

## RESEARCH ARTICLE

## Cancer Therapy and Prevention



# Reproductive late effects and testosterone replacement therapy in male childhood cancer survivors: A population-based study (the Fex-Can study)

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## Funding information

Vetenskapsrådet, Grant/Award Number: 2017-01530; Barncancerfonden, Grant/Award Numbers: KP2020-0012, PR2014-0177, PR2016-0075, PR2017-0037, TJ2014-0050, TJ2019-0045; Lastentautien Tutkimussäätiö; Cancerfonden, Grant/Award Number: CAN 2013/886; Forskningsrådet om Hälsa, Arbetsliv och Välfärd, Grant/Award Numbers: 2014-4689,

## Abstract

Childhood cancer survivors are at risk of various endocrine late effects affecting their quality of life. The aim of this study was to assess the prevalence and predictors of endocrine and reproductive outcomes in young adult survivors. A secondary aim was to assess possible associations between testosterone replacement therapy (TRT) and other endocrine, cardiovascular and psychosocial late effects. This nationwide study comprised 1212 male childhood cancer survivors aged 19–40 years, identified through the National Quality Registry for Childhood Cancer in Sweden. Median age at diagnosis during 1981–2017 was 7 (range 0–17) and at study 29 (19–40) years. The study combined self-report survey data with cancer treatment data from the national registry. Hormone-induced puberty was self-reported by 3.8% of the survivors and ongoing TRT by 6.0%. In separate logistic regression analyses, these treatments were associated with hematopoietic stem cell transplantation and cranial radiotherapy. Hormone-induced puberty was additionally associated with younger age at diagnosis. Men with TRT had a higher prevalence of other endocrine deficiencies, cholesterol medication, depressive symptoms and fatigue as well as a lower probability of living with a partner, having a biological child or current occupation. In the total male cohort, 28.2% reported having a biological child. Reassuring reproductive outcomes after less intensive therapies and low frequency of TRT were observed in young adult male childhood cancer survivors treated in the most recent treatment era. However, men with TRT suffered from several other endocrine, cardiovascular and psychosocial late effects, indicating a need for long-term monitoring of this high-risk group.

## KEYWORDS

childhood cancer survivors, late effects, registry study, subfertility, testosterone replacement therapy

**Abbreviations:** CNS, central nervous system; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Questionnaire; HADS, The Hospital Anxiety and Depression scale; HSCT, hematopoietic stem cell transplantation; ITR-3.0, intensity of treatment rating scale; TBI, total body irradiation; TRT, testosterone replacement therapy.

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2019-00839; Birgitta and Carl-Axel Rydbeck's Research Grant for Paediatric Research, Grant/Award Numbers: 2020-00335, 2021-00079; Syöpäsäätiö

### What's new?

Childhood cancer survivors are at risk of various endocrine late effects affecting their quality of life. This population-based study in a recent cohort of childhood cancer survivors assessed prevalence rates of testosterone replacement therapy and fertility outcomes, providing valuable information for current patients. Among young adult men with a history of childhood cancer, 6% reported ongoing testosterone replacement therapy. Testosterone replacement was associated with self-reported treatment with other hormones and cardiovascular medication as well as psychological and sociodemographic factors. The findings indicate a need for long-term follow-up in male childhood cancer survivors with testosterone substitution.

## 1 | INTRODUCTION

The majority of children diagnosed with cancer survive, yet serious late effects of cancer therapy are common and include endocrine disorders<sup>1,2</sup> and compromised reproductive function.<sup>3</sup> Cancer treatment may cause gonadal damage either by direct treatment-related effects on the gonad or indirectly through damage to the hypothalamo-pituitary axis with resulting downstream effects on gonadal function and fertility.

In male survivors of cancer in childhood, adolescence or young adulthood, the treatment-related risk of gonadal dysfunction is mainly related to conditioning therapies for hematopoietic stem cell transplantation (HSCT), very high cumulative doses of alkylating agents and radiation treatment volume that include the testes.<sup>4,5</sup> Cytotoxic therapies and irradiation exposing the testes may damage the seminiferous epithelium leading to oligo- or azoospermia, which causes reduced or lost fertility. There may also be damage to the Leydig cells resulting in impaired testosterone production causing a delayed puberty in children and a range of adverse physiological and psychological consequences in adults.<sup>6,7</sup> Consequently, many childhood cancer survivors have a lower probability of partnering and experience impaired fertility in adulthood.<sup>8,9</sup>

In follow-up care after cancer treatment, timely identification of the failure to develop signs of puberty is important for the teenager's psychosocial development as well as for optimizing growth and bone health.<sup>10</sup> Receiving testosterone replacement therapy (TRT) has in previous studies on allogeneic HSCT recipients been associated with lower muscle mass, poorer physical fitness,<sup>11</sup> and a higher android/gynoid fat ratio increasing the risk of cardiometabolic disease.<sup>12</sup> In case of central hypogonadism, testosterone deficiency may be accompanied by deficiencies of other pituitary hormones.<sup>10</sup> Testosterone deficiency is further associated with fatigue, depression and sexual dysfunction.<sup>13</sup> Hence, besides secondary physical development, the goal of hormone-induced puberty or TRT is to assure growth, muscle mass and bone density<sup>14</sup> as well as improved mood, fatigue and sexual function.<sup>7</sup>

This study provides data on young adult survivors of childhood cancer from a recent treatment era and includes a national population of male survivors aged 19–40 years treated at pediatric oncology units in Sweden. The aim of this study was to assess the prevalence and predictors of three endocrine and reproductive outcomes: namely, hormone-induced puberty, ongoing TRT and having a

biological child. A secondary aim was to assess possible associations between TRT and other endocrine, cardiovascular, psychological and sociodemographic factors. The findings can be used to inform currently treated patients about fertility prospects and potential need of testosterone substitution, and to improve surveillance.

## 2 | METHODS

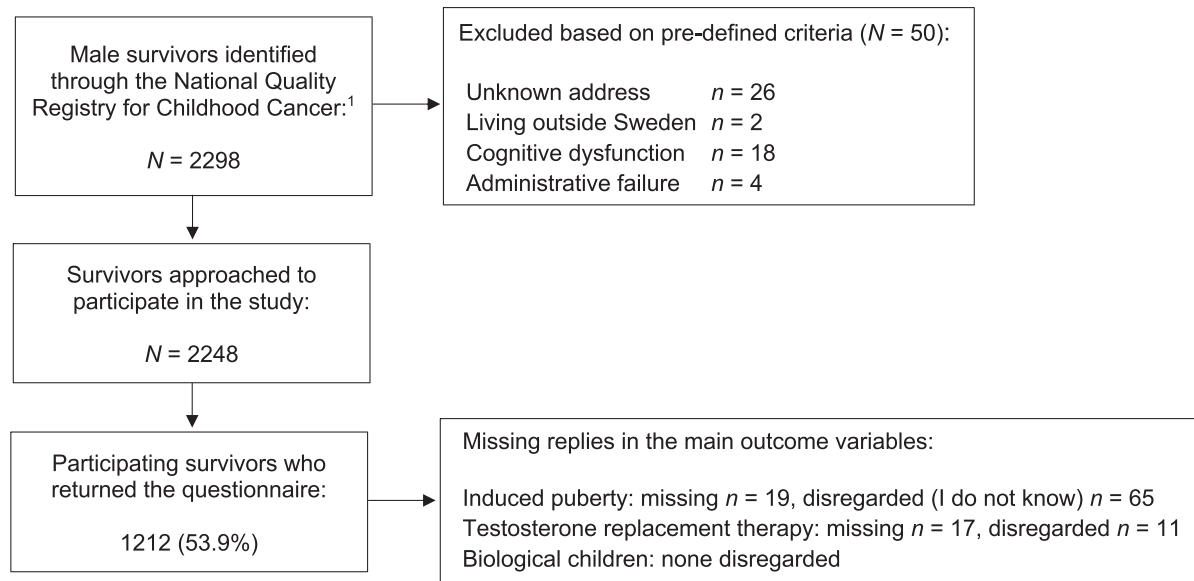
### 2.1 | Participants

This study is part of the Fex-Can Childhood project, which is a nationwide population-based research initiative investigating the prevalence and predictors of sexual dysfunction and fertility-related distress in young adult survivors of childhood cancer.<sup>15</sup> The project included all survivors who had been diagnosed with cancer before the age of 18 years and who were 19–40 years old and residents in Sweden at the time of enrolment. Participants were identified from the National Quality Registry for Childhood Cancer in Sweden. This registry includes all individuals who received a cancer diagnosis before the age of 18 years with one exception: during the 1980s and part of the 1990s only patients diagnosed before the age of 16 were treated at the child oncology units and, hence, included in the registry.

Participants were excluded from the Fex-Can Childhood project if they had difficulties reading/writing in Swedish or if they had cognitive impairments that compromised study participation. Among the 2298 potential male participants identified through the National Quality Registry for Childhood Cancer, 50 were excluded (see Figure 1). Ultimately, of the 2248 eligible participants, 1212 (53.9%) returned questionnaires and took part in the present study. These participants had been diagnosed with cancer between 1981 and 2017. When comparing clinical characteristics between male participants and non-participants, participating survivors were older at the time of study and had a longer follow-up time since diagnosis, but there were no significant differences in terms of cancer diagnoses or treatments (Table S1).

### 2.2 | Procedure

The National Quality Registry for Childhood Cancer in Sweden was used both to identify patients and to collect data on diagnoses



<sup>1</sup>All male survivors in Sweden who had been diagnosed with cancer before the age of 18 years and who were 19–40 years at the time of the study were included.

**FIGURE 1** Flow chart of the exclusion process, and missing responses in the main outcome variables. <sup>1</sup>All male survivors in Sweden who had been diagnosed with cancer before the age of 18 years and who were 19–40 years at the time of the study were included.

and previous cancer treatments. A survey, along with a letter describing the study, was sent to all eligible participants. Vital status was controlled for all eligible participants from a national registry over death records before sending out the surveys. The survey included both validated self-report instruments on depressive symptoms and fatigue as well as study-specific questions assessing socio-demographic data, current medication use, information on semen quality and fertility.<sup>15</sup> The participants had the option to complete the survey on paper, Web or by telephone interview. The non-responders received two reminders. Data collection took place between September 2019 and February 2020.

### 2.3 | Measures

The three outcome measures in this study were self-reported need of induced puberty, ongoing TRT and having a biological child. These data were derived from three study-specific questions in the survey: (1) Have you received medication to induce puberty (No/I do not know or remember/Yes)? (2) During the past 2 years, have you used male sex hormone to replace testosterone during a minimum of 1 month (No/I do not know or remember/Yes)? (3) Do you have a biological child (Yes/No)? Participants also had the possibility to provide additional details through open-ended responses. If the survivors had indicated “I do not know or remember”, the reply was disregarded, unless written replies on the questionnaire gave enough information to reclassify the response. In total, 65 replies were disregarded regarding induced puberty, 11 regarding TRT and 0 regarding

biological children. Prevalence is indicated as observed  $n/n$  for all yes/no-replies on that item (%).

For sociodemographic characteristics, the participants were asked about their level of education, current occupation, and if they had ever cohabitated with or been married to a partner. For clinical background characteristics, study-specific questions on previous growth hormone injections and ongoing thyroid, cardiac and cholesterol medications were utilized from the survey: Have you ever received injections with growth hormone (No/I do not know or remember/Yes)? During the past 2 years, have you used medication for thyroid function during a minimum of 1 month (No/I do not know or remember/Yes)? During the past 2 years, have you used medication for hypertension or other cardiac medication during a minimum of 1 month (No/I do not know or remember/Yes)? During the past 2 years, have you used medication for high cholesterol during a minimum of 1 month (No/I do not know or remember/Yes)? For current medication use, 0.9–1.1% of respondents had indicated “I do not know” and these responses were disregarded. For previous growth hormone injections somewhat more data was missing (6.2%). Further, the survivors' perception about their poor semen quality was assessed with one study-specific question, namely: Have you received information that you have poor semen quality (No/I do not know or remember/Yes)?

For self-reported depressive symptoms and fatigue, two validated instruments were used. The Swedish version of The Hospital Anxiety and Depression scale (HADS) was used to assess depressive symptoms with a cutoff for clinical symptoms set at >7 points.<sup>16</sup> The Fatigue symptom scale from the Swedish

version of the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) was also used,<sup>17</sup> with higher scores indicating a greater burden of symptoms (range 0–100).

Clinical data on primary cancer diagnoses, dates of diagnoses, cancer treatments, disease relapses and data on therapy for second malignancy was retrieved from the National Quality Registry for Childhood Cancer. However, information about total body irradiation (TBI) was unavailable. For abdominal radiotherapy possibly exposing the testes and for cranial radiotherapy, only local irradiation doses were available. Diagnoses were classified according to the International Classification of Childhood Cancer, 3rd revision.<sup>18</sup> Treatments were categorized by the last author using the Intensity of Treatment Rating scale (ITR-3.0),<sup>19</sup> assigning different disease and/or treatment modalities to one of the four intensity levels (ranging from minimally intensive to most intensive).

## 2.4 | Statistical analyses

For continuous variables, data is presented as median (range), as all data was not normally distributed. Categorical data is presented as frequencies and percentages. Group comparisons of the background variables were performed using the Mann–Whitney *U*-test and Pearson  $\chi^2$ -test.

To explore background and clinical characteristics associated with the outcome variables, three binary logistic regression analyses were conducted. The independent variables included treatment-related variables (previous chemotherapy, local abdominal radiotherapy potentially exposing the testes, cranial radiotherapy, HSCT; yes/no) and age at diagnosis. In relevant analyses, age at study and partner status (whether the participant had ever been married or cohabitated with a partner; yes/no) were also included. These predictors were selected a priori based on their theoretical significance. Cancer diagnosis and classification of treatment intensity (ITR-3.0) were not included in the regression analyses due to their strong correlation with the cancer treatment variables. Statistical calculations were performed using IBM SPSS Statistics 28.0. All tests of significance were two-sided ( $p < .05$ ).

## 3 | RESULTS

### 3.1 | Sociodemographic characteristics

Characteristics for the 1212 male participants are presented in Table 1. The median age of the survivors at the time of the study was 29 years. They were a minimum of 1 year and a maximum of 37 years post-diagnosis (median 21). The majority of survivors had a secondary or tertiary education (92.0%) and were either working or studying full- or part-time, or on parental leave (89.4%). Almost 60% of the survivors had cohabitated with a partner or been married.

**TABLE 1** Characteristics of the 1212 male childhood cancer survivors.

Sociodemographic variables	Median (range)
Age at diagnosis, years	7 (0–17)
Age at study, years	29 (19–40)
Follow up time since diagnosis, years	21 (1–37)
Age at study, years	<i>n</i> (%)
19–25	371 (30.6%)
26–30	328 (27.1%)
31–35	270 (22.3%)
36–40	243 (20.0%)
Country of birth	
Sweden (vs other)	1156/1206 (95.9%)
Partner status	
Ever cohabitated or been married	714/1200 (59.5%)
Highest level of education (ongoing or finished)	
High school	51/1207 (4.2%)
Secondary level	588/1207 (48.7%)
Tertiary level	523/1027 (43.3%)
Other	45/1207 (3.7%)
Occupation	
Full-time employment/parental leave	802/1209 (66.4%)
Part-time employment	91/1209 (7.5%)
Student	187/1209 (15.5%)
Unemployed	48/1209 (4.0%)
Sick leave, early retirement	72/1209 (5.9%)
Other	9/1209 (0.7%)
Self-reported clinical variables	
Growth hormone injections	128/1118 (11.4%)
Thyroid hormone medication	123/1183 (10.4%)
Cholesterol medication	23/1177 (2.0%)
Hypertension/cardiac medication	51/1182 (4.3%)
Depressive symptoms, above cut-off <sup>a</sup>	185/1197 (15.5%)
Fatigue score, median (range) <sup>b</sup>	22.2 (0–100), <i>n</i> = 1195

Note: Data is presented as median (range) or *n* (%). In case of missing values, the total number of responses are indicated in the table.

<sup>a</sup>HADS, The Hospital Anxiety and Depression scale.

<sup>b</sup>EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Questionnaire.

### 3.2 | Clinical characteristics

Table 2 presents the outcome variables by diagnosis and treatment modality. Hematological cancers were the most common diagnosis, accounting for 50.7% of the cases, while the most common treatment modality was moderately intensive (Table 2). Of the 1212 male participants, 17 (1.4%) had undergone a uni- or bilateral orchiectomy due to gonadal tumors.

### 3.3 | Hormone-induced puberty

Of the 1128 survivors who had replied to this question, 43 (3.8%) had received hormone-induced puberty (Table 2). In the majority of cases (32/43, 74.4%) hormone-induced puberty was combined with growth hormone treatment. In a logistic regression model [ $\chi^2(5) = 22.74, p < .001$ ] receiving hormone treatment to

induce puberty was significantly associated with HSCT, local cranial radiotherapy and younger age at diagnosis (Table 3). However, two subgroups with slightly different outcomes were found within this group.

Of the 43 men with induced puberty, 20 men reported ongoing TRT. Compared to the group with neither induced puberty nor ongoing TRT [ $\chi^2(5, n = 1058) = 18.65, p = .002$ ], having both hormone

**TABLE 2** Outcome variables per diagnostic group and per treatment modality for the young adult male survivors of childhood cancer.

	n (%)	Age, median	Outcome variables		
			Induced puberty	TRT	Biological children
All diagnoses	1212 (100%)		43/1128 (3.8%)	71/1184 (6.0%)	342/1212 (28.2%)
Hematological cancers (median age: 29 years)					
Acute lymphoblastic leukemia	330 (27.2%)	29	14/300 (4.7%)	25/324 (7.7%)	104/330 (31.5%)
Standard/intermediate risk	233 (70.6%)	29	9/216 (4.2%)	14/230 (6.1%)	80/233 (34.3%)
High risk	97 (29.4%)	29	5/84 (6.0%)	11/94 (11.7%)	24/97 (24.7%)
Myeloid leukemia	47 (3.9%)	27	2/41 (4.9%)	7/46 (15.2%)	7/47 (14.9%)
Lymphoma	198 (16.3%)	29	3/188 (1.6%)	8/192 (4.2%)	53/198 (26.8%)
Non high stage	161 (81.3%)	30	3/154 (1.9%)	8/158 (5.1%)	48/161 (29.8%)
High stage	37 (18.7%)	28	0/34 (0%)	0/34 (0%)	5/37 (13.5%)
Histiocytosis	40 (3.3%)	29.5	2/36 (5.6%)	1/40 (2.5%)	13/40 (32.5%)
Neuroblastoma, sarcoma, gonadal tumors (median age: 28 years)					
Neuroblastoma	39 (3.2%)	28	0/37 (0%)	0/38 (0%)	10/39 (25.6%)
Non high stage	25 (64.1%)	28	0/24 (0%)	0/25 (0%)	7/25 (28.0%)
High stage	14 (35.9%)	25	0/13 (0%)	0/13 (0%)	3/14 (21.4%)
Sarcoma	130 (10.7%)	28	4/126 (3.2%)	6/129 (4.7%)	37/130 (28.5%)
Germ cell and gonadal tumors	43 (3.5%)	29	1/42 (2.4%)	2/43 (4.7%)	16/43 (37.2%)
Other non-CNS tumors (median age: 30 years)					
Renal tumors	62 (5.1%)	29	0/58 (0%)	0/62 (0%)	21/62 (33.9%)
Non high stage	44 (71.0%)	27.5	0/42 (0%)	0/44 (0%)	11/44 (25.0%)
High stage	18 (29.0%)	32.5	0/16 (0%)	0/18 (0%)	10/18 (55.6%)
Hepatic tumors	14 (1.2%)	29.5	0/14 (0%)	0/13 (0%)	2/14 (14.3%)
Retinoblastoma	20 (1.7%)	26.5	1/20 (5.0%)	0/20 (0%)	5/20 (25.0%)
Carcinoma	13 (1.1%)	26	2/13 (15.4%)	0/13 (0%)	3/13 (23.1%)
Miscellaneous tumors	9 (0.7%)	32	0/8 (0%)	0/9 (0%)	3/9 (33.3%)
CNS tumors (median age: 30 years)					
Low-malignant CNS tumors	177 (14.6%)	30	7/170 (4.1%)	8/173 (4.6%)	49/177 (27.7%)
Malignant CNS tumors	90 (7.4%)	31	7/75 (9.3%)	14/82 (17.1%)	19/90 (21.1%)
Treatment modality					
Intensity of treatment (ITR-3)					
Minimally intensive	118 (9.7%)		2/113 (1.8%)	0/117 (0%)	44/118 (37.3%)
Moderately intensive	613 (50.6%)		16/582 (2.7%)	19/601 (3.2%)	199/613 (32.5%)
Very intensive	312 (25.7%)		14/284 (4.9%)	20/301 (6.6%)	79/312 (25.3%)
Most intensive	169 (13.9%)		11/149 (7.4%)	32/165 (19.4%)	20/169 (11.8%)
Chemotherapy	887/1207 (73.5%)		32/817 (3.9%)	61/866 (7.0%)	233/887 (26.3%)
Any local irradiation	262 (21.6%)		15/238 (6.3%)	26/254 (10.2%)	71/262 (27.1%)
Local cranial radiotherapy	141 (11.6%)		10/122 (8.2%)	19/134 (14.2%)	38/141 (27.0%)
Local abdominal radiotherapy	20 (1.7%)		1/19 (5.3%)	1/20 (5.0%)	7/20 (35.0%)

(Continues)

TABLE 2 (Continued)

Surgery	411 (33.9%)	15/382 (3.9%)	24/397 (6.0%)	109/411 (26.5%)
HSCT with or without TBI	99 (8.2%)	9/82 (11.0%)	29/96 (30.2%)	9/99 (9.1%)
Allogeneic	73 (6.0%)	8/58 (13.8%)	25/72 (34.7%)	9/75 (12.0%)
Autologous	26 (2.1%)	1/25 (4.0%)	5/26 (19.2%)	0/26 (0%)
Relapse therapy	116 (9.6%)	6/108 (5.6%)	13/114 (11.4%)	22/116 (19.0%)
Therapy for second malignancy <sup>a</sup>	9 (0.7%)	0/8 (0%)	2/8 (25.0%)	2/9 (22.2%)

Note: Diagnostic groups were based on the International Classification of Childhood Cancer, 3rd revision, but some groups were combined due to a low number of observations. There were some missing data for most of the outcome and clinical variables. Prevalence is indicated as observed  $n/n$  for all yes/no-replies on that item (%).

Abbreviations: CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; TRT, testosterone replacement therapy.

<sup>a</sup>The data was collected from the National Quality Registry for Childhood Cancer and, hence, only includes therapy for second malignancies diagnosed before the age of 17 years.

TABLE 3 Logistic regression analyses of the three outcome variables.

Predictors	Outcome variables					
	Induced puberty ( $n = 1123$ )		TRT ( $n = 1179$ )		Biological children ( $n = 1195$ )	
	OR (95% CI)	$p$	OR (95% CI)	$p$	OR (95% CI)	$p$
Chemotherapy	0.86 (0.41–1.80)	.689	1.33 (0.64–2.77)	.442	1.01 (0.71–1.44)	.946
Local cranial radiotherapy	3.08 (1.44–6.55)	.004	4.19 (2.23–7.86)	<.001	0.76 (0.45–1.28)	.296
Local abdominal radiotherapy	0.85 (0.10–7.03)	.881	0.37 (0.05–3.05)	.355	0.92 (0.27–3.12)	.891
HSCT with or without TBI	4.54 (1.96–10.49)	<.001	12.99 (7.10–23.78)	<.001	0.33 (0.15–0.74)	.007
Age at diagnosis, years	0.92 (0.86–0.98)	.008	0.99 (0.94–1.04)	.597	0.99 (0.96–1.02)	.428
Age at study, years	NA	NA	1.02 (0.97–1.06)	.521	1.21 (1.17–1.25)	<.001
Ever cohabitated	NA	NA	NA	NA	58.64 (21.44–160.39)	<.001

Note: For all outcome variables and all predictors except for age: 0 = no, 1 = yes. There were some missing data for most of the outcome and predictor variables. The number of responses analyzed in each regression analysis is stated beneath the outcome variable.

Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplantation; NA, not applicable; OR, odds ratio; TRT, testosterone replacement therapy.

induced puberty and ongoing TRT was significantly associated with HSCT (OR 10.50, 95% CI: 3.40–32.38,  $p < .001$ ) and younger age at diagnosis (OR 0.90, 95% CI: 0.82–0.99,  $p = .027$ ), but not with local cranial radiotherapy. For men with hormone-induced puberty and ongoing TRT, it was less common to have a partner [15.0% vs 50.0%,  $\chi^2 (1, n = 42) = 5.78, p = .016$ ] and a biological child [0% vs 27.3%,  $\chi^2 (1, n = 42) = 6.36, p = .012$ ] compared to men who had received induced puberty but had no ongoing TRT ( $n = 22$ ). There were no significant group differences in age [29.5 vs 28.5 years,  $p = .990$ ], the prevalence of men who were currently working/studying [80.0% vs 81.8%,  $\chi^2 (1, n = 42) = 0.02, p = .881$ ], depressive symptoms [15.0% vs 27.3%,  $\chi^2 (1, n = 42) = 0.94, p = .333$ ] or the fatigue symptom score [44.4 vs 27.8,  $p = .770$ ].

### 3.4 | Testosterone replacement therapy

Of 1184 survivors, 71 (6.0%) indicated current use of TRT (Table 2). In a logistic regression model [ $\chi^2 (6) = 85.34, p < .001$ ] ongoing TRT was

significantly associated only with HSCT and local cranial radiotherapy (Table 3). Despite being of similar age, survivors on TRT had more social and clinical late effects compared to survivors without TRT (Table 4).

### 3.5 | Biological children

Of all 1212 male survivors, 342 (28.2%) had a biological child (Table 2). In the logistic regression model [ $\chi^2 (7) = 547.94, p < .001$ ] having a biological child was significantly associated with having had a partner, older age at study and no HSCT treatment (Table 3). In total, 118 survivors reported that they had received information that they had poor semen quality. Poor semen quality was reported particularly by men with the most intensive treatments, such as HSCT and those with relapse therapies. For the patients who had indicated their age at which poor semen quality was stated ( $n = 108$ ), the majority ( $n = 86$ ) were 18 years or older at the time (md = 22.5, range 12–38 years). Interestingly,

**TABLE 4** Sociodemographic and clinical variables of the young adult male survivors of childhood cancer with ongoing testosterone replacement therapy compared to non-substituted survivors.

	TRT (n = 71)	No TRT (n = 1113)	p <sup>a</sup>
Sociodemographic variables			
Age at diagnosis, years	7 (0–17)	7 (0–17)	.609
Age at study, years	29 (19–40)	29 (19–40)	.751
Follow up time since diagnosis, years	23 (3–35)	21 (1–37)	.772
Ever cohabitated or been married	26/71 (36.6%)	678/1101 (61.6%)	<.001
Biological children	7/71 (9.9%)	330/1113 (29.6%)	<.001
Currently working/studying	58/71 (81.7%)	1003/1101 (91.1%)	.009
Highest level of education			.238
High school	4/67 (6.0%)	43/1069 (4.0%)	
Secondary level	39/67 (58.2%)	534/1069 (50.0%)	
Tertiary level	24/67 (35.8%)	492/1069 (46.0%)	
Self-reported clinical variables			
Prior induced puberty	20/58 (34.5%)	22/1065 (2.1%)	<.001
Growth hormone injections	43/65 (66.2%)	80/1045 (7.7%)	<.001
Thyroid hormone medication	39/69 (56.5%)	80/1107 (7.2%)	<.001
Cholesterol medication	6/69 (8.7%)	17/1103 (1.5%)	<.001
Hypertension/cardiac medication	6/69 (8.7%)	44/1105 (4.0%)	.060
Depressive symptoms, above cut-off <sup>b</sup>	20/70 (28.6%)	161/1112 (14.5%)	.001
Fatigue score <sup>c</sup>	44.4 (0–100) (n = 71)	22.2 (0–100) (n = 1110)	<.001

Note: Data is presented as median (range) or n (%). Information on testosterone replacement therapy was missing for 28 participants.

Abbreviation: TRT, testosterone replacement therapy.

<sup>a</sup>p values were derived from the Mann–Whitney U-test for continuous data and  $\chi^2$ -test for categorical data.

<sup>b</sup>HADS, The Hospital Anxiety and Depression scale.

<sup>c</sup>EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Questionnaire.

33 (28.0%) of the men with self-reported poor semen quality had a biological child.

## 4 | DISCUSSION

The present study combined national registry and self-report survey data from 1212 adult male survivors of childhood cancer. To our knowledge, this study is the most comprehensive population-based study on self-reported hormonal treatments and the ability to father a biological child in long-term survivors of childhood cancer from the most recent treatment era. All men aged 19–40 years who had survived childhood cancer diagnosed between 1981 and 2017 in Sweden were invited to participate. In this nationwide cohort, 3.8% of the survivors had undergone hormonal treatment to induce puberty, 6.0% indicated ongoing TRT and 28.2% reported having a biological child. The endocrine and reproductive sequelae were particularly associated with HSCT and local cranial radiotherapy. Men with TRT were more likely to suffer from additional sequelae, such as increased fatigue and depressive symptoms, lower likelihood of having a partner, children or an occupation, and more endocrine and cardiovascular late effects.

In all, 3.8% of the participants reported that they had undergone hormone therapy to induce puberty. Treatment with HSCT and local cranial radiotherapy were the most significant risk factors for hormone-induced puberty. Of the HSCT recipients, 11.0% received hormone induction. This finding is well in line with a prior review on pediatric HSCT recipients, where 11.8% of the patients underwent hormone therapy to induce puberty (calculated from Table 2, 55 out of 466 participants).<sup>20</sup> However, even higher prevalence rates have been reported after pediatric allogeneic HSCT, with mainly TBI-based conditioning regimens, where hormone induction therapy was received by as many as 21.1% of the patients.<sup>21</sup> In the present national sample, for the majority of patients who underwent hormone-induced puberty, testosterone was combined with growth hormone therapy. This observation suggests that besides for pituitary dysfunction, growth hormone therapy may have been used with other indications such as promoting pubertal growth. Reassuringly, half of the survivors who had undergone hormone therapy to induce puberty had no ongoing TRT at young adult age and showed a good prognosis for partnering and having biological children. The slightly higher prevalence of depressive symptoms (n.s.) may indicate a need for follow up of current testosterone levels. However, another half of the survivors with hormone-induced puberty had ongoing TRT, indicating

long-term Leydig cell failure. Men with HSCT were 11 times more likely to have a continued need of TRT after induction. Furthermore, younger age at diagnosis was identified as a significant risk factor. Previous research has observed that undergoing HSCT during the pre-pubertal stage is associated with a higher likelihood of requiring TRT in the future.<sup>21</sup> This high-risk group of males with hormone-induced puberty and ongoing TRT also reported significant social sequelae. None had conceived a biological child and only 15.0% had ever lived with a partner.

The majority of TRT were initiated in survivors who had undergone spontaneous pubertal development, suggesting a decline in Leydig cell function during early adulthood. The 6.0% prevalence of TRT in the present study is comparable to the 10.7% prevalence in a Southern Sweden study cohort after a slightly longer median follow up time of 24 years.<sup>22</sup> Most studies do not report the prevalence of TRT, but indicate hypogonadism based on laboratory measurements. In the St. Jude Lifetime Cohort Study, 6.7% of cancer survivors had Leydig cell dysfunction in laboratory measurements at a similar time point as in the present study (median age 30.8 and 22.0 years since cancer diagnosis).<sup>23</sup> However, of these, only 37.3% were treated with testosterone, leading to a lower prevalence of TRT (2.5%) than in the present study. The consideration of TRT is always based on individual needs and can thus be considered a more robust indicator of Leydig cell failure than a single abnormal laboratory measurement. In the present study, the odds for TRT were 13-fold after HSCT and 4-fold after local cranial radiotherapy. The observed 30.2% prevalence of TRT after HSCT (with and without TBI) is very high but comparable to the 23.4–24.5% previously reported after pediatric allogeneic HSCT.<sup>20,21</sup> In the former study, HSCT recipients who had a TBI based conditioning therapy had a 35.5% prevalence of TRT and those with a non-TBI based conditioning 18.8% (calculated from Table 2).<sup>20</sup> These results are consistent with the recent International Guideline Harmonization Group recommendation that men who have undergone HSCT with TBI based conditioning or received  $\geq 12$  Gy of radiotherapy potentially exposing the testes should receive surveillance of testosterone concentrations at clinically appropriate intervals.<sup>6</sup>

In line with previous findings on the relationship between TRT and endocrine/cardiovascular risk factors,<sup>10,12</sup> survivors with TRT in the present study had 7–8 times higher prevalence of other hormonal deficiencies (prior growth hormone, ongoing thyroid medication) compared to survivors without ongoing TRT. Further, survivors with TRT had 2–5 times higher prevalence of ongoing medication for cardiovascular risk factors. The increased cardiovascular risk among survivors with ongoing TRT supports advocacy of a healthy lifestyle as well as active follow-up and intervention for cardiovascular risk factors during early adulthood.<sup>11</sup> Additionally, testosterone deficiency has previously been associated with an increased risk for fatigue, depressive symptoms and poor sexual function.<sup>7,10,13</sup> In the present study, approximately a third of the survivors with TRT had never

cohabitated with a partner and only one in 10 had a biological child, despite being of similar age as survivors without TRT. Almost a third reported clinically significant depressive symptoms, which was twice as many as in the rest of the population of survivors. The overall prevalence of depressive symptoms exceeding the clinical cut-off was in this national sample similar to that in the general population of men under the age of 40 years.<sup>24</sup> Similarly, the fatigue score in men with TRT was twice as high as in the rest of the population of survivors and exceeded the cut-off score set for young adult cancer patients with need of support.<sup>25</sup> Overall, the fatigue score in the whole cohort was somewhat higher compared to the general population of 40–49-year-old men in Sweden.<sup>17</sup> These results suggest that survivors with testicular damage requiring hormonal substitution may suffer from symptoms associated with testosterone deficiency. This could indicate that their substitution is not optimal or has been initiated with delay. In a prior study, Leydig cell dysfunction treated with TRT was associated with e.g., erectile dysfunction and depression in long-term survivors of childhood cancer.<sup>23</sup> Because fatigue and depressive symptoms may reduce help seeking, adult surveillance after HSCT, testicular or cranial radiotherapy might facilitate timely detection of testosterone deficiency.

Male survivors of childhood cancer have a lower probability of paternity compared to the general population.<sup>9,26</sup> Livebirth rates have ranged from 25.3% in a study of patients treated 1970–1999<sup>27</sup> to 39.4% in a more recent population-based study of 35–39-year-old male childhood cancer survivors in Sweden.<sup>26</sup> In the present study, 28.2% of the male survivor population had to date a biological child, with older survivors being more likely to have an offspring. As younger survivors were more likely to decline study participation, this could have increased the prevalence of biological children in the sample. On the other hand, since the sample consists of young adults many have not yet tried to conceive a child. Only 9.1% of men who had received an HSCT had a biological child. This is consistent with a previous report where 9.2% of men with allogeneic HSCT had sired a pregnancy after a median follow up time of 18 years.<sup>21</sup> Abdominal irradiation was not associated with these endocrine or offspring-related outcomes, which is contrary to our observation in a recently reported population-based female cohort.<sup>28</sup> Since only 20 survivors had abdominal irradiation, this analysis may have been underpowered. We also lacked information about scatter doses to the testes. Having a biological child was in the regression analysis most strongly associated with the ability to find a partner. As childhood cancer survivors are less likely to partner,<sup>9</sup> support for social and psychosexual development is essential also for later paternity outcomes.

In all, 118 men indicated that they had received information about poor semen quality. Most had undergone semen analysis in adulthood, suggesting that referrals had mainly been done for men with pregnancy prospects. This is further supported by the high percentage of men with biological children in this group. In

a minority, semen analyses were undertaken in adolescence, possibly as part of surveillance of testicular function and estimation of post-treatment infertility. Nevertheless, 28.0% of the men who reported poor semen quality had a biological child, which is equal to the percentage in the total study population. Since the severity of the poor semen quality is not known, one must assume that these men were not azoospermic and may, hence, have been able to conceive, some presumably with the help of assisted reproductive technology. Survivors may also have had the wrong perception about the severity of the poor semen quality and its fertility implications. A prior study on male childhood cancer survivors reported similar results where 37% of men with self-reported infertility were able to father a biological child.<sup>3</sup> Previously, both under- and overreporting of perceived infertility risk by male adult childhood and young adult cancer survivors have been reported.<sup>29,30</sup> Semen quality analysis and fertility counseling are psychologically complicated matters. The information about poor semen quality is bound to affect the survivor's perspective of his fertility and may affect his identity and sense of masculinity.<sup>31,32</sup> Consequently, counseling should be comprehensive and clear to avoid misconceptions.

#### 4.1 | Methodological considerations

This population-based sample of male childhood and adolescent cancer survivors was identified from a national quality registry with clinical treatment data available. The survey had a fair response rate. Participants were older and had a longer follow-up time since diagnosis than non-participants. No other response bias regarding clinical variables was detected, and hence, except age, the sample seems representative for the population.

This study had a cross-sectional design and timing of the outcome variables (e.g., the age when TRT was initiated) was not assessed. Further, since outcome variables were based on self-reported data, there was no laboratory data to confirm testosterone or gonadotrophin levels or sperm quality. Hence, it was not possible as part of this study to e.g., analyze how many survivors had a suboptimal testosterone substitution, lacked substitution despite low testosterone levels or were azoospermic. Further, respondents who have children as a result of fertilization by donor sperm may or may not have interpreted that as having a biological child. Due to the lack of comprehensive information on possible use of assisted reproductive methods, this could not be controlled for.

The major limitations of this study were the lack of the following information: specific doses of alkylating agents, the use of TBI as conditioning therapy for HSCT, local gonadal irradiation use and the scatter doses to the testes from abdominal irradiation. Chemotherapy was not associated with any of the outcome variables in the regression analyses. This result reflects the fact that chemotherapy was used as a dichotomous variable, and we lacked the possibility to identify the gonadotoxic high-dose alkylating

treatments from less toxic alternatives. Also, it is important to note that HSCT is a surrogate for treatment intensity and associated with, for example, TBI, high cumulative doses of alkylating agents, and relapsed disease.

#### 4.2 | Clinical implications

In this recently treated patient cohort of male childhood cancer survivors, 6.0% had ongoing TRT in young adulthood. Particularly men who had undergone cranial radiotherapy or HSCT and those who were younger at diagnosis had increased odds of hormone-induced puberty and reported more ongoing TRT, indicating a need of long-term follow up. TRT was associated with self-reported treatment with other hormones, cholesterol and cardiac medication. These associated morbidities can predispose survivors to increased cardiovascular risk, early aging and premature death. Survivors with TRT also had a reduced likelihood of forming a partnership, experiencing paternity or having a current occupation, and they reported increased fatigue and depressive symptoms, potentially decreasing their quality of life. Hence, long-term endocrine and cardiovascular follow up, timely initiated effective TRT and psychosocial support should be ensured even decades after survival.

#### AUTHOR CONTRIBUTIONS

Conceptualisation: Jahnukainen, Lampic, Wettergren, Haavisto; Data curation: Lähteenmäki, Jahnukainen, Lampic, Wettergren; Formal analysis: Haavisto; Funding acquisition: Jahnukainen, Lampic, Wettergren; Investigation: Lähteenmäki, Jahnukainen, Lampic, Wettergren; Methodology: Jahnukainen, Haavisto, Lähteenmäki, Lampic, Wettergren; Project administration: Jahnukainen, Lampic, Wettergren; Resources: Lampic, Wettergren; Software: N/A; Supervision: N/A; Validation: Haavisto, Jahnukainen; Visualisation: Haavisto, Jahnukainen; Writing—original draft: Haavisto, Jahnukainen; Writing—review and editing: All authors. The study reported in the article has been performed by the authors, unless clearly specified in the text.

#### ACKNOWLEDGEMENTS

We would like to thank all survivors participating in this study for their valuable contributions. We would also like to thank the Swedish National Quality Registry for Childhood Cancer for identifying potential participants for our study and providing the data.

#### FUNDING INFORMATION

The Swedish Cancer Society (CAN 2013/886), the Swedish Childhood Cancer Foundation (TJ2014-0050, TJ2019-0045, PR2014-0177, PR2016-0075, PR2017-0037 and KP2020-0012), the Swedish Research Council for Health, Working Life and Welfare (2014-4689, 2019-00839), the Swedish Research Council (2017-01530), the Birgitta and Carl-Axel Rydbeck's Research Grant for Paediatric Research (2020-00335 and 2021-00079), The Cancer Foundation Finland, and the Finnish Foundation of Paediatric Research.

## CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data used in the present study was population-based register data from the National Quality Registry for Childhood Cancer database as well as self-report surveys. Data is available upon reasonable request to the corresponding author.

## ETHICS STATEMENT

The Regional Ethical Review Board in Stockholm, Sweden, granted ethical approval (2015/1609-31; 2018/2688-32; 2019/01066; 2019/04603). Informed consent was obtained from all participants.

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## SUPPORTING INFORMATION

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

**How to cite this article:** Haavisto A, Lampic C, Wettergren L, Lähteenmäki PM, Jahnukainen K. Reproductive late effects and testosterone replacement therapy in male childhood cancer survivors: A population-based study (the Fex-Can study). *Int J Cancer*. 2024;1-11. doi:[10.1002/ijc.34890](https://doi.org/10.1002/ijc.34890)