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Increased risk of mental health problems after cancer during adolescence: A register-based cohort study

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Abstract

In this nationwide, register-based study, we estimated the risk of mental health problems in 2822 individuals diagnosed with cancer in adolescence (13-19 years). Mental health problems were assessed by psychiatric diagnoses and/or prescribed psychotropic drugs. Cox proportional hazards models estimated hazard ratio (HR) for a psychiatric diagnosis and prescription of psychotropic drug compared to a matched comparison group (n = 28 220). Estimates were adjusted for calendar period and parent characteristics (eg, history of psychiatric diagnosis, education, country of birth). We found an increased risk of a psychiatric diagnosis during the first 5 years after the cancer diagnosis (females: HR 1.23, 95% CI, 1.06-1.44; males: HR 1.32, 95% CI, 1.11-1.56), and at >5 years after diagnosis (females: HR 1.31, 95% CI, 1.09-1.58, males: HR 1.45, 95% CI, 1.18-1.77). The risk of being prescribed antidepressant (females: HR 1.54, 95% CI, 1.30-1.84, males: HR 2.06, 95% CI, 1.66-2.55), antipsychotic (females: HR 2.28, 95% CI, 1.56-3.34, males: HR 3.07, 95% CI, 2.13-4.42), anxiolytic (females: HR 1.95, 95% CI, 1.64-2.31, males: HR 4.02, 95% CI, 3.34-4.84) and sedative drugs (females: HR 2.24, 95% CI, 1.84-2.72, males: HR 3.91, 95% CI, 3.23-4.73) were higher than for comparisons during the first 5 years after diagnosis. Median age at first psychiatric diagnosis and first prescribed psychotropic drug were 18 years. In conclusion, cancer during adolescence is associated with increased risk of mental health problems that may develop in close proximity to treatment. The findings emphasize the need for comprehensive care during treatment and follow-up.

KEYWORDS

adolescence, cancer, mental health problems, psychiatric diagnoses, psychotropic drugs

1 | INTRODUCTION

Due to earlier detection and treatment advances, improved survival rates are resulting in an increasing number of childhood and adolescent cancer survivors. These survivors, however, are at increased risk

Abbreviations: ATC, anatomical therapeutic chemical; CNS, central nervous system; CIs, confidence intervals; DSM, diagnostic and statistical manual of mental disorders; HR, hazard ratio; ICD, International Statistical Classification of Diseases and Related Health Problems; N/A, not applicable.

of chronic or late-occurring health conditions and late mortality.[1,2] Childhood cancer survivors have been found to be at increased risk of neurocognitive dysfunction,[3] depression[4-6] and anxiety,[5,6] but results on the risk of adverse psychosocial outcomes are inconsistent.[6-11] Individuals diagnosed with cancer during adolescence report reduced quality of life, increased psychological distress and mental health problems compared to individuals diagnosed at younger ages.[10,11] Psychological stress as well as adverse treatment effects, such as pain, physical disability and treatment induced psychiatric morbidity,[12] might have lasting effects in particular when occurring during years important for identity formation.[13] Treatment is often intensive, including frequent hospital visits and significant side effects, which may hinder peer interaction and cause adolescents to be more dependent on their parents than before the disease.[14] Changes in physical appearance and concerns about occupational possibilities, future fertility and health problems, may be particularly distressing for adolescents diagnosed with cancer.[14,15] Moreover, adolescence is a period characterized by the intense development of the central nervous system, relevant in the context of treatment-related effects on the integrity of white matter.[16,17]

A recent review concludes that more work is needed to determine the risk of mental health problems after childhood and adolescent cancer.[18] Existing studies have mostly relied on self-reports, which are subject to selection and self-report biases.[19,20] Previous register-based studies have found childhood cancer survivors to be at increased risk for mental health problems that need psychiatric care,[21,22] as well as increased prescription rates of anxiolytic, hypnotic,[23] and antidepressant drugs.[24-26] Despite recognition of the specific psychosocial challenges in adolescents with cancer, existing register-based studies have focused on survivors of childhood cancer.[18] This register-based study, carried out in a recent treatment era, aimed to determine the short- and long-term risk of mental health problems (assessed by psychiatric diagnoses and/or prescribed psychotropic drugs) after a cancer diagnosis during adolescence (13-19 years of age).

What's new?

Survivors of childhood and adolescent cancer often are at increased risk of health conditions later in life, including neurocognitive dysfunction and depression. However, the risk of developing mental health conditions specifically after cancer during adolescence is unclear. In this study, using a matched cohort design and national register data, the authors found that adolescents with cancer are at increased risk of later psychiatric diagnosis and are likely to be prescribed psychotropic drugs, including antidepressants and antipsychotics. The findings suggest that mental health problems develop early following cancer treatment, highlighting the importance of comprehensive care and follow-up for adolescent cancer patients.

2 | METHODS

This is a nationwide population and register-based study using a matched cohort design. Register linkages were carried out using the unique personal identification numbers assigned to all residents of Sweden.

2.1 | Study population

The study population comprised 2822 individuals born in Sweden from 1980 to 2003, who were residing in Sweden at Age 12, with a primary cancer diagnosis during adolescence (13-19 years). Information on cancer diagnoses, age at diagnosis and sex, was obtained from the Cancer Register, with an overall completeness of at least 96%.[27] Adolescents with cancer were compared to an age-, sex- and geographically-matched (county of residence at the date of diagnosis) population-based comparison group (ratio 1:10), without cancer during childhood or adolescence (0-19 years). The comparison group (n = 28 220) was identified via the Total Population Register.[28] A total of 60 583 parents of adolescents with cancer and comparisons were identified via the Swedish Multigeneration Register.[29] All adolescents with cancer could be linked to at least one parent, and for the absolute majority (99.3%) two parents were identified. Date of death was ascertained from the Swedish Cause of Death Register[30] and on migration from the Migration Register.[28]

2.2 | Exposure

The date of primary cancer diagnosis was set as index date. Date of inclusion for comparisons was matched to the index date. Cancer diagnoses were classified according to the International Classification of Childhood Cancer, third edition,[31] and then categorized into three main diagnostics groups: hematological malignancies, CNS tumors and solid tumors (Table 1).

2.3 | Outcomes

Mental health problems were assessed by diagnoses reported to the Swedish Patient Register[28,32] and filled prescriptions from the Swedish Prescribed Drug Register.[33]

The Swedish Patient Register contains information on all psychiatric in-patient and out-patient discharge diagnoses in Sweden, with complete nationwide coverage since 1987 and all specialized out-patient care since 2001.[28,32] Data on discharge diagnoses are only from specialized psychiatric care (in-patient and out-patient), with no information on psychiatric diagnoses identified by general practitioners/family doctors. Diagnoses are recorded according to the Swedish version of the ninth and 10th revision of the International Statistical Classification of Diseases and Related Health Problems

TABLE 1 Characteristics of adolescents diagnosed with cancer and population-based comparisons at index (date of diagnosis/inclusion)

	Adolescents with cancer		Matched population comparisons	
	Female (n = 1451)	Male (n = 1371)	Female (n = 14 510)	Male (n = 13 710)
Age, median	17	16	17	16
Period of diagnosis, n (%)				
1993-2000	292 (20.1)	288 (21.0)	2920 (20.1)	2880 (21.0)
2001-2008	591 (40.7)	509 (37.1)	5910 (40.7)	5090 (37.1)
2009-2016	568 (39.2)	574 (41.9)	5680 (39.2)	5740 (41.9)
Type of cancer (ICCC-3 groups)[a], n (%)				
Hematological cancers	304 (21.0)	465 (33.9)	–	–
Leukemia (I)	119 (8.2)	205 (15.0)	–	–
Lymphoma (II)	185 (12.8)	260 (19.0)	–	–
CNS tumors (III)	348 (24.0)	290 (21.1)	–	–
Solid tumors	780 (53.8)	602 (43.9)	–	–
Neuroblastomas and other peripheral nervous cell tumors (IV)	2 (0.1)	7 (0.5)	–	–
Retinoblastomas (V)	0 (0.0)	0 (0.0)	–	–
Renal tumors (VI)	7 (0.5)	6 (0.4)	–	–
Hepatic tumors (VII)	21 (1.4)	18 (1.3)	–	–
Malignant bone tumors (VIII)	77 (5.3)	112 (8.2)	–	–
Soft-tissue sarcomas (IX)	75 (5.2)	101 (7.4)	–	–
Germ-cell, trophoblastic, and other gonadal tumors (X)	163 (11.2)	154 (11.2)	–	–
Carcinomas and other malignant epithelial neoplasms (XI)	435 (30.0)	204 (14.9)	–	–
Other and unspecified malignant neoplasms (XII)	19 (1.3)	14 (1.0)	–	–
Parents' education[b], n (%)				
Basic	77 (5.3)	62 (4.5)	1126 (7.8)	990 (7.2)
Upper secondary	716 (49.3)	639 (46.6)	6704 (46.2)	6276 (45.8)
Higher	658 (45.4)	669 (48.8)	6606 (45.5)	6304 (46.0)
Missing	0 (0.0)	1 (0.1)	74 (0.5)	140 (1.0)
Parents' country of birth[c], n (%)				
Sweden and Sweden/Nordic country	1267 (87.3)	1203 (87.7)	11 583 (79.8)	10 766 (78.5)
Sweden/ Nordic country and Other country	88 (6.1)	74 (5.4)	898 (6.2)	873 (6.4)
Other country and Other country	96 (6.6)	94 (6.9)	1983 (13.7)	1953 (14.2)
Missing	0 (0)	0 (0)	46 (0.3)	118 (0.9)
Mothers' marital status, n (%)				
Married/Registered partner	883 (60.8)	797 (58.1)	8455 (58.3)	8103 (59.1)
Divorced/Widow(er)	284 (19.6)	264 (19.2)	2975 (20.5)	2721 (19.8)
Not married	271 (18.7)	286 (20.9)	2628 (18.1)	2, 462 (18.0)
Missing	13 (0.9)	24 (1.8)	175 (1.2)	142 (1.0)
N/A[d]	–	–	277 (1.9)	282 (2.1)
Fathers' marital status, n (%)				
Married/Registered partner	865 (59.6)	818 (59.7)	8378 (58.0)	8038 (58.6)
Divorced/Widow(er)	266 (18.3)	237 (17.3)	2613 (18.0)	2389 (17.4)
Not married	263 (18.1)	267 (19.5)	2437 (16.8)	2344 (17.1)
Missing	44 (3.0)	43 (3.1)	175 (1.2)	424 (3.1)
N/A[d]	13 (1.0)	6 (0.4)	613 (4.2)	515 (3.8)
Mother's history of mental health problems[e], n (%)				
No	1350 (93.0)	1283 (93.6)	13 442 (92.6)	13 691 (92.6)
Yes	101 (7.0)	88 (6.4)	791 (5.5)	737 (5.4)
N/A[d]	–	–	277 (1.9)	282 (2.0)

(Continues)

TABLE 1 (Continued)

	Adolescents with cancer		Matched population comparisons	
	Female (n = 1451)	Male (n = 1371)	Female (n = 14 510)	Male (n = 13 710)
Father's history of mental health problems[e], n (%)				
No	1365 (94.1)	1299 (94.7)	13 222 (91.1)	12 601 (91.9)
Yes	73 (5.0)	66 (4.8)	675 (4.7)	594 (4.3)
N/A[d]	13 (0.9)	6 (0.4)	613 (4.2)	515 (3.8)

Abbreviations: CNS, central nervous system; N/A, not applicable.
[a]According to the International Classification of Childhood Cancer, third edition (ICCC-3).
[b]Highest attained education of the parent/parent couple.
[c]Country of birth for parents was categorized as: (a) both parents/the sole parent born in in a Nordic country (Denmark, Finland, Iceland, Norway, Sweden), (b) one parent born in a Nordic country and the other born outside Nordic countries and (c) both parents/the sole parent born outside the Nordic countries.
[d]Not applicable, information available only from one parent.
[e]Defined as any in-patient or out-patient psychiatric diagnosis during the 5 years prior to index (date of diagnosis/inclusion).

TABLE 2 Risks of psychiatric diagnoses after cancer during adolescence compared with matched population comparisons

Time since index (date of diagnosis/inclusion)								
	0-5 years				>5 years			
	Females		Males		Females		Males	
Outcome	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]
Any psychiatric diagnosis	199	1.23 (1.06-1.43)	152	1.32 (1.11-1.56)	126	1.31 (1.09-1.58)	107	1.45 (1.18-1.77)
Mood disorders	126	1.31 (1.09-1.58)	62	1.32 (1.01-1.72)	109	1.42 (1.17-1.74)	66	1.31 (1.01-1.69)
Psychotic disorders	5	1.68 (0.65-4.34)	6	1.99 (0.83-4.74)	4	1.11 (0.40-3.10)	6	1.14 (0.50-2.64)
Personality disorders	12	1.30 (0.71-2.37)	0	N/A	12	0.96 (0.53-1.73)	4	1.01 (0.36-2.81)
Substance use disorders	32	1.03 (0.71-1.48)	29	0.99 (0.68-1.45)	20	1.14 (0.72-1.81)	37	1.44 (1.02-2.02)
Eating disorders	15	0.90 (0.53-1.53)	1	1.00 (0.13-7.88)	5	0.52 (0.21-1.37)	1	N/A
Neurodevelopmental disorders	69	1.40 (1.09-1.80)	75	1.29 (1.02-1.65)	58	1.47 (1.12-1.93)	46	1.66 (1.22-2.25)
Any psychiatric diagnosis by type of cancer								
Hematological cancers	40	1.19 (0.86-1.65)	41	1.13 (0.82-1.57)	23	1.05 (0.68-1.61)	31	1.20 (0.83-1.74)
CNS tumors	51	1.39 (1.04-1.86)	35	1.41 (0.99-2.01)	27	1.35 (0.91-2.01)	31	1.89 (1.29-2.77)
Solid tumors	104	1.17 (0.95-1.43)	75	1.39 (1.09-1.77)	75	1.40 (1.10-1.78)	44	1.49 (1.09-2.04)

Abbreviations: CI, confidence interval; CNS, central nervous system; HR_{adj}, hazard ratio adjusted; N/A, not applicable.
[a]Adjusted for calendar period of diagnosis, parents' country of birth, parents' education level (highest) at index, parents' marital status at index and parental history of psychiatric disorders.

(ICD).[34] The following ICD codes (primary diagnosis) were included: F01-F99, X60-X84, Y10-Y34 (ICD-10) and 290-319, E950-E959, E980-E989 (ICD-9). The inclusion of ICD codes Y10-Y34 and E980-E989 was based on findings of a Swedish study showing that it is hard to distinguish deaths classified as suicide and deaths classified as undetermined intent.[35] ICD codes were subsequently categorized into six groups: mood disorders, psychotic disorders, personality disorders, substance use disorders, eating disorders, and neurodevelopmental disorders (Supporting Information). The Swedish Prescribed Drug Register includes information on all drugs prescribed to patients since July first, 2005.[33] It covers the entire Swedish population and contains data on drugs according to the Anatomic Therapeutic Chemical Classification System.[36] Prescribed psychotropic drugs were grouped according to the following Anatomic Therapeutic Chemical (ATC) codes: antidepressants (N06A), psychostimulants (N06B), antipsychotics (N05A), anxiolytics (N05B) and sedatives (N05C).

2.4 | Covariates

Calendar period was defined as index date between 1993 and 2000, 2001 and 2008 or 2009 and 2016. Information on parents' country of birth, education level and marital status at index (categorized as shown in Table 1) was obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies.[37] Parents' history of mental health problems was defined as any in-patient or out-patient psychiatric diagnosis during the 5 years prior to index, obtained from the Swedish Patient Register.[32]

2.5 | Statistical analysis

Adolescents with cancer and comparisons were followed from index until first psychiatric diagnosis (any) or first prescribed psychotropic drug (any). Adolescents with cancer and comparisons were censored at death, emigration, second cancer diagnosis or end of follow-up (December 31, 2016). Cox proportional hazards models were carried out to estimate the hazard ratio (HR) with 95% confidence intervals (CIs) for psychiatric diagnoses and psychotropic drugs for adolescents with cancer with comparisons as referents. Cox regression analyses were performed separately by sex and for different time periods since index (0-5 years or >5 years after index). Analyses were adjusted for calendar period, parents' country of birth, education level (highest of the parent/parent couple) at index, mothers' marital status at index and parental history of mental health problems. For a subset of the cohort (ie, individuals with an index date from July 1, 2005) cumulative risk was calculated to examine the occurrence of prescribed psychotropic drugs during follow-up and to assess risk of being prescribed with such drugs among adolescent cancer survivors and comparisons. Risk was defined as 1 − survival, where survival was defined as the common Kaplan-Meier product limit estimator. Estimates were derived separately for each sex and class of psychotropic drug. To reduce multiple testing and owing to the risk of

TABLE 3 Cumulative risk of prescribed psychotropic drugs from diagnosis up to 10 years after index among female and male adolescents diagnosed with cancer and matched population comparisons

Time since index (date of diagnosis/inclusion)					
Outcome	<1 year n, % (95% CI)	1-2 years n, % (95% CI)	2-3 years n, % (95% CI)	3-5 years n, % (95% CI)	>5 years n, % (95% CI)
Any psychotropic drug					
Females with cancer	174, 19% (17-22)	212, 23% (21-26)	240, 27% (24-29)	269, 31% (27-34)	320, 47% (41-52)
Female comparisons	569, 7% (6-7)	837, 10% (9-11)	1094, 13% (13-14)	1468, 19% (18-20)	1983, 33% (31-34)
Males with cancer	198, 22% (20-25)	234, 27% (24-29)	252, 29% (26-32)	285, 34% (31-37)	308, 40% (36-44)
Male comparisons	508, 6% (6-7)	660, 8% (8-9)	811, 10% (10-11)	1034, 14% (13-15)	1352, 26% (24-28)
Antidepressants					
Females with cancer	70, 8% (6-10)	96, 11% (9-14)	119, 15% (12-17)	148, 19% (16-22)	194, 35% (29-40)
Female comparisons	334, 4% (4-4)	510, 6% (6-7)	676, 8% (8-9)	951, 13% (12-14)	1352, 26% (24-27)
Males with cancer	48, 6% (4-8)	64, 8% (6-10)	76, 10% (8-12)	101, 15% (12-18)	118, 22% (17-26)
Male comparisons	181, 2% (2-3)	265, 3% (3-4)	376, 5% (5-6)	523, 8% (7-8)	745, 17% (15-19)
Psychostimulants					
Females with cancer	18, 2% (1-3)	24, 3% (2-4)	28, 4% (2-5)	31, 4% (3-6)	37, 7% (4-9)
Female comparisons	132, 2% (1-2)	176, 2% (2-2)	202, 3% (2-3)	240, 3% (3-4)	288, 5% (4-6)
Males with cancer	28, 4% (2-5)	36, 5% (3-6)	37, 5% (3-6)	42, 6% (4-8)	45, 8% (4-12)
Male comparisons	253, 3% (3-4)	291, 4% (3-4)	322, 4% (4-5)	361, 5% (4-5)	397, 6% (5-7)
Antipsychotics					
Females with cancer	22, 3% (2-4)	26, 3% (2-4)	27, 3% (2-5)	33, 5% (3-6)	40, 9% (5-12)
Female comparisons	39, 0% (0-1)	66, 1% (1-1)	96, 1% (1-2)	143, 2% (2-2)	221, 5% (4-6)
Males with cancer	26, 3% (2-5)	29, 4% (2-5)	31, 4% (3-6)	38, 6% (4-7)	45, 9% (6-11)
Male comparisons	51, 1% (0-1)	71, 1% (1-1)	98, 1% (1-2)	132, 2% (2-2)	191, 4% (4-5)
Anxiolytics					
Females with cancer	75, 9% (7-11)	100, 12% (10-14)	123, 15% (13-17)	158, 21% (18-23)	194, 33% (27-38)
Female comparisons	232, 3% (2-3)	388, 5% (4-5)	558, 7% (7-8)	825, 11% (11-12)	1214, 24% (22-26)
Males with cancer	99, 12% (10-14)	127, 16% (13-18)	137, 17% (14-20)	157, 21% (18-24)	181, 28% (24-32)
Male comparisons	112, 1% (1-2)	190, 2% (2-3)	277, 4% (3-4)	426, 6% (6-7)	659, 15% (14-17)
Sedatives					
Females with cancer	63, 7% (6-9)	88, 11% (8-13)	109, 14% (11-16)	126, 16% (14-19)	147, 22% (18-26)
Female comparisons	164, 2% (2-2)	270, 3% (3-4)	385, 5% (4-5)	565, 8% (7-9)	830, 18% (16-20)
Males with cancer	85, 10% (8-12)	112, 14% (12-16)	128, 16% (14-19)	147, 20% (17-23)	162, 26% (21-30)
Male comparisons	149, 2% (2-2)	222, 3% (2-3)	288, 4% (3-4)	407, 6% (5-7)	572, 13% (12-15)

Note: Psychotropic drugs according to Anatomic Therapeutic Chemical codes, antidepressants (N06A), psychostimulants (N06B), antipsychotics (N05A), anxiolytics (N05B) and sedatives (N05C).

Abbreviation: CI, confidence interval.

underpowered statistics, only risk estimates for any psychiatric diagnosis and any prescribed drug were calculated for the three main diagnostics groups. To assess whether newer treatment regimens change the risk estimates of any psychiatric diagnosis, we included period of cancer diagnosis in a sensitivity analysis. Additional sensitivity analyses were performed by repeating analyses of any psychotropic drug and antidepressants for the first time period (0-5 years after index), respectively, excluding prescriptions of tricyclic antidepressant (ATC code N06AA). All statistical analyses were carried out using R.3.5.3.

3 | RESULTS

Sample characteristics are shown in Table 1. The median follow-up time was 9.21 years (3363 days). Just over half of adolescents with cancer were female (n = 1451; 51%). In males, the predominant cancer diagnoses were central nervous system (CNS) tumors (21.1%), lymphoma (19.0%) and leukemia (15.0%). In females, the most common diagnoses were carcinomas and other malignant epithelial neoplasms (30.0%), CNS tumors (24.0%) and lymphoma (12.8%).

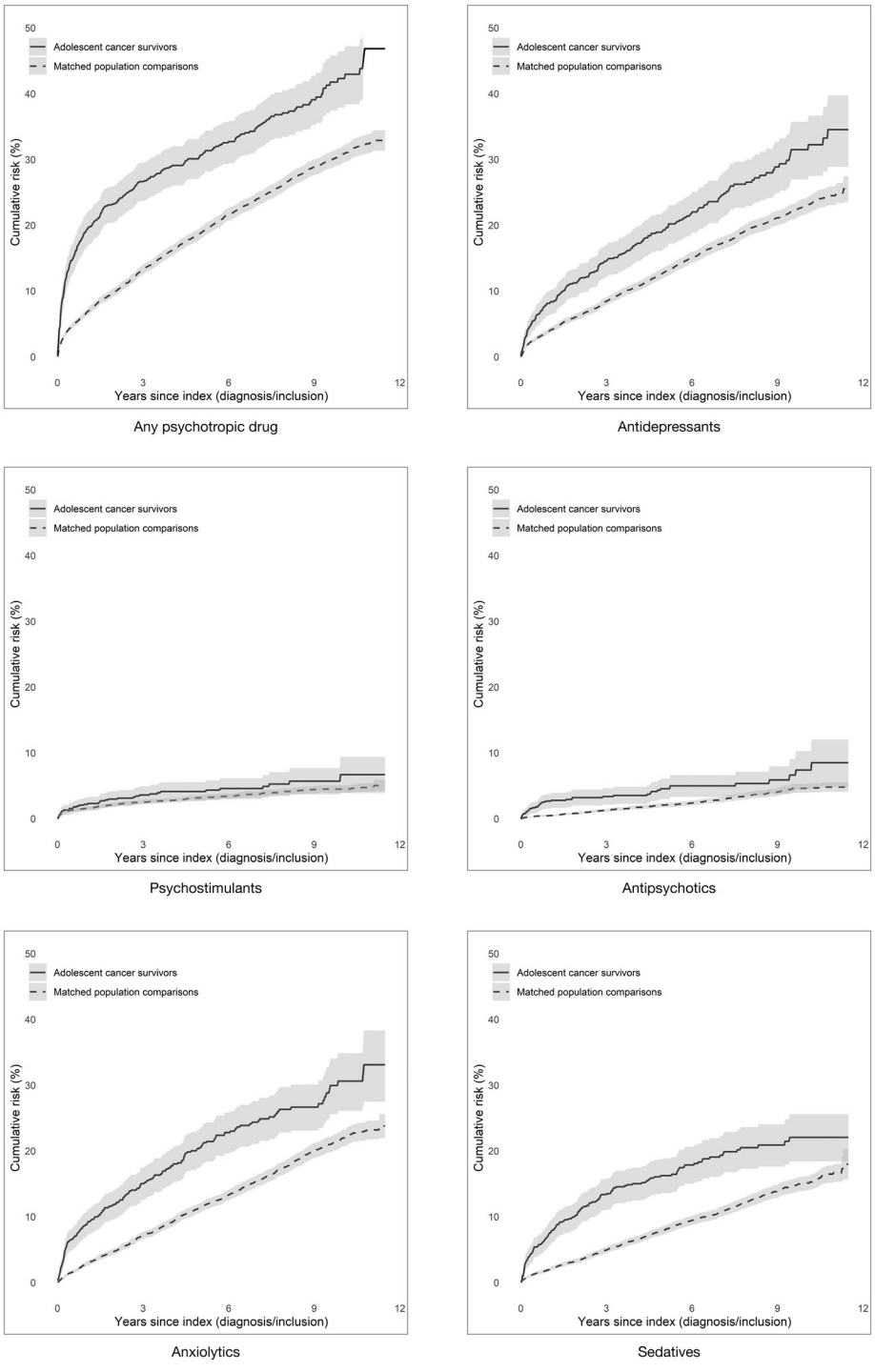

FIGURE 1 Cumulative risk of psychotropic drugs in female adolescents with cancer and comparisons

3.1 | Mental health problems

The risk of psychiatric diagnoses is shown in Table 2. Median age at first psychiatric diagnosis among adolescents with cancer was 18 years. Overall, the risk of a psychiatric diagnosis compared with comparisons during the first 5 years after index was significantly higher for both female (HR_{adj} 1.23, 95% CI, 1.06-1.43) and male (HR_{adj} 1.32, 95% CI, 1.11-1.56) adolescents with cancer. This risk remained elevated after 5 years from index (HR_{adj} 1.31, 95% CI, 1.09-1.58, and HR_{adj} 1.45, 95% CI, 1.18-1.77, for females and males, respectively). Adolescents diagnosed with CNS tumors and solid tumors had the highest risk estimates (Table 2). Analysis of specific psychiatric diagnosis showed that adolescents with any type of cancer were at increased risk of mood disorders both during the first 5 years (females: HR_{adj} 1.31, 95% CI, 1.09-1.58; males: HR_{adj} 1.32, 95% CI, 1.01-1.72), and after 5 years from index (females: HR_{adj} 1.42, 95% CI, 1.17-1.74; males: HR_{adj} 1.31, 95% CI, 1.01-1.69). An increased risk of neurodevelopmental disorders was observed for female (HR_{adj} 1.40, 95% CI, 1.09-1.80) and male (HR_{adj} 1.29, 95% CI, 1.02-1.65) adolescents with cancer during the initial 5 years after index. This risk remained

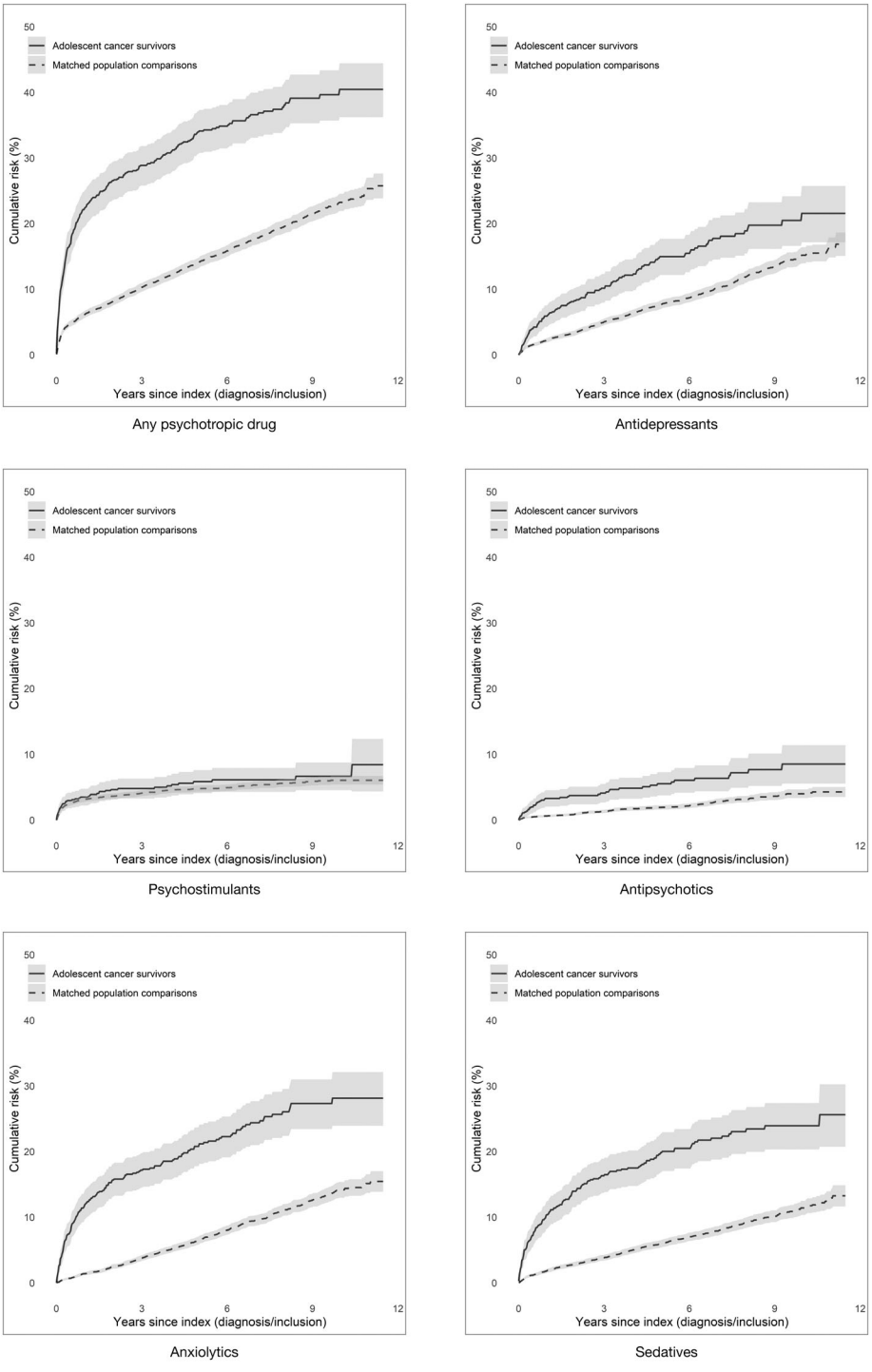

FIGURE 2 Cumulative risk of psychotropic drugs in male adolescents with cancer and comparisons

TABLE 4 Risks of being prescribed psychotropic drugs after cancer during adolescence compared with matched population comparisons

Time since index (date of diagnosis/inclusion)								
	0-5 years				>5 years			
	Females		Males		Females		Males	
Outcome	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]	n	HR_{adj} (95% CI)[a]
Any psychotropic drug	269	1.83 (1.60-2.08)	285	2.90 (2.54-3.31)	51	1.20 (0.90-1.61)	23	1.11 (0.73-1.70)
Antidepressants	148	1.54 (1.30-1.84)	101	2.06 (1.66-2.55)	46	1.32 (0.97-1.79)	17	0.96 (0.59-1.58)
Psychostimulants	31	1.21 (0.83-1.76)	42	1.13 (0.82-1.56)	6	1.31 (0.60-3.07)	3	1.10 (0.34-3.60)
Antipsychotics	33	2.28 (1.56-3.34)	38	3.07 (2.13-4.42)	7	1.00 (0.46-2.19)	7	1.56 (0.71-3.45)
Anxiolytics	158	1.95 (1.64-2.31)	157	4.02 (3.34-4.84)	36	1.09 (0.77-1.53)	24	1.37 (0.90-2.09)
Sedatives	126	2.24 (1.84-2.72)	147	3.91 (3.23-4.73)	21	0.93 (0.59-1.45)	15	1.28 (0.75-2.18)
Any psychotropic drug by type of cancer								
Hematological cancers	67	2.33 (1.78-3.04)	93	3.05 (2.42-3.85)	8	1.07 (0.517-2.20)	6	0.894 (0.391-2.05)
CNS tumors	59	1.89 (1.43-2.50)	72	3.77 (2.87-4.94)	14	1.77 (1.00-3.11)	6	1.97 (0.845-4.60)
Solid tumors	140	1.64 (1.37-1.96)	119	2.43 (1.99-2.97)	29	1.08 (0.736-1.59)	11	0.989 (0.534-1.83)

Note: Anatomic Therapeutic Chemical codes, antidepressants (N06A), psychostimulants (N06B), antipsychotics (N05A), anxiolytics (N05B) and sedatives (N05C).

Abbreviations: CI, confidence interval; CNS, central nervous system; HR_{adj}, hazard ratio adjusted.

[a]Adjusted for calendar period of diagnosis, parents' country of birth, parents' education level (highest) at index, parents' marital status at index and parental history of psychiatric disorders.

beyond 5 years following index (females: HR_{adj} 1.47, 95% CI, 1.12-1.93, males: HR_{adj} 1.66, 95% CI, 1.22-2.25). The sensitivity analysis showed no clear influence of period of diagnosis on the estimation of risk of a psychiatric diagnosis (data not shown).

Prescribed psychotropic drugs in individuals with a cancer diagnosis after July 1, 2005, and comparisons are shown in Table 3. For adolescents with any type of cancer, median age at first prescribed psychotropic drug was 18 years. During the first year after diagnosis, 19% of female adolescents with cancer, and 22% of male adolescents with cancer, were prescribed a psychotropic drug, compared with 7% and 6% of female and male comparisons, respectively. Antidepressants, anxiolytics and sedatives were most commonly prescribed. At >5 years after index, the cumulative risk of any psychotropic drug among female adolescent cancer survivors was 47% (95% CI, 41-52) compared with 33% (95% CI, 31-34) in comparisons. The corresponding numbers were 40% (95% CI, 36-44) for male adolescents with cancer and 26% (95% CI, 24-28) in comparisons. The cumulative risk curves displayed in Figures 1 and 2 illustrate higher prescription rates of antidepressant, antipsychotics, anxiolytic and sedative drugs among adolescents with any type of cancer throughout the follow-up period compared with comparisons.

The risk of being prescribed any psychotropic drug was elevated among female (HR_{adj} 1.83, 95% CI, 1.60-2.08) and male (HR_{adj} 2.90, 95% CI, 2.54-3.31) adolescents with any type of cancer during the first 5 years after index, compared with comparisons (Table 4). The risk was increased in all three main diagnostic groups, ranging from 3.8 times the risk in males diagnosed with CNS tumors to 1.6 times the risk in women diagnosed with solid tumors. In particular, the risk of being prescribed antidepressant (females: HR_{adj} 1.54, 95% CI, 1.30-1.84, males: HR_{adj} 2.06, 95% CI, 1.66-2.55), antipsychotic (females: HR_{adj} 2.28, 95% CI, 1.56-3.34, males: HR_{adj} 3.07, 95% CI, 2.13-4.42), anxiolytic (females: HR_{adj} 1.95, 95% CI, 1.64-2.31, males: HR_{adj} 4.02, 95% CI, 3.34-4.84) and sedative drugs (females: HR_{adj} 2.24, 95% CI, 1.84-2.72, males: HR_{adj} 3.91, 95% CI, 3.23-4.73) were higher among adolescents with any type of cancer than among comparisons during the first 5 years after index, but the increased risks were attenuated >5 years after index (Table 4). At 5 years after index, only female adolescents diagnosed with CNS tumors showed slightly elevated HR of being prescribed any psychotropic drug compared with matched comparisons (HR_{adj} 1.77, 95% CI, 1.00-3.11).

In the sensitivity analysis excluding prescriptions of tricyclic antidepressant, the adjusted HR of being prescribed any psychotropic drug during the first 5 years was 1.76 (95% CI, 1.53-2.01) for female adolescents with any type of cancer and 2.80 (95% CI, 2.45-3.20) for male adolescents with any type of cancer. Moreover, when excluding tricyclic antidepressant from the analysis, the risk of being prescribed antidepressants during the first 5 years was 1.24 (95% CI, 1.02-1.51) for female adolescents with any type of cancer and 1.56 (95% CI, 1.22-2.00) for male adolescents with any type of cancer.

4 | DISCUSSION

This nationwide, register-based study showed that adolescents with cancer were at increased risk of mental health problems when compared to a matched population group. Both female and male adolescents with cancer showed an elevated risk of a psychiatric diagnosis during the first 5 years after the cancer diagnosis. The elevated risk of a psychiatric diagnosis was present even after 5 years from diagnosis, when compared with the comparisons. Especially adolescents

diagnosed with CNS tumors and solid tumors showed an increased risk for a psychiatric diagnosis. Both female and male adolescents with cancer, all main cancer groups, showed an excess risk of being prescribed any psychotropic drug during the first 5 years after the cancer diagnosis. Specifically, our data suggest that adolescents with cancer have increased risk of being prescribed antidepressants, antipsychotics, anxiolytics and sedatives during the first 5 years after diagnosis.

The treatment of children and adolescents with cancer has changed considerably over the last decades with important steps taken for a decreased use of cranial irradiation in children, which is a known risk factor for physical and psychological sequelae.[4,38] Contemporary treatment protocols do however often involve intensive multimodal therapy. Also, chemotherapy has been associated with concurrent risk of negative mood and depression,[39] and has furthermore been hypothesized to induce epigenetic changes in the brain.[40] Accordingly, up-to-date assessments of illness and treatment-related adverse psychiatric and health-related outcomes are necessary to provide accurate guidance for care. The present study identifies an increased short- and long-term risk of a psychiatric diagnosis in female and male adolescents treated for cancer in a very recent treatment era, indicating that contemporary treatments are associated with adverse effects on adolescents' mental health. In a sensitivity analysis, we used period of diagnosis as a proxy for treatment era but did not find that risk estimates differentiate between those diagnosed earlier and those diagnosed later. While acknowledging that more studies are needed to determine if the newer treatment protocols can result in less adverse mental health outcomes for survivors of childhood and adolescent cancer,[21,22,41] it is important to consider treatment era when comparing the results of our study to those of previous studies.

Our results show an increased risk of mood disorders in the first 5 years after a diagnosis of any type of cancer. A registry-based study on psychiatric late effects after childhood cancer in Finland, analyzed outcomes for survivors treated in different eras (1975-1982, 1983-1992, 1993-2004).[22] For the entire group of survivors, they reported similar HRs to ours for any psychiatric diagnosis and mood disorders. Also, in accordance with our results, they found survivors of CNS tumors to be particularly susceptible to psychiatric morbidity. However, for survivors treated in 1993-2004, which best corresponds to the herein studied treatment era, they found no increased risk for mood disorders. The contrasting finding might reflect that our definition of mood disorders was more inclusive than theirs (including only ICD codes F30-F39). Other possible explanations are the use of sibling controls in the Finnish study, which may have resulted in an underestimation of risk as siblings are also affected by the cancer experience,[42] and the fact that our study focused on adolescents diagnosed with cancer treated in a more recent treatment era.

Our results indicate a slight increased risk over time for neurodevelopmental disorders. The HR at >5 years for male survivors is similar to a registry-based study on hospital contacts for mental disorders among survivors of childhood cancer treated between 1975 and 2010 in Denmark.[21] However, we observed a slightly lower HR for neurodevelopmental disorders among female survivors than the Danish study. The difference may reflect different study populations, our study capturing more recent treatment eras, and that our risk estimates were adjusted for calendar period as well as a variety of indicators of parents' socioeconomic position.

We found that male and female adolescents with any type of cancer were at excess risk of being prescribed a psychotropic drug the first 5 years after the cancer diagnosis. Only female adolescents diagnosed with CNS tumors were at risk beyond 5 years after diagnosis. This finding is in line with previous studies that have shown that survivors of CNS tumors are among the highest at risk of being prescribed psychotropic drugs.[23-25] In particular, similar to previous reports on mixed samples of childhood and adolescent cancer survivors,[23-26,43] our data shows that adolescents with any type of cancer were at increased risk of being prescribed antidepressants and anxiolytics. During the first 5 years after diagnosis, the risk of antidepressants among adolescents diagnosed with cancer was 50% higher for females and two times higher for males compared to matched comparisons. Our risk estimates are higher than what has been reported in a study of cancer survivors diagnosed ≤25 years in 1965 to 2000,[25] but in line with the risk observed for survivors of childhood cancer treated in a more recent treatment era (2000-2009).[24] While we did not have information on indication for prescribed antidepressant, the most common indication of antidepressant medication is mild-to-moderate depression. Depression is a serious mental illness associated with significant comorbidity and lower quality of life. The excess risk of being prescribed antidepressants after diagnosis taken together with the observed increased risk for mood disorders, underscore the importance of comprehensive care including mental health screening not only during the time of the cancer treatment but also during follow-up.

Compared with comparisons, female and male adolescents diagnosed with cancer showed a twofold and fourfold increased risk, respectively, for being prescribed sedatives. Sedatives are often prescribed to treat conditions like anxiety and sleep disorders. Inconsistent results have been reported for sleep problems after childhood cancer.[44,45] These studies have however been based on self-report data, as such being subject to recall and selection bias. The increased risk for sedatives observed in our study may suggest that sleep problems are more prevalent in adolescent cancer survivors than comparisons.

In previous studies based on questionnaires, female survivors of childhood cancer have reported a higher rate of depression[4] and have also been found to be more likely to report use of antidepressants than males.[7] Furthermore, in a study of adolescent cancer survivors, only female survivors reported more symptoms of depression and anxiety compared to controls.[6] Inconsistent results have been reported in registry-based studies of childhood cancer survivors, with some reporting females being more susceptible to psychiatric morbidity,[22,23,26] while others show no significant effect of sex.[41] Interestingly, our results show that male survivors have higher HR than females in the first 5 years after diagnosis. The reason for this could be explained by females in general more often being prescribed psychotropic drugs,[46] including anxiolytics and antidepressants,

resulting in cancer not being an equally significant event for women's risk for psychotropic drugs use.

To the best of our knowledge, this is the first registry-based study that focuses on a range of mental health outcomes after cancer in adolescence specifically. A notable finding is the low age (median = 18 years) for a first psychiatric diagnosis and prescribed drug. This is lower than what has been reported previously for antidepressant prescriptions (median = 38 years) for survivors of cancer diagnosed ≤25 years earlier.[25] This finding, coupled with the observed increased risk of a psychiatric diagnosis and/or a prescribed psychotropic drug warrants further consideration. Mental health problems so close in time after diagnosis as observed in the present study can have detrimental long-term effects. Young people in general who experience mental health problems are at risk for extended, severe mental ill-health, limiting the opportunities to enter the workforce and lead fulfilling lives as adults.[47] Taken together, our findings emphasize the need for mental health evaluation and access to services during treatment and also during follow-up.

The strengths of this nationwide, population-based study is the reliance on registries with complete nationwide coverage.[19,20] Furthermore, by taking parents' socioeconomic position and history of mental health problems into account we could provide more accurate risk estimates for the impact of cancer. However, our findings should be interpreted in the context of certain limitations. One was that the Swedish Prescribed Drug Register was established first in July 2005, and we do not have information on any drugs prescribed to individuals before that time. Additionally, risk estimates might be subject to detection bias. It has been reported that survivors of childhood cancer are more likely to utilize mental healthcare than siblings who experience similar mental health problems.[48] The observed increased risk of a psychiatric diagnosis or a psychotropic drug may reflect differences in incidence, but may also be related to an increased likelihood of seeking help or having a better access to healthcare services among adolescent cancer survivors than comparisons. Of note is that clinicians and psychiatrists in Sweden use the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[49] to diagnose psychiatric illnesses, while the national registers of psychiatric illnesses are based on the ICD classification system.[50,51] Furthermore, it is possible that our study underestimates occurrence of mental health problems, as some milder forms of mental ill-health treated by primary healthcare, without prescription for a psychiatric drug, would not be captured in our data. The lack of cancer treatment data is an additional limitation. The inclusion of such data would have allowed us to identify specific treatments associated with increased risk and differentiate risk between those on and off active cancer treatment. Furthermore, information on indication for the prescribed psychotropic drug was not available. Tricyclic antidepressants can, for example, be used to treat neuropathic pain and anxiety in adolescents with cancer, and this should be taken into account when looking at the estimates of risk of prescribed antidepressants for the first years after the cancer diagnosis. Therefore, we performed sensitivity analyses excluding tricyclic antidepressants, which showed similar risk estimates. In addition, it must be noted that anxiolytics and sedatives prescribed early after diagnosis may represent treatment not only of anxiety but also sleep problems. Future studies are however encouraged to expand on the present study by investigating risk of specific types of drugs (eg, SSRI and tricyclic antidepressants) and multiple and recurrent prescriptions of psychotropic drugs and psychiatric diagnosis. As in all observational studies, we could not fully rule out residual confounding due to a lack of intact information on the exposure variable and other potential confounders.

In conclusion, our study demonstrates increased risks of psychiatric diagnoses, in particular mood disorders and neurodevelopmental disorders, and the use of a range of psychotropic drugs after cancer in adolescence. Our findings suggest the emergence of mental health problems very early after treatment, underscoring the importance of close monitoring of adolescents' mental health in the early post-therapy period. Improved psychosocial services during treatment and in early survivorship have the possibility to facilitate psychosocial adjustment to the cancer experience.

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CONFLICT OF INTEREST

R. L. is also employed at the Swedish Medical Products Agency, SE-751 03 Uppsala, Sweden. The views expressed in this article do not necessarily represent the views of this Government agency.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to ethical restrictions. The data that support the findings of our study are available from the corresponding author, upon reasonable request and with necessary ethics approval.

ETHICS STATEMENT

Our study was approved by the Regional Ethical Review Board, Uppsala, Sweden (approval number 2017/117). Data confidentiality was approved by the National Board of Health and Welfare and Statistics Sweden.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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