Prescriptions rates of psychotropic medications amongst survivors of cancer in childhood, adolescence and young adulthood – a population-based study

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ABSTRACT

Background. Survivors of cancer diagnosed in childhood, adolescence or young adulthood (CAYAS) are at risk of psychological morbidities later in life. The study purpose was to compare prescription rates of anxiolytics or hypnotics amongst survivors to rates in age- and gender-matched controls. **Methods**. The population-based cohort included 5,341 cancer survivors, diagnosed ≤25 years during 1965–2000. For each survivor, three age and gender matched controls were randomly selected from the general population. Data were identified from nationwide registries and then linked. A Cox proportional hazard model was applied to estimate hazard ratios (HRs) of prescriptions during 2004-2012 to the survivors with controls as referents. **Results**. Survivors had an increased risk of being prescribed anxiolytics with crude rates of 16.9/1000 person years compared to 11.8/1000 person years in controls (HR 1.41; 95% confidence interval (CI) 1.29-1.54). The relative risk was highest for survivors of neuroblastomas (HR 2.62; 1.11-6.16), bone tumors (HR 2.00; 1.26-3.18) and CNS tumors (HR 1.90; 1.40-2.51). The risk of being prescribed hypnotics was also increased with crude rates of 20.8/1000 person years compared to 14.3/1000 person years in controls (HR 1.44; 95% CI 1.32 -1.56). The relative risk was highest for gastrointestinal tumors (HR 1.80; 1.04-3.10), leukemias (HR 1.78; 1.32-2.38) and soft tissue cancers (HR 1.70; 1.09-2.64). **Conclusion**. Certain groups of CAYAS have an increased risk for being prescribed anxiolytics or hypnotics compared to their controls. Without the knowledge of diagnostic reasons for prescriptions, the results may indicate an increased emotional burden amongst these groups of survivors.

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INTRODUCTION

Due to the mental, physical and emotional stress that cancer treatment entails, the psychological impact can continue for many years after succession of treatment (1). When cancer strikes in childhood, adolescence or early adulthood, normal development can be complicated by the intensive treatment with need for hospitalizations, isolation from peers and uncertainty regarding future health (1, 2). Older adolescents and young adults may have problems with establishing identity and developing a positive body image and sexual identity during a period when they normally should be separating from their parents and making decisions about education, careers and family (3). In sum, these factors can increase the risk for adjustment problems and adverse psychological outcomes later in life (2, 3).

Survivors of cancer in…adolescent and young adult cancer may be the group most affected by psychological late effects, as they to a larger degree are able to comprehend the seriousness of the disease (4).

Studies on psychological distress in survivors of cancer in childhood, adolescence and young adulthood (CAYAS) have yielded inconsistent findings; some have demonstrated increased levels of anxiety and depression amongst survivors compared to population norms or matched controls (4-7) whilst others have not found such differences (8-10). A few studies have reported increased resilience amongst CAYAS (2, 11-13). The authors presume that these survivors experience cancer as a significant but manageable event that may offer opportunity for coping?mastery and more positive view of life and self (2, 11, 12).

These differences in psychological health outcomes may reflect challenges in assessing such outcomes in cancer survivors since no common assessment method has been established (14). Standardized interviews are costly and often difficult to administer, resulting in relatively small sample sizes that are prone to be biased. The use of patient-reported outcomes can entail barriers like time and resource constraints and selection bias (15, 16). Population-based studies of health registry data have the advantage of including well-defined populations, thus eliminating self-

selection or recall bias (17). Additionally, large numbers allow for identification of rare events (17).

Psychotropic medications are drugs affecting the mind, emotions and behavior. Anxiolytics and hypnotics are two of the most commonly prescribed psychotropic medications. Knowledge on the use of these medications amongst CAYAS yields information on how psychological problems are handled and indirectly also on the prevalence of some psychological problems. There are few publications on the use of psychotropic medication in CAYAS. Brinkman et al. found increased use of psychotropic medication amongst childhood cancer survivors compared to their siblings in a questionnaire-based study (18). In addition, increased prescription rates of antidepressants amongst CAYAS compared to controls from the general population have been described in register-based studies (19-21).

The aim of the present report was to study the prescription rates of anxiolytic and hypnotic medication amongst Norwegian survivors diagnosed with cancer at the age of 0–25 years and compare the rates to rates in the general population of similar age and gender. We also wanted to study if prescription rates differed between different diagnostic groups of CAYAS.

Bsed upon…We hypothesized that CAYAS would have a higher prescription rate of anxiolytics or hypnotics than matched controls. We also hypothesized that the prescription rate would increase with increasing age at diagnosis and that survivors of tumors in the central nervous system (CNS) would have the highest prescription rates due to direct treatment to the CNS.

METHODS

The data in the present study were achieved from three national registries: The Cancer Registry of Norway, the Population Registry of Norway and the Norwegian Prescription Database. The unique personal identification number, assigned to each Norwegian citizen, made linkage between registries possible.

Data sources

Cancer Registry of Norway

The Cancer Registry was established in 1951 and contains nationwide data on all patients diagnosed with cancer in Norway. The mandatory reporting is based on several sources of information: 1) Pathology and autopsy reports from all laboratories in the country, 2) registration forms reporting the localization of the cancer, extent of disease and initial treatment 3) copies of all death certificates that state neoplastic disease and 4) all hospital discharge diagnosis.

Population Registry of Norway

The Population Registry contains basic demographic characteristics on all residents in Norway since 1960, including date of birth, place of residence and date of migration or death (22).

Norwegian Prescription Database (NorPD)

From January 1st 2004 all Norwegian pharmacies have been obliged to submit data electronically to the Norwegian Institute of Public Health on all prescribed drugs, irrespective of reimbursement, dispensed to individuals in ambulatory care (23). The prescribed drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (24).

Study population

Cohort of cancer survivors

The study included all registered patients in Norway diagnosed with cancer before 25 years of age during the period 1965–2000. Survivors who were alive, still residing in Norway and 18 years or older at the start of follow-up January 1st 2004 were identified from the Cancer Registry of Norway and then linked to data from the NorPD. A total of 5341 survivors were included in the analyses (Fig. 1).

Definition of cancer types was according to International Classification of Childhood Cancer (ICCC-3) (17) with a few exceptions: 1. Due to different gender distributions of incidence rates

of germ cell tumors, these cancer types were reported for each gender separately. 2. Thyroid gland cancer and gastrointestinal cancers are included in the group "other neoplasms" in ICCC3, but as the incidences of these cancer types generally increase in young adults, they are reported separately in our analyses. 3. In our data, there were few survivors who had been treated for liver cancers and these were therefore included in the group "other tumors".

Controls

For each included survivor we randomly selected three age- and gender matched controls from the Norwegian Population Registry. The controls had to be alive and without cancer and residing in Norway at the time of the survivor`s cancer diagnosis. At the start of follow- up on January 1st 2004 some had emigrated or deceased and data on these controls were therefore not available. Thirteen controls were found to have had cancer before 25 years of age and were excluded, while cancer diagnosed after age 25 was not an exclusion criterion. In total, 14855 controls were included in the analyses (Fig. 1).

Psychotropic medications

Anxiolytics are a class of drugs used in the control of anxiety, behavioral agitation, and occasional insomnia (25). Hypnotics are a class of drugs that induce sleep or depress the central nervous system at a cortical level (25). Diagnostic causes of prescriptions for these two medications can sometimes overlap. In Norway, all anxiolytics and hypnotics are available only on prescription. Information on all prescriptions for anxiolytics in the ATC group N05B and for hypnotics in the ATC group N05C in the period of January 1st 2004 (start of NorPD registration) – December 31st 2012 was obtained from NorPD.

Analysis strategy and statistical methods

Both cohorts were followed from January 1st 2004 until the first of the following events: First prescription for anxiolytic or hypnotic medication (primary endpoints), emigration, death or end of study period (December 31st 2012) (Fig. 1). To be included the participants had to have at least two independently redeemed prescriptions of anxiolytics or hypnotics within 365 days.

Separate analyses were performed for the two primary outcomes (anxiolytics and hypnotics).

The crude rates for prescription of anxiolytics or hypnotics per 1000 person years were calculated for survivors and controls. The crude rates were calculated separately for each gender and for survivors of different cancer types. Hazard ratios (HRs) for use of anxiolytics or hypnotics were estimated in Cox proportional hazard models with 95% confidence interval (CI) for CAYAS with controls as referents, with separate models for each cancer type. Analyses were adjusted for gender and age at start of follow-up (2004). Cox regression analyses were also performed separately for each gender.

For the secondary analyses, the effect of age at cancer diagnosis was assessed by using a Cox proportional hazard model with age as a continuous variable.

RESULTS

Cohort characteristics

Table 1 shows descriptive statistics for the survivor (N=5,341) and control (N=14,855) cohorts. About half of the survivors (51.8%) were males. Young adults (19-25 years) constituted the largest age group at diagnosis (Table 1). At the start of follow-up in 2004, 20 years or more had passed since the time of cancer diagnosis for 43% of the participating survivors. Mean age at start of follow-up (in 2004) was 36 years (range 18-65 years). Skin cancer (mostly melanoma), lymphomas and testicular cancer were the most frequent cancer diagnoses.

Overall, 717 survivors (13.4%) and 1435 controls (9.7%) had been prescribed anxiolytics while 869 survivors (16.3%) and 1718 controls (11.6%) had been prescribed hypnotics during the study period (Table 1)

Prescriptions of anxiolytics

Survivors had higher crude rate for prescriptions of anxiolytics (16.9 /1000 person years) compared to controls (11.8/1000 person years) (Table 1). The highest rates were found amongst survivors of female genital cancer, followed by thyroid cancer and bone cancer (Table 2).

The Cox model showed an increased risk of anxiolytic prescription amongst survivors compared to controls (HR 1.41; 95% CI 1.29 -1.54) (Fig. 2). Amongst the different cancer types, neuroblastomas, bone cancers, CNS tumors and lymphomas had the highest risk estimates. Males had a HR of 1.56 (95% CI 1.36 -1.79) and females had a HR of 1.31 (95% CI 1.16-1.47) compared to controls?.

Prescriptions of hypnotics

As for anxiolytics, the survivors had higher crude rate for prescriptions of hypnotics (20.8 /1000 person years) compared to the controls (14.3/1000 person years) (Table 1). The highest crude rates were found amongst survivors of female genital cancer, followed by thyroid cancer and other tumors (Table 2). The Cox model showed an increased risk of prescription of hypnotics amongst survivors (HR 1.44; 95% CI 1.32 -1.56) compared to controls (Fig. 2). Gastrointestinal tumors, leukemias and soft-tissue cancers had the highest risk estimates. Male survivors had a HR of 1.52 (95% CI 1.33 -1.73) and females had a HR of 1.39 (95% CI 1.25-1.54) compared to controls?.

In the secondary analysis we found no increased risk of anxiolytic or hypnotic prescriptions with increasing age at cancer diagnosis after adjusting for age attained at start of follow-up in 2004.

DISCUSSION

This study is to our knowledge the first to report prescription rates of anxiolytics or hypnotics amongst CAYAS by using nationwide registries and comparing these rates to prescription rates

in a population-based control cohort. The results of the present study support the hypothesis of increased prescription rates of anxiolytics or hypnotics medication to CAYAS compared to controls.leste jeg det riktig at kvinner med gyn cancer var spesilt utsatte for å få orskrivninger

The ability of CAYAS to demonstrate psychological adjustment is well documented (11-13, 26). Still, a proportion of survivors report increased psychological problems later in life (4, 6, 7, 27). Increased use of psychotropic medication amongst survivors is also reported indicating an increased need for pharmacological interventions amongst CAYAS as interpreted by the health services (18, 19, 21). In the present study, the risk for CAYAS being prescribed anxiolytics or hypnotics was more than 40% higher than in the controls. Without knowing the doctors' therapeutic evaluations for prescribing these psychotropic drugs, the results may indicate that the survivors are more anxious and worried than their peers. Many survivors have reported worries about their future health and possible late effects after the cancer and its treatment (28-30). They also often worry about vocational possibilities, fertility problems and the health of their future children (31-35). This applies especially to adolescents and young adults that have experienced a premature confrontation with mortality, changes in physical appearance and disruptions in social life and their life perspectives may have changed as a result of their cancer experience (3, 34). Constant worry can negatively affect both psychological and physical well-being of CAYAS (36). It can precipitate lower self-esteem, worse self-image and outlook on life and unresolved worries can be expressed as somatic complaints (3, 34, 37, 38).

In the study of Brinkman et al. based on data from the CCSS (Childhood Cancer Survivor Study), the risk of survivors reporting the use of prescribed anxiolytics/hypnotics was 64% higher than in their siblings in the first questionnaire (18). In subsequent questionnaires the risk was 27% higher, but the authors do not reflect on this reduction in difference.

Being a survivor of neuroblastoma, bone cancer or CNS tumor carried the highest risk of prescriptions of anxiolytics. These survivors had in general received an intensive, multimodal treatment, including chemotherapy, radiotherapy and surgery and are at increased risk of

developing late effects. The presence of late effects amongst CAYAS has been shown to increase the risk of worrying (30, 32).

Survivors of gastrointestinal intestinal tumors, leukemias and soft-tissue cancers had the highest risk of prescriptions of hypnotics. Why the prescription rates of anxiolytics vs. hypnotics differ between survivors of different cancer types is unclear. Both groups are prescribed for anxiety and sleep problems (39). Mulrooney et al. found that childhood cancer survivors, including survivors of acute lymphatic leukemia, soft-tissue sarcomas, bone cancers and brain tumors, had poorer sleep quality and increased daytime sleepiness compared to their siblings (40). Noen tanker rundt at noen diagnosegrupper får mer anxiolytica og andre mer hypnotica?? JH; enig.

Female survivors were more often prescribed anxiolytics and hypnotics than male survivors. This also applied to the controls and is compatible with what is seen in the general population (41). Cancer diagnosed in adolescence or young adulthood has been shown to have a greater impact on later psychological health than if the disease strikes in preschool age (4, 27). However, as in our study on antidepressants prescriptions, age at diagnosis did not seem to have an effect on prescription rates (21).

A major strength of this study is the use of population-based registries. All Norwegian citizens have their unique ID number and can therefore be tracked in the registries by their encrypted ID number, which enables a comprehensive follow-up. Linking large administrative databases enables the creation of a large cohort that can give more power to late effect studies amongst CAYAS.

One limitation of the present study is that the Norwegian Prescription Database was first established in 2004. Information on prescriptions of anxiolytics or hypnotics before that time is therefore unattainable. In addition, the indications for prescribing anxiolytics or hypnotics are not included in the database. Antidepressants are sometimes prescribed for anxiety or the combination of anxiety/depression. Other treatment modalities such as psychotherapy including cognitive-behavioral interventions could not be controlled for. A possible selection bias cannot

be excluded as disease- or treatment-related mortality may have resulted in a healthier cohort of cancer survivors with fewer psychosocial problems (42).

CONCLUSIONs

Subgroups of CAYAS had an increased risk of being prescribed anxiolytics or hypnotics compared to controls. This strengthens the knowledge of an increased occurrence of psychological problems in these groups of survivors. Excessive and chronic worrying negatively affects the well-being of CAYAS. Recognizing the predictors of prescriptions of anxiolytics or hypnotics to survivors of cancer in a young age is relevant for the follow-up care of CAYAS.

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