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Brief Communication

Antidepressant Use in Siblings of Children With Cancer: A Danish Population-Based Cohort Study

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Abstract

Siblings of children with cancer experience severe stress early in life. Most studies of mental health problems in these siblings are limited by being small, cross-sectional, or self-reporting. In a population-based cohort study, we investigated the risk for antidepressant use by linking several nationwide, population-based registries comparing 6644 siblings of children diagnosed with cancer from 1991-2009 with 128 436 population-based sibling comparisons using the Cox proportional hazards model. Irrespective of cancer type, no increased risk of antidepressant use in siblings of children with cancer was found (hazard ratio = 1.00, 95% confidence interval = 0.91 to 1.11). However, data suggested that siblings being young at cancer diagnosis had an increased risk (2-sided $P_{trend} = .01$). Interaction analyses showed no modifying effect of parental socioeconomic position or antidepressant use. Findings from this study with a very low risk of bias are reassuring and important for families facing childhood cancer and for clinicians counseling these families.

Being a sibling of a child with cancer is most likely to be a troublesome, tumultuous, and traumatic experience. However, nearly all previously published studies, most using cross-sectional design, reported no increased risk of mental late effects such as depression or distress in siblings of children with cancer (1). To our knowledge, this is the first population-based cohort study using nationwide information on prescriptions of antidepressant medicine to assess the risk of antidepressant use in a cohort of 6644 siblings of children with cancer compared with a population-based sibling comparison cohort of 128 436 individuals without childhood cancer in the family.

We identified all 7494 siblings of the 4089 children born in Denmark and diagnosed with cancer from 1991-2009 together with their 6917 parents by linking information from the Danish Cancer Registry (2) with the Central Population Registry (3) and the Family Database (4), using the personal identification number as the key as previously reported (5). These siblings constituting the study cohort were grouped according to the cancer type of the cancer child into 3 main diagnostic groups based on the International Classification of Childhood Cancer (6): hematological malignancies, central nervous system tumors, and solid tumors (Table 1).

For each child with cancer, we identified 20 age- and sex-matched persons in the Family Database free of childhood cancer at the date of inclusion and identified both their parents and their 147 493 siblings (the sibling comparison cohort).

In Denmark, antidepressant medication is available only by prescription. The Danish National Prescription Registry contains information on all prescriptions and prescription dates for drugs dispensed at all pharmacies in Denmark from 1995 onwards (7). We linked siblings and sibling comparisons as well as their parents to this register and obtained information on all prescriptions for antidepressant medication (Anatomical Therapeutic Chemical Classification code (ATC) group N06A) from January 1, 1998 (when prescriptions were assigned to the child's own personal identification number) through July 2011, defining use of antidepressant medication as 2 independently redeemed prescriptions within 365 days. We marked children

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Table 1. Characteristics of the siblings of children diagnosed with cancer in 1991-2009 and a population-based sibling comparison cohort

Characteristics	Siblings of children with cancer No. (%)	Population-based sibling comparisons No. (%)
Total[a]	6644[b] (100)	128 436[c] (100)
Sex		
Male	3364 (50.6)	65 925 (51.3)
Female	3280 (49.4)	62 511 (48.7)
Age of sibling at cancer diagnosis of the affected child		NA
Born after diagnosis	1180 (17.8)	
0-4	1078 (16.2)	
5-9	1262 (19.0)	
10-14	1117 (16.8)	
>15	2007 (30.2)	
Major cancer group of the affected child[d]		
Leukemia and lymphoma (I, II)	4801 (37.6)	91 171 (37.2)
CNS tumors (III)	3329 (26.1)	63 058 (25.8)
Solid tumors (IV-XI)[e]	4640 (36.3)	90 602 (37.0)
Socioeconomic position of parents[f]		
Father's education[g]		
Basic education	1085 (16.3)	23 438 (18.2)
Vocational	3830 (57.6)	71 148 (55.4)
Higher	1538 (23.1)	30 256 (23.6)
Unknown	191 (2.9)	3594 (2.8)
Mother's education[g]		
Basic education	938 (14.1)	12 794 (10.0)
Vocational	3753 (56.5)	71 511 (55.7)
Higher	1792 (27.0)	32 377 (25.2)
Unknown	161 (2.4)	3191 (2.5)
Household income		
1st quartile (lowest)	1792 (27.0)	33 499 (26.1)
2nd quartile	1624 (24.4)	32 518 (25.3)
3rd quartile	1676 (25.2)	31 872 (24.8)
4th quartile (highest)	1552 (23.4)	30 547 (23.8)
Previous psychiatric disease in a parent or sibling		
No psychiatric admission in parents or siblings	6243 (94.0)	121 640 (94.7)
Psychiatric admission in parents or siblings	401 (6.0)	6796 (5.3)
No antidepressant use in parents or sibling	6020 (90.6)	116 904 (91.0)
Antidepressant use in parents or sibling	624 (9.4)	11 532 (9.0)

[a]A total of 434 siblings of children with cancer had 2 individually redeemed prescriptions of antidepressant medicine equivalent to a crude rate of 7.2 per 1000 person-years. The number of antidepressant users in siblings with no childhood cancer in the family was 8472 with a crude rate of 7.3 per 1000 person-years. CNS = central nervous system; IDA = Integrated Database for Labor Market Research; NA = not applicable (age at cancer diagnosis was only applicable for siblings of children with cancer).

[b]Exclusions: siblings who died or emigrated before the start of registration of antidepressant medication use: 141 (1.9 %); who were hospitalized for psychiatric disease 5 years before cancer diagnosis: 115 (1.5%); who used antidepressants 2 years before cancer diagnosis of survivor: 50 (0.7%); whose parents were not in the IDA database: 523 (7.0%); siblings in families with more than 1 child with cancer: 44 (0.3%).

[c]Exclusions: population-based sibling comparisons who died or emigrated before the start of registration of antidepressant medication use: 3638 (2.5%); who were hospitalized for psychiatric disease 5 years before inclusion: 2403 (1.6%); who used antidepressants 2 years before inclusion: 1171 (0.8%); whose parents were not in the IDA database: 11 845 (8.0%).

[d]Siblings grouped according to type of cancer of the affected child classified according to the International Classification of Childhood Cancer first edition (6).

[e]Other and unspecified malignant neoplasms (XII) not included.

[f]Socioeconomic position was recorded 1 year before cancer diagnosis of the affected child or inclusion in sibling comparisons.

[g]Highest attained education of the parent. Basic education: 7-12 years of education in basic or high school; vocational education: 10-12 years of education; higher education: more than 13 years of education.

whose parents had used antidepressants 2 years before inclusion date. To identify those with a family history of mental disorder, all siblings and sibling comparisons and their parents were linked to the nationwide Danish Psychiatric Central Research Registry to check for in- or outpatient contacts in the 5 years before the inclusion date as previously reported (8).

To study the potential modifying effect of parental socioeconomic position, we linked all parents to the Integrated Database for Labor Market Research (IDA) in Statistics Denmark holding yearly data on socioeconomic position of all residents in Denmark (4) and identified each parent's highest attained education and household income 1 year before inclusion.

After excluding 850 (11.3%) siblings and 19 057 (12.9%) sibling comparisons (see Table 1 for details), 6644 siblings and 128 436 sibling comparisons were eligible for analysis, contributing 60 375 and 1 159 152 person-years of follow-up, respectively.

We used a Cox proportional hazards model stratified on sex and with age as the underlying time scale to estimate the relative risk of antidepressant use in siblings, with sibling comparisons as referent. Siblings and sibling comparisons entered the

Table 2. The effect of parental socioeconomic position and previous psychiatric disease on the use of antidepressant medication in 6644 siblings of children with cancer and in their 128 436 population-based comparisons, presented as univariate hazard ratios (HRs) for each cohort separately and the *P* value for interaction analysis for the potential modifying effect

Characteristics	Siblings of children with cancer HR (95% CI)	Population-based sibling comparisons HR (95% CI)	$P_{interaction}$[a]
Socioeconomic position of parents			
Father's education[b] 1 y before cancer diagnosis of affected child or inclusion in sibling comparison			
Basic education	1(ref)	1(ref)	.26
Vocational	0.89 (0.70 to 1.14)	0.84 (0.70 to 0.88)	
Higher	0.88 (0.66 to 1.17)	0.68 (0.63 to 0.72)	
Unknown	1.01 (0.52 to 1.94)	0.93 (0.81 to 1.07)	
Mother's education[b] 1 y before cancer diagnosis of affected child or inclusion in sibling comparison			
Basic education	1(ref)	1(ref)	
Vocational	0.95 (0.73 to 1.23)	0.85 (0.80 to 0.89)	.30
Higher	0.84 (0.62 to 1.14)	0.72 (0.67 to 0.77)	
Unknown	0.48 (0.18 to 1.32)	0.86 (0.75 to 1.00)	
Household income 1 y before cancer diagnosis of affected child or inclusion in sibling comparison			
Lowest quartile	1(ref)	1(ref)	.17
2nd quartile	0.92 (0.72 to 1.18)	1.02 (0.96 to 1.07)	
3rd quartile	1.06 (0.82 to 1.36)	0.96 (0.90 to 1.02)	
Highest quartile	1.01 (0.75 to 1.35)	0.80 (0.75 to 0.86)	
Previous psychiatric disease in a parent			
Antidepressant use in a parent 2 y before cancer diagnosis of affected child or inclusion in sibling comparison			
No	1(ref)	1(ref)	
Yes	1.57 (1.19 to 2.06)	1.60 (1.50 to 1.70)	.78
Psychiatric hospital contact in a parent 5 y before cancer diagnosis of index child or inclusion			
No	1(ref)	1(ref)	.04
Yes	1.03 (0.64 to 1.65)	1.69 (1.56 to 1.83)	

[a]Test for a potential modifying effect of precancer parental socioeconomic position and parental history of psychiatric disease on the association between siblings of children with cancer and antidepressant use. The statistical significance of interaction terms was tested using the likelihood ratio test.
[b]Highest attained education of the parent: basic education, vocational education, and higher education as well as household income 1 year before cancer diagnosis of the affected child (sibling cohort) or inclusion in sibling comparisons.

risk set from the date of cancer diagnosis of the affected child or inclusion (for sibling comparisons defined as the date of cancer diagnosis in the affected child to whom they were matched), date of birth (for siblings who were born after cancer diagnosis age 0 years), or start of valid registration of antidepressants in the National Prescription Registry, whichever occurred last. Follow-up ended at the age of the second redeemed prescription of antidepressant medication within 365 days (the outcome), psychiatric hospital contact, emigration, death, or end of study period, whichever occurred first.

We performed interaction analysis to study the potential modifying effect of 1) parental socioeconomic position, and 2) parent's prior antidepressant use or psychiatric hospitalization (yes or no) on the association between being a sibling of a child with cancer and antidepressant use. The statistical significance of interaction terms was tested in a likelihood ratio test and reported as *P* values. To evaluate the impact of siblings' age at cancer diagnosis of the affected child, we used a test for trend. Effect estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using the statistical software R version 2.14.0 (9).

With population-based siblings as reference, we found that siblings of children with cancer were at no increased risk of having antidepressants prescribed (HR = 1.00, 95% CI = 0.91 to 1.11; not shown). No effect of cancer type of the affected child (hematological cancers: HR = 1.03, 95% CI = 0.87 to 1.21; central nervous system tumors: HR = 1.01, 95% CI = 0.84 to 1.22; solid tumors: HR = 0.99, 95% CI = 0.85 to 1.16) or of sibling's sex using same-sex comparisons was found (not shown). Low parental educational level, low household income, and parental use of antidepressants before cancer diagnosis of the affected child were all associated with an increased risk for antidepressant use in siblings, but not differently from children without cancer in the family and thus did not modify the risk of antidepressant use in siblings of children with cancer (Table 2). Siblings both having a sister or a brother with cancer and a parent with a hospital contact for a psychiatric disorder were at statistically significantly lower risk of having antidepressants prescribed than sibling comparisons only having a parent with psychiatric hospital contact, an unexpected finding that might be due to multiple testing. Age of the sibling at the time of diagnosis of the affected brother or sister, however, modified the risk of having antidepressants prescribed, with siblings being young at the time of diagnosis having the highest risk (P_{trend} = .01). This is in accordance with one of our previous findings that siblings older than 15 years at diagnosis had a lower risk of hospital contacts for mental disorders than the general population, whereas siblings who were young at cancer diagnosis of the cancer child

had an increased risk (8). The increased risk for antidepressant use in siblings being young at cancer diagnosis of the affected child may be explained by psychological stress resulting in emotional distress and altered patterns of interaction with parents (10). Alternatively, it may be mediated through changes in brain development in accordance with previous studies reporting high levels of maternal stress associated with increased risk of depression later in life (11).

The strengths in this study include a complete and unbiased ascertainment of children with cancer and a complete identification of their family members through nationwide population-based registries, allowing virtually complete follow-up. Although risk of selection bias is very low due to the use of nationwide population-based registries with information collected independent of the study, we used antidepressant use as a proxy for depression, introducing misclassification of the outcome. Not all individuals using antidepressants have depression (obsessive cumpulsive disorder or anxiety are also indications for some antidepressants and are more prevalent in people with, eg, attention deficit hyperactivity disorder) and similarly not all with a depression use antidepressants. It is possible that siblings of children with cancer have more confidence in medical treatment of depression than persons not exposed to childhood cancer, in which case we would overestimate the risk of depression in siblings of childhood cancer. On the other hand, it is also possible that some siblings would be reluctant to seek medical help for a condition thought to be existential rather than medical. In that case, the hazard ratio would be underestimated. Both are potential biases, but we have no means to evaluate the direction or effect of this misclassification. However, we propose that misclassification of the outcome is independent of being exposed to childhood cancer, making it nondifferential and not a bias.

In conclusion, our data indicate that siblings experiencing the stress of having a brother or sister affected with cancer are at no increased risk for antidepressant use. Additionally, children exposed to the traumatic experience of having a sibling with cancer do not seem to be more vulnerable regarding other risk factors for psychopathology such as familial psychiatric disease or low socioeconomic position. This is reassuring and of great importance for families facing cancer in a child, the healthy siblings, and the clinicians treating cancer patients and counseling the families.

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