prevalence of persistent and high dose use of opioids was only moderately increased compared to the general population is somewhat reassuring because it indicates that in the vast majority of cancer survivors their chronic non-malignant pain was not treated as cancer pain even though the pain in many cases probably was a consequence of cancer treatment.

There are several issues of concern regarding how opioids were used in the study population. First, the majority of patients receiving opioids used either a short acting opioid or a combination of short and long acting opioids, and secondly the majority co-medicated with high doses of benzodiazepines and/or benzodiazepine-related hypnotics. This treatment is in conflict with existing guidelines for the treatment of chronic non-malignant pain [15;16] and co-medication with benzodiazepines and opioids is associated with increased risk of drug overdoses [17]. As in other patients with chronic non-malignant pain opioid treatment should be based either on intermittent use of low doses of short acting opioids as needed, or on a fixed low to moderate dose of a long acting opioid. The principles for treatment of breakthrough pain in cancer do not apply for exacerbations of chronic pain. Accordingly, the use of large doses of short acting opioids or combinations of short and long acting opioids is in conflict with guidelines for chronic non-malignant pain [8;15;16].

Except the small groups with survivors of cancers of the lungs and upper gastrointestinal tract there were no overall patterns regarding whether gender or cancer diagnosis was associated with increased prevalence of persistent or high-dose opioid use compared to the age adjusted general population. This was surprising as different types of cancer have different treatments and thus probably different risks of developing chronic treatment related pain.

The finding that the prevalence of opioid use, persistent opioid use, high-dose opioid use and use of benzodiazepines was higher in survivors of cancers of the lungs and upper gastrointestinal tract needs to be interpreted with caution. These are two of the smallest groups in the study population and accordingly the confidence intervals are wide. A likely explanation for this finding is that curative treatment for these types of cancer often involve major surgery that probably carries a higher risk of chronic postoperative pain. Non-smokers constitute an increasing proportion of those developing lung cancer and these patients are due to better survival probably overrepresented in our study of survivors [5]. Nevertheless, it can be speculated that the addictive behaviors of smoking and high alcohol consumption are risk factors for both cancers of the lungs and oesophagus [11;14] and for problematic and/or persistent opioid use.

As in other patients with chronic non-malignant pain the co-medication with high doses or regular use of benzodiazepines or benzodiazepine related hypnotics is not indicated. The combination of these drugs and opioids is likely to increase the risk of developing problematic opioid use and addiction. Accordingly, anxiety and sleep disturbances should be addressed with non-pharmacological treatment, alternatively with drugs without addictive properties.

The complete national registers, which this study is based on, do not contain data on the pain conditions and the indications for analgesic use in the study population. Thus, it cannot be established whether the increased use of analgesics in the age and gender adjusted study population compared to the general population is due to the treatment of pain that is related to previous cancer treatment or due to other chronic pain conditions. It can be argued that chronic pain after surgery, radiotherapy or chemotherapy is more well-defined than many other chronic pain conditions and might respond better to opioids compared to less defined pain conditions. However, pain after surgery, radiotherapy and chemotherapy have a large neuropathic component [4] where opioids because of moderate analgesic efficacy and safety concerns should only be considered for third line treatment [9]. Thus, opioids should only rarely be used in long-time cancer survivors, and when they are used, they should be prescribed as fixed doses of long acting formulations.

The finding that the one year periodic prevalence of receiving gabapentinoids was 13.4 in the age and gender adjusted study population compared to 10.0 in the general population is probably explained by neuropathic pain conditions in cancer survivors due to surgery and chemotherapy. Gabapentinoids are the first line treatment for these pain conditions [9], and the finding of higher prevalence of gabapentinoids use indicate that opioids are not used as first line treatment for neuropathic pain in Norwegian cancer survivors.

The major strengths of the study is the long period of follow-up and data from complete national registries thus eliminating selection bias. A further strength is that the analyses are based on age and gender adjusted data. The importance of age and gender adjustment is demonstrated in table 3 where there is a quite large difference between unadjusted and adjusted data.

Inherent weaknesses to studies based on data from NorPD are that it is not known whether the patients actually use the dispensed drugs and that data are neither available for over the counter sales of paracetamol and NSAIDs nor from hospitals and nursing homes.

The data sources the study was based on do not provide information about whether long term survivors after cancer diagnoses have been cured, are in remission or have a stable or very slowly progressing disease. To minimize the risk of including persons who at ten years after diagnosis had rapidly progressing disease, persons who died within fifteen years after diagnosis were excluded. It must be admitted that this five year cut-off is arbitrary. However, the application of the criterion of more than five years of survival as a criterion for being cured, in remission or having stable disease at ten year follow-up probably has a high sensitivity for excluding patients who at ten years follow-up had rapidly progressing disease.

In conclusion, the consumption of analgesics and benzodiazepines is only moderately increased in long time cancer survivors compared to the general population. However, the majority of those using

opioids do not adhere to guidelines regarding opioid formulation and co-medication with other drugs with addictive properties.

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

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Figure legends

Figure 1 – Flow-sheet of inclusion of patients

Figure 2 Age distribution for males and females within each diagnostic group. Age is ten years after diagnosis. The area under all curves is the same, not reflecting the size of each group. The density is the proportion of each group being in each one-year age group. As an example, a density of 0.035 for 73 years corresponds to 3.5% of patients in this group being 73 years old ten years after diagnosis. The peak of each curve is marked with the curve's key character. Alternativ: The area under each curve equals 1, and the density for a specific cancer at a specific age indicates roughly the proportion of the patients with that cancer being in that one-year age group. For example, around 4.5% of the male lung cancer patients were 67 years old ten years after diagnosis. The peak of each curve is marked with the curve's key character.

Figure 3 Age adjusted prevalence ratios with 95 % confidence intervals of study drugs and prescription patterns for study population stratified by cancer type (x-axis on the two lowest panels). Men in blue, women in red. If 95 % confidence interval does not include the horizontal line, there is statistically significant difference between this group of the study population and the general population (marked with darker color and cancer type abbreviation on x-axis). Confidence intervals are narrow in groups with many patients and wider in groups with fewer patients. The exact number of patients in each group is available in table 1.

Figure 4 – Co-medication 10 years after cancer diagnosis in patients who had either high doses of benzodiazepines, benzodiazepine-related hypnotics and persistent opioid use or high dose opioid use, respectively. White numbers are numbers of patients. The four percentages at the center of the each circle indicate the proportions of patients in that circle that were also in the other circles. For example, of the 158 persistent opioid users, 22% had high use of both BZDs and BZDRs, 25% of BZDs only, 22% of BZDRs only, and 32% of neither (do not sum to 100 due to rounding off).

Table 1 – Characteristics of the study population

Main groups of cancer diagnoses	N	Age* mean (SD)	% Females
Upper GI	172	68.9 (12.1)	44
Lower GI	2419	72.0 (10.8)	57
Pancreas	57	65.0 (13.9)	72
Lung	255	66.6 (11.3)	52
Melanoma	1838	59.9 (14.0)	60
Breast	4769	65.8 (10.2)	100
Female genitals	2173	62.8 (13.0)	100
Male genitals	923	45.5 (10.8)	0
Prostate	2688	74.3 (7.0)	0
Kidney and urinary tract	1296	69.5 (11.5)	33
Hematological	1322	58.9 (15.2)	48
Other incl. CNS	3514	62.3 (15.3)	57
Total	21426		

* Age at follow-up ten years after diagnosis.

Table 2 – 1 year periodic prevalence of use of analgesics, benzodiazepines and benzodiazepine-related hypnotics, prevalence of persistent and high-dose opioid use and high-dose use of benzodiazepines and benzodiazepine-related hypnotics 10 years after cancer diagnosis in the age age and gender adjusted study population compared to the general population.

	Study population			General population	
	Unadjusted	Adjusted			
	N/1000	N/1000	N	N/1000	N
One year periodic prevalence of opioid use*	176.0	143.5	3772	129.6	392927

One year periodic prevalence of benzodiazepine use*	132.9	88.3	2847	77.9	236071
One year periodic prevalence of benzo-related hypnotic use*	193.3	118.1	4141	97.4	295295
One year periodic prevalence of paracetamol use*/**	128.9	88.3	2761	80.7	244728
One year periodic prevalence of NSAID use*/**	244.1	229.1	5230	221.7	672057
One year periodic prevalence of gabapentinoid use*	18.1	13.4	387	10.0	30349
Prevalence of persistent opioid use	7.4	6.5	158	4.8	14646
Prevalence of high-dose opioid use	2.5	2.7	54	1.3	3940
Prevalence of high-dose benzodiazepine use	42.4	27.4	909	23.9	72500
Prevalence of high-dose benzo-related hypnotic use	104.5	56.4	2239	44.8	135740

* The one year periodic prevalence is the proportion of the study population receiving at least one prescription of the drug during the defined 365-day period.

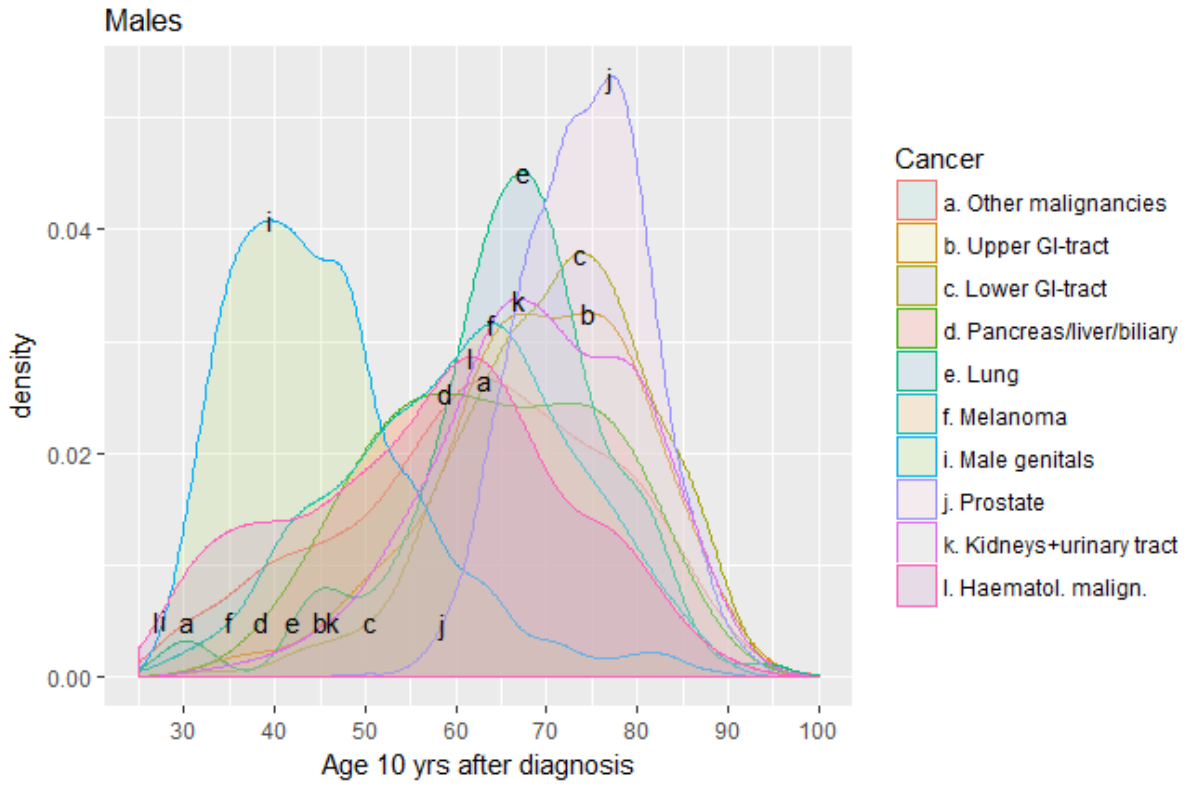
** Only prescribed drugs. Also available in small quantities over the counter, which are not captured by Norwegian prescription database

Table 3 – Opioid formulations during tenth year after cancer diagnosis in patients with persistent and high-dose opioid use.

			Mean dose		
	N	%	DDD	(SD)	% short acting*
Persistent opioid users	158				
Long acting only	12	7.6	1543	(1210)	
Short acting only	74	46.8	1419	(1101)	
Long and short acting	72	45.6	1782	(1027)	18.4
High-dose-opioid users	54				
Long acting only	5	9.3	2594	(1201)	
Short acting only	16	29.6	2412	(1769)	
Long and short acting	33	61.1	2422	(1113)	20.4

* % of DDD with short acting formulations in patients receiving both short and long acting formulations.

All patients aged 18+ diagnosed with cancer in Norway between 01.01.1998 and 30.04.2002	83993
>Dead within 10 years after diagnosis	57063
Cancer patients alive 10 years after diagnosis	26930
> Dead between 10 and 15 years after diagnosis	5504
Cancer patients alive 15 years after diagnosis	21426


Males
density
0.04
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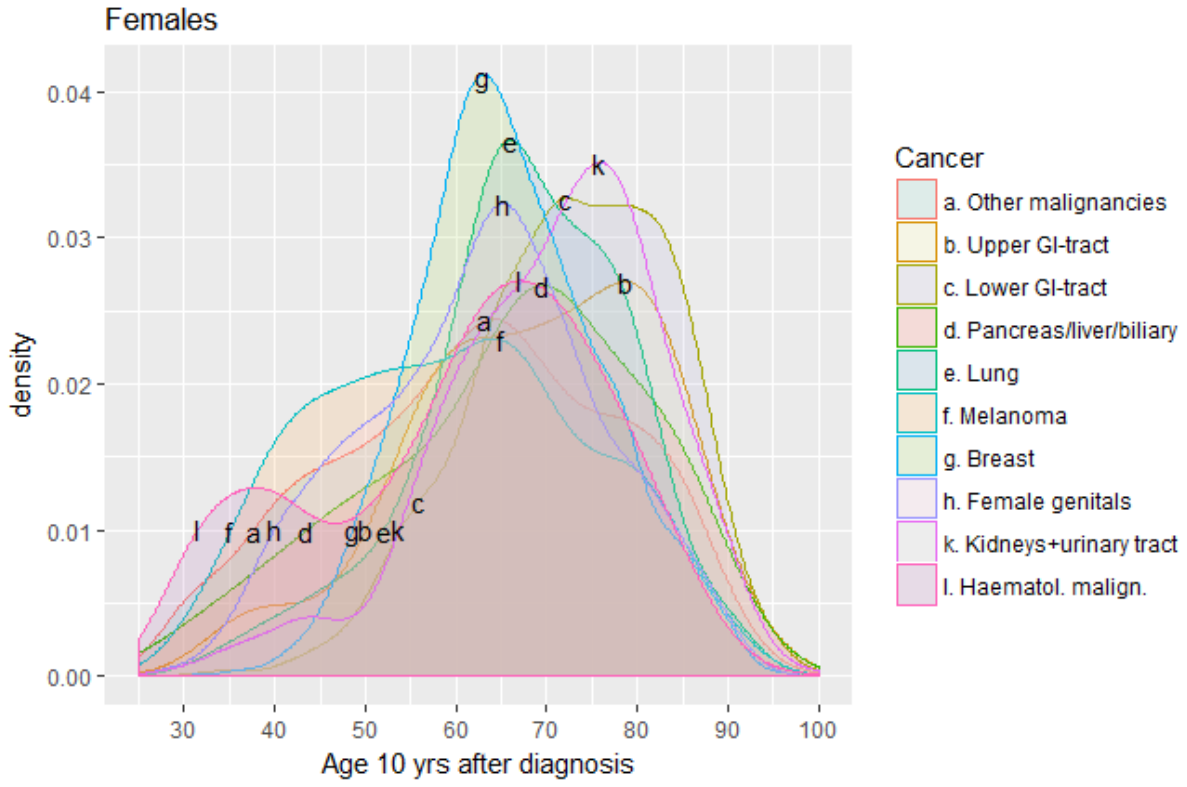
30
40
50
60
70
80
90
100
Age 10 yrs after diagnosis
Cancer
a. Other malignancies
b. Upper GI-tract
c. Lower GI-tract
d. Pancreas/liver/biliary
e. Lung
f. Melanoma
i. Male genitals
j. Prostate
k. Kidneys+urinary tract
l. Haematol. malign.


Females
density
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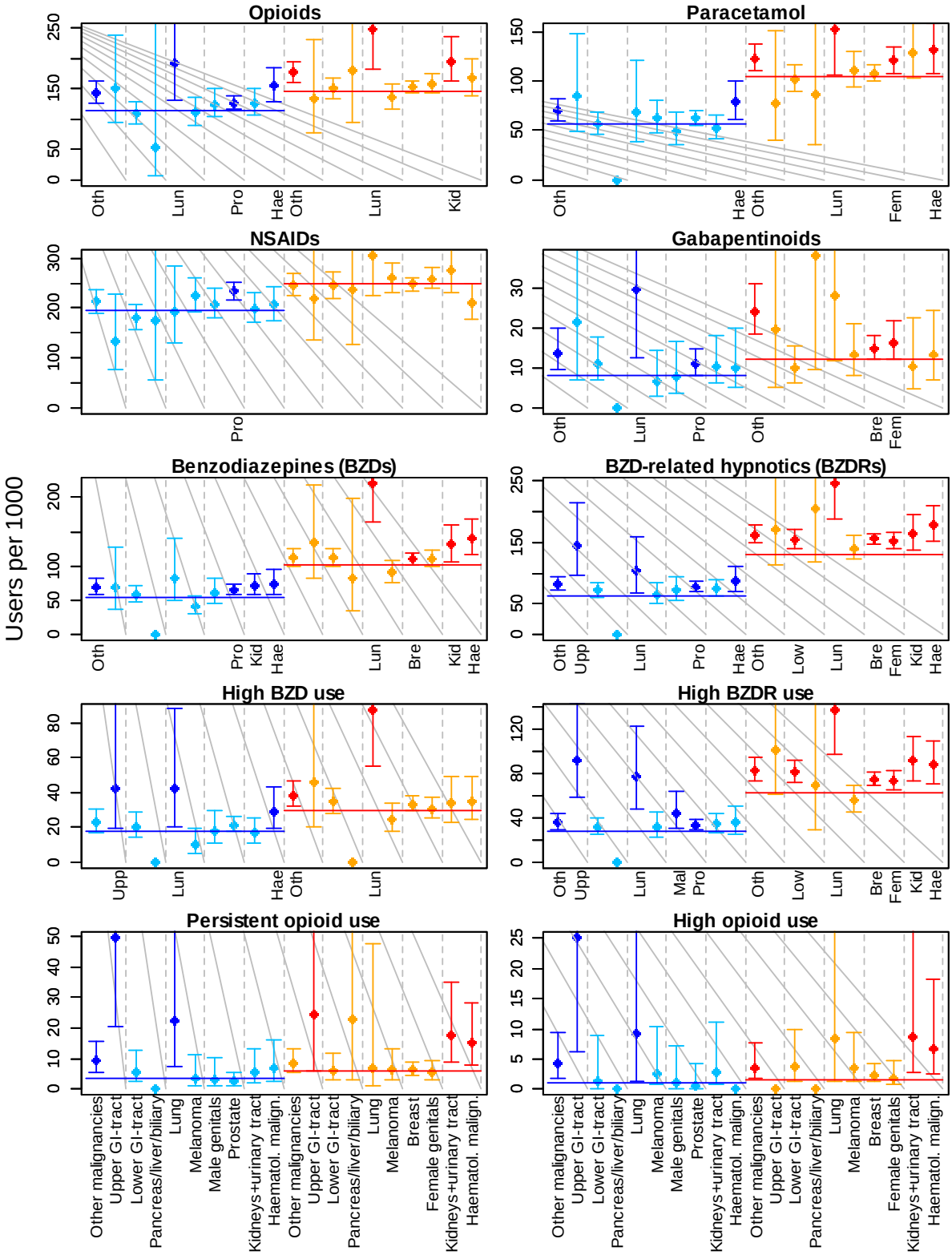
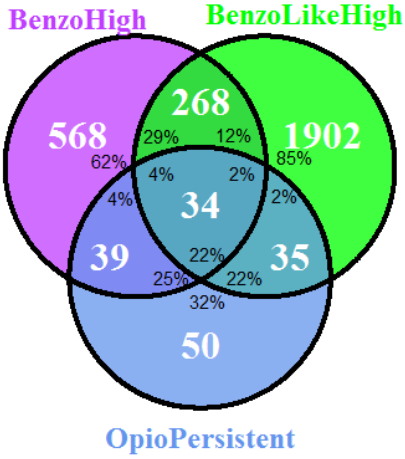
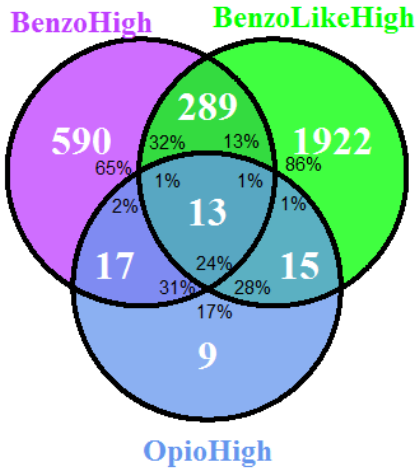
Age 10 yrs after diagnosis
Cancer
a. Other malignancies
b. Upper GI-tract
c. Lower GI-tract
d. Pancreas/liver/biliary
e. Lung
f. Melanoma
g. Breast
h. Female genitals
k. Kidneys+urinary tract
l. Haematol. malign.


Opioids
Paracetamol
NSAIDs
Gabapentinoids
Benzodiazepines (BZDs)
BZD-related hypnotics (BZDRs)
High BZD use
High BZDR use
Persistent opioid use
High opioid use
Users per 1000
Oth
Lun
Pro
Hae
Kid
Fem
Bre
Upp
Low
Mal
Other malignancies
Upper GI-tract
Lower GI-tract
Pancreas/liver/biliary
Lung
Melanoma
Male genitals
Prostate
Kidneys+urinary tract
Haematol. malign.
Breast
Female genitals



Persistent opioid use

>100 DDD Benzodiazepines/year



High-dose opioid use

>100 DDD Benzodiazepines/year