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Increased risk of antidepressant use in childhood cancer survivors: A Danish population-based cohort study

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Abstract ***Aim:*** Childhood cancer survivors are at risk of both somatic and mental late effects, but large population-based studies of depression are lacking.
Methods: Risk of antidepressant use was evaluated in a population-based cohort of 5452 Danish children treated for cancer in 1975–2009 by linkage to the National Prescription Drug Database, which worldwide is the oldest nationwide registry of prescription medication. Hazard ratios (HRs) for antidepressant use were estimated in a Cox proportional hazards model stratified on sex, with population comparisons as referents.
Results: Overall, childhood cancer survivors were at increased risk of having antidepressants prescribed (HR, 1.4; 95% confidence interval (CI), 1.3–1.5). The excess absolute risk of antidepressant use was 2.5 per 1000 person-years (95% CI, 1.7–3.3), equivalent to an excess of 2.5 survivors for every 100 survivors followed for 10 years. Increased HRs of 30–50% were seen for survivors of cancers of all main groups (haematological malignancies, central nervous system (CNS) and solid tumors); the highest risk was among children treated with haematopoietic stem cell transplantation (HR, 1.9; 95% CI, 1.2–3.1). Our data suggested that the risk was most pronounced for children treated in the most recent calendar periods (test for interaction between cancer and calendar periods: $P < 0.001$), especially for survivors of haematological cancers ($P = 0.007$). Interaction analysis of the effect of parental socioeconomic position and psychiatric disease on the association between childhood cancer and antidepressant use indicated no modifying effect.

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Conclusion: Childhood cancer survivors should be followed-up for depression. Our results indicate an increasing need for follow-up especially in survivors treated by more recent, intensive anticancer treatment.

1. Introduction

Childhood cancer is a disturbing, distressing, life-threatening event invoking stress both during diagnosis, during treatment and after treatment [1]. The event may involve treatment toxic to the central nervous system (CNS) such as cranial irradiation [2], numerous somatic [3] and psychosocial late effects [4] and family crises [5] in the nearly 80% of children who now survive their cancer [6]. Several studies conducted within the Childhood Cancer Survivor Study (CCSS) showed increased risk of depression [2,7] although use of antidepressant medication was not increased [8]. However, the CCSS studies were based on self-report or on parental reports and have been limited by low response rates and use of siblings as unexposed comparisons [4]. A Canadian population-based cohort study of 2389 survivors of cancers diagnosed in 1970–1995 found an increased risk of antidepressant use; however, the survivors were followed-up for only 4 years, from 2001 to 2004 [9].

Recently, we reported an overall increased risk of hospital contacts for mental disorders, including a two-fold increased risk of unipolar depression among male survivors of haematological cancers identifying the most severely affected [10]. The total burden of depression, however, is probably larger.

Treatment of childhood cancer is a success story of modern medicine. Just two generations ago, survival was counted in weeks. Due to advances in chemotherapy, in equipment, in surgical techniques and in supportive therapy 5 year survival is now over 80% [6]. As a result of their curative treatment, survivors, however, have an increased risk of both somatic and mental late effects.

To determine whether children treated for cancer including those treated with contemporary anticancer protocols involving intensive multimodal therapy are at increased risk of use of antidepressants, we compared antidepressant use of a nationwide cohort of 5452 children in Denmark in whom cancer was diagnosed in 1975–2009 with that of a population-based comparison group in a register-based matched cohort study.

2. Patients and methods

2.1. Childhood cancer cohort

From the nationwide, population-based Danish Cancer Registry [11] we identified 7573 people in whom cancer was diagnosed between 1st January 1975 and 15th December 2009, before they were 20 years old. Their cancers were grouped into 12 diagnostic groups [12], and three main diagnostic groups were formed: haematological malignancies, CNS tumors and solid tumors (Table 1).

To examine the potential impact of scarring or amputation on antidepressant use, we identified one subgroup of survivors of solid tumors primarily located in the extremities and one of survivors of solid tumors primarily located in the abdomen. Survivors of haematological cancers treated by haematopoietic stem cell transplantation (hSCT) were identified from a database of all such patients in Denmark.

Information on death and emigration was obtained from the Central Population Registry, with personal identification numbers (PINs) for all citizens, allowing linkage among registries [13]. The Family Database within the Central Population Registry is administered by the National Board of Health and holds information on first-degree relatives [14]. In order to include only children born in Denmark, we restricted the childhood cancer cohort to individuals listed in the Family Database. This gave 7235 childhood cancer survivors; 14,367 parents were identified.

2.2. Comparison cohort

For each child with cancer, we identified 20 age- and sex-matched persons in the Family Database, constituting 144,570 population-based comparisons free of childhood cancer at the date of cancer diagnosis of the index person to whom they were matched – the date of inclusion. We also identified their parents.

2.3. Use of antidepressant medication

The study subjects in the two cohorts and their parents were linked to the nationwide Danish National Prescription Registry [15]. Antidepressants are available only on prescription, and the database contains information on all prescriptions for drugs dispensed at all pharmacies in Denmark from 1995, linked to the patient's PIN. Since 1996, all prescription drugs have been linked to the children's own PINs. In 1998, 99% of drugs and since 1999 all psychotropic drugs prescribed have been linked to children's PINs. Accordingly, we obtained information on all prescriptions for antidepressant medication (ATC group N06A) from

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