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Prevalence and predictors for fertility-related distress among 1010 young adults 1.5 years following cancer diagnosis – results from the population-based Fex-Can Cohort study

Kenny A. Rodriguez-Wallberg[a,b], Johan Ahlgren[c,d], Karin E. Smedby[e,f], Jessica R. Gorman[g], Kristina Hellman[h], Roger Henriksson[i], Olof Ståhl[j], Lena Wettergren[k,l]* and Claudia Lampic[k,l,m]*

[a]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [b]Department of Reproductive Medicine, Division of Gynecology and Reproduction, Karolinska University Hospital, Stockholm, Sweden; [c]Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [d]Regional Cancer Centre, Mid-Sweden, Uppsala, Sweden; [e]Department of Medicine Solna, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden; [f]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [g]College of Public Health and Human Sciences, Oregon State University, Corvallis, OR, USA; [h]Department of Gynecologic Cancer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; [i]Department of Radiation Science and Oncology, Umeå University, Umeå, Sweden; [j]Department of Oncology, Skåne University Hospital, Lund, Sweden; [k]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [l]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; [m]Department of Psychology, Umeå University, Umeå, Sweden

ABSTRACT

Background: Cancer treatment during reproductive ages may negatively impact fertility and there is a need of firm knowledge about the prevalence and predictors of fertility-related distress. The aim was to examine fertility-related distress in a population-based sample of young women and men recently treated for cancer and to identify predictors for this outcome.

Material and methods: This nationwide cohort study included 1010 individuals (694 women and 316 men), mean age 34.5 ± 4.9 and 32.1 ± 5.5, respectively, diagnosed with breast, cervical, ovarian, testicular cancers, brain tumors or lymphoma at ages 18–39 in Sweden. Participants completed a survey 1.5-year post-diagnosis to assess fertility-related distress (RCAC), emotional distress (HADS) and self-efficacy, as well as sociodemographic and clinical factors and fertility preservation. Logistic regression was used to examine associations between explanatory factors and high fertility-related distress (RCAC subscale mean >4).

Results: Many participants (69% of women and 47% of men) had previous children and about half reported a wish for future children. High fertility-related distress was more prevalent among women (54%) than men (27%), and women were more likely than men to report distress concerning all but one RCAC dimension after adjustment for sociodemographic factors. Use of fertility preservation was unevenly distributed (15% of women and 71% of men) and was not associated with decreased fertility-related distress. In multivariable logistic regression models, a wish for future children, being single, not having previous children, symptoms of anxiety and low self-efficacy regarding one's ability to handle threats of infertility were associated with high fertility-related distress.

Conclusion: This nationwide study found a high prevalence of fertility-related distress in young women and men recently treated for cancer and identified sociodemographic and psychological predictors. Fertility preservation was not found to act as a buffer against fertility-related distress, indicating the continuous need to identify strategies to alleviate fertility distress following cancer.

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Cohort study; fertility distress; parenthood concerns; cancer survivorship; young adults

Background

Globally, more than 1 million adults younger than 40 years of age are diagnosed with cancer each year [1,2]. Survival rates for this group have steadily improved over the last decades [3], however, these young patients suffer an increased risk of premature mortality and morbidity in comparison to the general population [4]. A cancer diagnosis in young adulthood also disrupts major life milestones, such as starting a career, finding a partner, and having children [5,6].

It is acknowledged that fertility in survivors of cancer may be directly threatened when the malignancies arise in the reproductive organs, but also by gonadotoxic effects of chemotherapy or negative effects of radiotherapy or surgery affecting the reproductive tract during cancer treatment [7–9]. Large epidemiological studies have shown that cancer survivors diagnosed before the age of 40 are less likely to achieve pregnancy [10] or to ever have biological children [11] when compared to unaffected controls. Unfortunately, fertility potential following cancer treatment cannot be

CONTACT Claudia Lampic claudia.lampic@umu.se Department of Psychology, Umeå University, Mediagränd 14, Umeå SE-90187, Sweden
*Joint last authorship

accurately predicted on an individual level yet, even if reliable biomarkers of ovarian reserve have been developed [12]. International guidelines recommend that discussions about fertility preservation (FP) options, such as cryopreservation of gametes and gonadal tissue, should take place when young adults (YAs) are planned for cancer treatment that will potentially affect their fertility [13,14].

Fertility-related concerns among cancer patients do not only include worry about fertility potential, but also parenthood-related issues, such as living long enough to raise children, the risk of genetic predisposition of cancer in the offspring, and disclosing fertility problems to a partner [15]. A fear of infertility, or knowing that one's fertility has been compromised, has been found to negatively impact the life course, gender identity, and long-term psychological well-being of female and male survivors [16]. Several studies report on lower levels of quality of life associated to fertility distress in cancer survivors, particularly in females [17–20] and those with depressive symptoms [18–20]. Survivors with no previous children [17] and a wish for future children [18,21,22] are at increased risk for high levels of fertility-related distress. Young age has been associated with increased levels of fertility distress in some studies [21,23], but not all [22]. In addition, findings from qualitative research have suggested that the use of FP may function as a buffer against fear of infertility among both female and male survivors [24–26]. A systematic review of fertility-related psychological distress in cancer patients diagnosed at reproductive age identified 47 studies published between 1999 and 2018 in high-income countries [27]. The results showed that fertility-related distress was persistent through survivorship and that the prevalence of fertility-related concerns varied markedly between individual studies, much depending on inclusion criteria (e.g., time since diagnosis) and sampling strategies (e.g., social media outreach).

Previous research has to a large extent relied on self-selected sampling [17,21,28,29] or inclusion of clinical groups with specific fertility needs or undergoing FP [30]. Therefore, the present population-based study aimed to expand knowledge by determining the prevalence of fertility-related distress in young women and men diagnosed with cancer and to identify sociodemographic, clinical, and psychological factors associated with fertility-related distress.

Material and methods

Participants and study design

The population-based prospective Fex-Can Cohort study was designed to investigate fertility-related distress and sexual dysfunction in YAs diagnosed with cancer, as reported in the study protocol [31]. The present study concerns the cross-sectional assessment of fertility-related distress 1.5 years following cancer diagnosis. Ethical approval for the study was granted by the Regional Ethical Review Board in Stockholm (record no: 2013/1746-31/4; 2014/2244-32; 2017/916-32; 2017/1416-32).

Sample

Inclusion criteria were having received a diagnosis of breast-, cervical, ovarian-, or testicular cancer, lymphoma or brain tumor at age 18–39 between January 2016 and August 2017 in Sweden. The selection of diagnoses was based on diseases and/or treatments having potentially negative consequences on future fertility or sexual life, and participants were identified *via* the Swedish National Cancer Quality Registers. Exclusion criteria were lack of valid address and inability to complete the survey due to self-reported cognitive impairment, poor health, or non-ability to read and/or understand Swedish language.

Data collection

Data collection was performed during 2017 and 2018, approximately 1.5 years after cancer diagnosis. Patient-reported outcomes and background data were collected using a self-administered survey. Clinical and disease-specific variables were extracted from the registers.

Measures

Fertility-related distress

Fertility-related distress was assessed using the multidimensional Reproductive Concerns After Cancer (RCAC) scale [15,32] to examine a range of concerns related to fertility and parenthood following cancer [33]. The scale includes 18 items in the six dimensions: (1) Fertility potential (concerns about one's ability to become a biological parent), (2) Partner disclosure (concerns related to telling a partner about possibly impaired fertility), (3) Child's health (concerns for an existing or future biological child's health in relation to the parent's previous cancer diagnosis and treatment, specifically genetic risks), (4) Personal health (concerns related to fear of not being able to or living long enough to raise a child), (5) Acceptance (the extent of reconciliation with not being fertile or not having biological children), and (6) Becoming pregnant (concerns related to efforts involved in achieving a pregnancy). High fertility-related distress was defined as a dimension mean score >4, as recommended by Gorman et al. [33]. The RCAC is available in a female and male version, and has demonstrated satisfactory internal consistency and construct validity [28,32,34]. The female version of the Swedish RCAC showed acceptable convergent and known-groups validity, but satisfactory reliability was not achieved for all dimensions [35]. The male version of the Swedish RCAC was well accepted by young men with testicular cancer and showed satisfactory internal consistency [23] but has not undergone extensive psychometric evaluation.

Anxiety and depression

Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) [36]. The subscales for anxiety and depression, respectively, have been reported to have satisfactory internal consistency and good to very good concurrent validity [37].

Self-efficacy

Self-efficacy related to fertility was assessed by five study-specific items measuring confidence in one's own ability to handle situations, thoughts and emotions related to the threat of infertility, e.g., 'I feel confident that I can handle negative thoughts and emotions about my ability to have children'. Internal consistency was high (Cronbach's alpha 0.81), with higher values indicating higher levels of self-efficacy (scale range 1–4).

Sociodemographic background variables

Background variables included sociodemographic information on country of birth, educational achievement, partner relationship, children, and current wish for children or additional children. In addition, self-report on received fertility-related information and the use of FP procedures was included.

Registry data

Clinical data were collected from the National Cancer Quality Registers for the diagnoses eligible for this study. Based on diagnosis, clinical stage, and type of treatment all patients were classified according to the Intensity Treatment Rating Scale for YAs (ITR-YA) [38].

Data analysis

Sociodemographic and clinical characteristics of men and women were compared using Student's *t*-test and Chi-Square statistics. Effect sizes were calculated to indicate the clinical significance of differences in means using Cohen's d, interpreted as small (0.20–0.49), medium (0.50–0.79), and large ($\geq$0.80) effect sizes. The prevalence of high fertility distress is presented for all six dimensions of the RCAC. Differences in fertility-related distress between men and women were tested with logistic regression, adjusted for sociodemographics (age, education, relationship status, having children, and child wish) reported in the survey. To identify factors associated with high fertility-related distress, logistic regression models (separate for females and males) were conducted for each of the six dimensions of the RCAC. The following explanatory factors were selected based on the literature [17–23]: age ($<$30, 30–35, $>$35 years), education (university/no university degree), relationship status (partner/no partner), previous children (yes/no), future child wish (yes/no or uncertain), country of birth (Sweden/other), treatment intensity (very or most intensive/least or moderately intensive), type of cancer (breast/cervical/ovarian/brain/lymphoma/testicular), FP (cryopreservation/no or other), anxiety (continuous), depression (continuous), self-efficacy (continuous). First, each factor was examined in bivariate analyses using simple logistic regression and Chi-Square tests, as appropriate. Factors significantly associated with distress in the respective outcome were thereafter analyzed using multivariable logistic regression. All tests were two-tailed and *p*-values $<$.05 were considered statistically significant.

Results

A total of 1535 men and women with cancer diagnoses identified in the registers met the inclusion criteria. Exclusions were due to a lack of a valid address and self-reported inability to complete the survey ($n = 36$) [39]. Of the remaining eligible individuals approached ($n = 1499$), 1010 (67%) accepted study participation and completed the survey. Comparison between responders and non-responders showed that women overall participated to a higher degree than men ($p < .0001$), that women's participation rate differed by a cancer diagnosis ($p < .0001$) and that male non-responders were significantly younger at the time of diagnosis than male responders ($p = .001$), as previously reported [39].

Sample characteristics

Sociodemographic and clinical characteristics of the study participants are presented in Table 1. The sample included 694 women and 316 men. At the time of the study, approximately 1.5 years post-diagnosis, the age range was 19–41 in the full cohort, with women's mean age 34.5 (SD 4.9) and men's 32.1 (SD 5.5). The most common diagnoses were breast cancer and testicular cancer, which constituted 50% of all women and 63% of all men, respectively. A majority reported being off treatment at the time of the study (71%), with those on treatment most often receiving hormonal treatment. Most participants were born in Sweden and were currently in a partner relationship. Many had children, (47% of the men, 69% of the women) and about half of the participants reported a wish for future children. Most participants reported having received information about the potential impact of the disease and its treatment on future fertility, as previously reported [40]. Among those informed about the impact on fertility, men to a higher degree than women recalled being informed about there being no or some risk to their fertility ($p < .001$). Still, most men (71%) and relatively few women (15%) had cryopreserved gametes or gonadal tissue for FP in connection with cancer treatment.

Prevalence of high fertility-related distress among women and men 1.5 years after diagnosis

Approximately 1.5 years after diagnosis, 54% of the women and 27% of the men reported high fertility-related distress in at least one RCAC dimension (Table 2). The most common areas of distress for both men and women concerned Fertility potential and Child's health. In logistic regression models adjusting for socio-demographic factors (age, education, relationship status, previous children, child wish at study), women were more likely than men to report distress in all RCAC dimensions, except Partner disclosure.

Emotional distress and self-efficacy

Women reported higher mean levels of emotional distress compared to men with regards to symptoms of anxiety (8.6 vs. 6.3, $p < .001$) and depression (5.0 vs. 4.2, $p = .001$). Overall, participants reported moderate to high levels of self-efficacy, but women's mean scores were significantly lower

Table 1. Sociodemographic and clinical characteristics of 1010 young adults participating in the Fex-Can study 1.5 years after cancer diagnosis.

	Women ($n = 694$) *n* (%)	Men ($n = 316$) *n* (%)	Chi-Square	*p*-value
Age at survey				
<30	121 (17)	102 (32)	40.18	<.001
30-35	222 (32)	114 (36)		
>35	351 (51)	100 (32)		
Country of birth				
Other	114 (16)	43 (14)	1.29	.256
Sweden	579 (84)	272 (86)		
Education				
No university degree[a]	275 (40)	174 (55)	20.62	<.001
University degree	417 (60)	142 (45)		
Relationship status				
No partner	106 (15)	71 (22)	7.60	.006
Partner	585 (85)	245 (78)		
Having children				
No	214 (31)	166 (53)	43.15	<.001
Yes	473 (69)	148 (47)		
Child wish at study				
No	254 (37)	141 (45)	6.23	.044
Yes	365 (53)	141 (45)		
Uncertain/don't recall	65 (10)	30 (10)		
Type of cancer				
Breast	349 (50)	0		
Cervical	190 (27)	0		
Ovarian	32 (5)	0		
Brain tumor	66 (10)	57 (18)		
Lymphoma	57 (8)	59 (19)		
Testicular	0	200 (63)		
Intensity Treatment Rating[b]				
Least intensive/extensive	163 (24)	65 (21)	41.70	<.001
Moderately intensive/extensive	151 (22)	121 (39)		
Very intensive/extensive	345 (51)	109 (35)		
Most intensive/extensive	14 (2)	17 (5)		
Current treatment status (at study)				
On treatment[c]	38 (12)	250 (36)	61.83	<.001
Off treatment	276 (88)	438 (64)		
Received any information about impact on fertility				
No	112 (16)	42 (13)	1.383	.501
Unsure	40 (6)	18 (6)		
Yes	538 (78)	254 (80)		
Information about risk of impact on own fertility[d]				
No or some risk	208 (40)	183 (72)	73.87	<.001
High risk	291 (55)	62 (25)		
Don't recall	27 (5)	8 (3)		
Fertility Preservation[e]				
Yes, cryopreservation	101 (15)	223 (71)	314.40	<.001
No/Other FP	590 (85)	91 (29)		

Numbers do not sum up to total due to missing values (<10 for all variables except intensity of treatment with 25 missing values).
[a]Includes elementary school, upper secondary school, folk high school.
[b]Patients classified according to the Intensity of Treatment Rating Scale Young Adult (ITR-YA) (Hedman et al. [38]).
[c]Includes hormonal treatment ($n = 212$), radiation ($n = 17$), chemotherapy ($n = 52$), and other treatments ($n = 48$); participants could report more than one current treatment.
[d]Based on responses from those 526 women and 253 men who recalled having received any information about impact on fertility (excluding missing data from 12 women and 1 man).
[e]Fertility preservation includes cryopreservation of gametes or gonadal tissue; Other FP includes GnRHa, fertility-sparing surgery and unsuccessful attempt to FP.

Table 2. Prevalence of fertility-related distress[a] in the six dimensions of the RCAC scale.

	Women ($n = 694$)		Men ($n = 316$)			
	M (SD)	Score indicating distress *N* (%)	M (SD)	Score indicating distress *N* (%)	OR	95%CI
RCAC						
Fertility potential	3.2 (1.1)	145 (21)	2.7 (1.2)	31 (10)	3.79	2.42–5.93
Acceptance	2.6 (1.1)	88 (13)	2.5 (1.0)	19 (6)	4.26	2.43–7.44
Becoming pregnant	2.9 (0.8)	47 (7)	2.5 (0.9)	12 (4)	1.97	1.00–3.85
Partner disclosure	2.7 (1.0)	53 (8)	2.6 (1.1)	25 (8)	1.63	0.95–2.79
Child's health	3.4 (1.1)	206 (30)	2.7 (1.2)	34 (11)	3.31	2.20–4.98
Personal health	3.2 (0.9)	95 (14)	2.5 (1.0)	17 (5)	2.55	1.47–4.41
≥1/6 dimension above cut-off		372 (54)		85 (27)		

Comparison of women and men 1.5 years after cancer diagnosis in logistic regression models adjusted for socio-demographics[b].
[a]Fertility-related distress defined as mean score >4 for each RCAC dimension (scale range 1–5).
[b]Adjusted for the following variables: age, education, relationship status, having children and child wish.

Table 3. Factors associated with high fertility-related distress[a] in young women 1.5 years following cancer diagnosis.

	Fertility potential		Partner disclosure		Child's health		Personal health		Acceptance		Becoming pregnant	
RCAC dimensions	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95% CI	OR	95%CI
Age at study												
>35 years (ref)												
<30 years	1.24	0.61–2.55	1.52	0.50–4.60			**2.51**	1.10–5.73	**3.04**	1.25–7.41		
30–35 years	0.77	0.42–1.39	1.57	0.61–4.06			**2.47**	1.46–4.18	1.36	0.59–3.16		
Education												
University degree vs No university degree (ref)			**0.40**	0.19–0.86	**0.53**	0.36–0.76						
Relationship status												
Partner vs No partner (ref)			**0.20**	0.09–0.45			1.84	0.81–4.20				
Having children												
Yes vs No (ref)	**0.36**	0.21–0.63	**0.29**	0.12–0.73	**2.95**	1.85–4.71	1.90	0.99–3.62	**0.25**	0.12–0.51	0.76	0.36–1.58
Child wish at study												
Yes vs No/uncertain (ref)	**11.43**	5.12–25.55	1.30	0.55–3.07	1.24	0.85–1.80			**11.74**	3.38–40.77	**2.80**	1.04–7.55
Country of birth												
Sweden vs other (ref)											**0.42**	0.20–0.90
Treatment intensity												
Very/most intensive vs Least/ moderately intensive (ref)					1.10	0.73–1.68	0.90	0.53–1.54	0.60	0.29–1.27		
Type of cancer												
Breast (ref)												
Cervical	0.74	0.38–1.42	1.17	0.45–3.05	**0.36**	0.21–0.61	**0.22**	0.10–0.47	1.28	0.50–3.23		
Ovarian	0.47	0.14–1.65	0.55	0.11–2.74	0.45	0.15–1.35	**0.11**	0.01–0.90	1.73	0.44–6.84		
Brain	1.09	0.43–2.78	0.92	0.23–3.74	0.50	0.24–1.02	**0.30**	0.11–0.83	1.94	0.58–6.46		
Lymphoma	1.05	0.40–2.74	1.43	0.43–4.71	0.97	0.50–1.88	0.57	0.24–1.35	1.28	0.43–3.83		
Fertility Preservation[c]												
Cryopreservation vs No/Other (ref)	**1.96**	1.02–3.77	0.94	0.36–2.46					1.72	0.74–4.00	1.78	0.83–3.79
HADS Anxiety	**1.10**	1.03–1.18	**1.21**	1.08–1.35	**1.12**	1.06–1.18	**1.11**	1.04–1.19	1.01	0.92–1.10	1.09	0.99–1.20
HADS Depression	0.99	0.91–1.07	1.02	0.91–1.14	0.97	0.91–1.03	1.01	0.94–1.10	1.02	0.91–1.13	1.04	0.94–1.16
Self-efficacy	**0.57**	0.39–0.83	**0.54**	0.33–0.88					0.37	0.23–0.60	0.71	0.44–1.12

Results of multivariable logistic regression models, each model including only factors associated with the respective outcome in bivariate analyses.
OR: Odds Ratio; CI: Confidence Interval.
[a]Fertility-related distress defined as mean >4 in RCAC dimensions.
[b]$p = .05$.
[c]'Cryopreservation' includes cryopreservation of gametes/gonadal tissue; 'No/Other' includes having used no FP or any of the following: GnRHa, fertility-sparing surgery, and hormonal stimulation for oocyte cryopreservation without producing a viable sample.

than men's (3.3 vs. 3.5, $p < .001$). The effect sizes, as measured by Cohen's d, were 0.54 for anxiety, 0.22 for depression and 0.41 for self-efficacy, indicating a small to medium effect.

Factors associated with high fertility-related distress in YAs 1.5 years after diagnosis

Results of multivariable logistic regression models for high fertility-related distress (RCAC dimension mean score >4) among women are shown in Table 3. Several sociodemographic factors (younger age, lower level of achieved education, birth country other than Sweden, and no current partner) were associated with high distress in different dimensions. Having previous children increased the likelihood for distress concerning Child's health and decreased the risk of distress concerning Fertility potential, Partner disclosure, and Acceptance (i.e., acceptance of a life without children). A wish for future children was strongly associated with distress related to Fertility potential, Acceptance, and Becoming pregnant. When breast cancer was used as the reference group, women treated for ovarian and cervical cancers or brain tumors were less likely to report distress related to Personal health, and women treated for cervical cancer were less likely to report distress concerning Child's health. Having used FP by cryopreservation methods increased women's likelihood of reporting high distress concerning Fertility potential. Among psychological factors, high anxiety and low self-efficacy were associated with high distress concerning Fertility potential and Partner disclosure. Treatment intensity and depression were not found to be significantly associated with fertility-related distress in the multivariable regression models.

A limited number of factors were found to be associated with high fertility-related distress among the men (Table 4). Not having any children and not having a partner was associated with distress concerning Partner disclosure, and a wish for future children was strongly associated with distress related to Fertility potential and Acceptance. Men treated for brain tumors were more than four times more likely to report distress related to Fertility potential than were men treated for testicular cancer. High anxiety and low self-efficacy were associated with fertility-related distress in different dimensions. Among men, FP was not associated to any of the outcomes in bivariate analyses and thus not included in the multivariable regression models.

Discussion

Fertility-related distress after gonadotoxic cancer treatment is well documented, but the true prevalence is unclear due to the self-selected sampling method in most studies

Table 4. Factors associated with fertility-related distress[a] in young men 1.5 years following cancer diagnosis.

	Fertility potential		Partner disclosure		Child's health		Personal health		Acceptance		Becoming pregnant	
RCAC dimensions	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95% CI	OR	95%CI
Age at study												
>35 years (ref)												
<30 years	1.86	0.50–6.89			0.96	0.39–2.38						
30–35 years	1.43	0.40–5.17			0.42	0.15–1.15						
Relationship status												
Partner vs No partner (ref)			**0.36**	0.14–0.92								
Having children												
Yes vs No (ref)	0.42	0.15–1.19	**0.18**	0.05–0.69					0.29	0.08–1.05		
Child wish at study												
Yes vs No/uncertain (ref)	**7.78**	2.41–25.06							**6.05**	1.34–27.38		
Treatment intensity												
Very/most intensive vs Least/moderately intensive (ref)					1.91	0.80–4.55	1.95	0.61–6.25				
Type of cancer												
Testicular (ref)												
Brain	**4.61**	1.35–15.73			2.33	0.83–6.59	1.14	0.23–5.75				
Lymphoma	1.56	0.50–4.80			1.65	0.61–4.47	1.86	0.55–6.22				
HADS Anxiety	1.14	0.99–1.22	1.04	0.91–1.20	**1.19**	1.07–1.33	**1.19**	1.06–1.32			**1.25**	1.06–1.47
HADS Depression	1.05	0.90–1.22	1.11	0.95–1.29	1.01	0.89–1.14					1	0.83–1.2
Self-efficacy	**0.37**	**0.18–0.78**	**0.38**	0.19–0.77								

Results of multivariable logistic regression models, each model including only factors associated with the respective outcome in bivariate analyses.
OR: Odds Ratio; CI: Confidence Interval.
[a]Fertility-related distress defined as mean >4 in RCAC dimensions.

[17,21,28,29]. The present study on a large population-based cohort of YAs recently treated for cancer expands knowledge about the prevalence and risk factors for developing fertility-related distress. Our results show that large proportions of young women and men suffer high levels of fertility-related distress following their treatment, which highlights the importance of supportive reproductive healthcare before and after treatment. The use of FP was unevenly distributed among women and men (15% vs. 71%) and was not associated with decreased fertility-related distress.

Predictors for increased fertility-related distress among women and men included being single, being childless, suffering from anxiety and having a wish for future children, in line with previously published data [5,17,18,21]. In addition, we found that female patients are negatively affected by additional sociodemographic factors, such as young age, low education level, and birth outside of Sweden. However, the low number of individuals in some groups (e.g., 16% of the women born outside Sweden) increases the risk of chance capitalization, which must be taken into consideration. Treatment intensity was not associated with fertility-related distress, which may reflect that the ITR-YA [38] is a generic measure of treatment intensity that is not specific to gonadotoxic treatment.

The population-based design with identification of patients with various cancer diagnoses in national quality registers, recruitment at a fixed time-period after diagnosis, a high response rate, and use of the validated RCAC for assessment of fertility-related distress constitute the main strengths of the study. In the present cohort half of women and a quarter of men reported fertility-related distress in at least one of RCAC dimensions. This is in line with our previous results on population-based samples of YAs treated for breast or testicular cancer [22,23]. Our sampling strategy likely affects the study outcome, and it should be noted that population-based studies have previously reported lower RCAC scores than studies using self-recruited samples [39]. In our cohort, women were found to be significantly more likely than men to report distress concerning most dimensions of the RCAC, after controlling for socio-demographic variables such as age and previous children. One explanation for this finding could be related to clinical factors. In comparison to men, women more often had received very/most intensive treatment, were more often informed of a high risk of infertility, and had rarely used FP. Also, these results could be related to reproductive-aged women's greater awareness of age-related fertility decline, infertility risk factors and consequences of delaying childbearing compared to men, as previously reported [41].

The most common areas of fertility-related distress for both women and men concerned the health of existing or future children, the risk of hereditary cancer, and own fertility potential. The wish for future children was a strong predictor of distress concerning own fertile ability and difficulty accepting a life without biological children, which is in line with previous reports [18,21,22]. As could be expected, being single and being childless was associated with more fertility distress in both genders. Additional sociodemographic predictors such as young age, low education, and being born outside Sweden were identified only in the female cohort, possible due to different sample sizes.

In both women and men, symptoms of anxiety were associated with increased fertility-related distress in several areas [22,23]. Despite YA survivors being at high risk of developing anxiety and depression, recent studies have shown that they might not actively seek, nor get, the support they need [42–44]. One way to support YAs with fertility-related distress might be to increase their confidence in own ability to handle situations, thoughts and emotions related to the threat of infertility. In the present study, higher levels of such self-efficacy were associated with less distress concerning Fertility potential and Partner disclosure. As part of the Fex-Can project, patients from this study cohort who reported high levels

of fertility distress were offered to participate in a randomized controlled trial evaluating a web-based psychoeducational intervention [45]. This intervention included components aimed to increase participants' self-efficacy related to infertility or an uncertain fertility status. While a majority of intervention participants reported a subjective decrease of their fertility distress, the results showed efficacy only with regard to Child's health.

Qualitative studies have indicated that FP may act as a buffer against increased fertility concerns among cancer patients [24–26], but this is not reflected in our population-based cohort. In Sweden, FP is available within the tax-funded healthcare for all individuals at risk of infertility [46]. Still, the present study found an unevenly distributed use of FP among female and male participants (15% vs. 71%), which is in line with findings from a recent multicentric study showing gender disparities in oncofertility healthcare provision in the Nordic countries [47]. While use of FP was not significantly associated with any of the outcomes among the men, FP was associated to a doubled risk for distress concerning Fertility potential among the women. These results might be attributed to several factors. A first explanation could be that the women undergoing FP are actually at higher risk for infertility and also aware of it. Another, more indirect, possibility is based on previous results showing that both male and female adolescent and YA cancer survivors undergoing fertility consultations report increased fertility concerns [29,39]. The consultations and procedures surrounding FP are more extensive for women than men and could therefore increase their risk awareness and reproductive concerns. This theory is supported by research indicating increased fertility concerns after fertility consultations irrespective of whether the consultation was followed by FP or not [39]. Drizin et al. also argue that individuals with higher fertility distress might be more likely to seek fertility consultations than those with lower distress [29]. This could be applicable to the women in our cohort, where FP was not as commonly used, while the high rate of sperm banking and lower prevalence of fertility-related distress among the men suggest that men used FP as a routine precaution rather than due to high fertility distress.

The results of the present study indicate a continuous need to monitor fertility-related distress and identify strategies to alleviate this distress in YAs following cancer treatments that could affect fertility. Studies have shown that patients value direct and honest communication with their caregivers, but there is a delicate balance between alleviating concerns and increasing risk awareness [40,48,49]. The information provided should be individualized according to the planned treatment and identified needs and wishes. Further studies are needed to investigate the effect of timing of information, as well as the effect of psychoeducational health care initiatives on fertility-related distress among YA cancer survivors.

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ORCID

Kenny A. Rodriguez-Wallberg http://orcid.org/0000-0003-4378-6181
Johan Ahlgren http://orcid.org/0000-0001-6392-273X
Jessica R. Gorman http://orcid.org/0000-0002-3950-4260
Kristina Hellman http://orcid.org/0000-0002-5124-7412
Roger Henriksson http://orcid.org/0000-0002-1467-9339
Lena Wettergren http://orcid.org/0000-0003-1279-2191
Claudia Lampic http://orcid.org/0000-0002-1739-4486

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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