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**ORIGINAL ARTICLE** ***Reproductive epidemiology***

# Reproductive intentions and use of reproductive health care among female survivors of childhood cancer

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**STUDY QUESTION:** Do female childhood cancer survivors (CCSs) express a decreased desire to have children and do they use reproductive health care more often compared to women without a history of cancer?

**SUMMARY ANSWER:** Overall, no difference was found in the desire to have children between CCSs and controls, whereas CCSs consult a fertility specialist more often, at a younger age, and sooner after their first attempt at conceiving.

**WHAT IS KNOWN ALREADY:** Female CCSs may face a shorter than anticipated reproductive window as a result of their cancer treatment. Little is known about their desire to have children and use of reproductive health care, especially in relation to their former cancer treatment.

**STUDY DESIGN, SIZE, DURATION:** This study is part of the DCOG LATER-VEVO study, a nationwide retrospective cohort study on female fertility in Dutch CCSs. In total, 1749 CCSs and 1673 controls were invited for the study. Data collection took place between January 2008 and May 2014.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Data on the desire to have children and use of reproductive health care were collected by questionnaire. The control group consisted of sisters from CCSs and females from the general population. In total, 1106 (63%) CCSs and 818 (49%) controls completed the questionnaire.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Overall, no difference was found in the desire to have children between CCSs and controls (86% and 89%, respectively). However, survivors of a CNS tumour were less likely to desire children and CCSs without biological children at time of study were more likely to report that their desire to have children was unfulfilled because of medical reasons (9%), compared to controls (1%). In total, 12% of CCSs ever consulted a fertility specialist compared to 10% of controls (OR = 1.7, 95% CI: 1.3–2.4). Mean (SD) age at time of their first visit was 27.7 (4.4) years for CCSs and 29.9 (3.9) years for controls ($P < 0.01$). In total, 43% of CCSs consulted a fertility specialist within 12 months after they had started trying to achieve a pregnancy, compared to 27% of controls. Risk factors for consulting a fertility specialist included a previous diagnosis of renal tumour, leukaemia, lymphoma or a CNS tumour, and treatment with alkylating chemotherapy,

gonadotoxic radiotherapy or both. In total, 70% of CCSs reported a female factor as cause of subfertility compared to 34% of controls (OR = 4.5, 95% CI: 2.3–8.7) and in this specific group, CCSs seemed more likely to use fertility treatment (OR = 2.9, 95% CI: 1.0–8.2).

**LIMITATIONS, REASONS FOR CAUTION:** Because of the low number of CCSs who used fertility treatment, we were not able to look at specific diagnoses and treatment types associated with using fertility treatment. Nevertheless, we were able to identify diagnostic- and treatment-related risk factors for consulting a fertility specialist. Details regarding consultations with a fertility specialist and fertility treatment were based on self-report and may therefore be subject to recall bias.

**WIDER IMPLICATIONS OF THE FINDINGS:** Decisions about parenthood affect all CCSs. It's important to evaluate reproductive intentions and function timely after cancer treatment, so CCSs can be adequately counselled regarding family planning and fertility treatment.

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**Key words:** childhood cancer survivors / desire to have children / reproductive health care / fertility treatment / infertility / fertility / pregnancy / referral and consultation

# Introduction

Advances in diagnosis and treatment of childhood cancer have led to major improvements in the 5-year survival rate, which now exceeds 80% (Gatta *et al.*, 2014). As a consequence, the number of childhood cancer survivors (CCSs) has substantially increased, and many of them have reached an age at which they consider parenthood. Reproductive intentions of cancer survivors of childbearing age may, however, be affected by reproductive concerns, such as fear of cancer recurrence, health of the child and partner issues (Schover, 1999; Schmidt *et al.*, 2016; Schover *et al.*, 1999). Despite these concerns, particularly young and childless cancer survivors express a desire for children (Canada and Schover, 2012; Lehmann *et al.*, 2017; Reinmuth *et al.*, 2008; Schover *et al.*, 1999). However, the number of quantitative studies that have addressed this issue are limited, specifically among CCSs and in reference to the general population, specific cancer sites and treatment groups (Schmidt *et al.*, 2016).

Female CCSs who wish to have children may face a shorter than anticipated reproductive window. Alkylating agents, total body irradiation (TBI), and lower abdominal/pelvic radiotherapy (RT) in particular, may adversely affect reproductive function, resulting in sub- or infertility and a premature menopause (Green *et al.*, 2009a, 2009b; Meirow, 2000; Reulen *et al.*, 2009). Together with the European trend to postpone childbearing to the early thirties, female CCSs may be at increased risk of reproductive health care use in order to achieve a pregnancy. However, data on how often they consult a fertility specialist and use ART are scarce. To our knowledge, only Barton *et al.* evaluated the likelihood of visiting a doctor for clinical infertility (defined as ever having tried to become pregnant for at least 1 year) among CCSs. They found no difference between CCSs and their siblings, and reported that, in fact, infertile CCSs were less likely to receive medical treatment to help them become pregnant (Barton *et al.*, 2013). Other studies found that 15% of female survivors sought fertility care after cancer, 4% used fertility drugs or pursued ART (Kim *et al.*, 2016), and among those who had given birth, the use of fertility treatments was almost twice as high compared to their siblings (Melin *et al.*, 2017). However, these studies were not exclusively performed among CCSs, did not take into account the cause of subfertility, and lacked detailed information on cancer treatment, precluding an evaluation of cancer-related factors associated with reproductive health care use. In addition, only Melin *et al.* (2017) specified the type of fertility treatment used, but this study was restricted to women who had given birth and, therefore, survivors with unsuccessful fertility treatments were not included. Therefore, the primary aim of this study was to evaluate the desire to have children, reasons for not wanting children, the prevalence of reproductive health care use, and the use of different types of fertility treatment among female CCSs. In addition, we aimed to identify cancer-related risk factors associated with a desire to have children and use of reproductive health care.

# Materials and Methods

## Study design and population

This study is part of the DCOG LATER-VEVO study, a nationwide, retrospective cohort study evaluating fertility, ovarian reserve and premature menopause among female 5-year survivors of childhood cancer by a one-time questionnaire, serum sample and transvaginal ultrasound of the reproductive organs. The study population consisted of female CCSs treated for childhood cancer between 1963 and 2002 in one of the seven Dutch Centres for Paediatric Oncology/Haematology, who were alive at least 5 years after diagnosis, living in the Netherlands, and at least 18 years of age at study entry. Five-year survivors who were not able to speak or read Dutch, who had severe mental sequelae, who were treated for a second malignant neoplasm at time of study inclusion, or who previously indicated not to be willing to participate in research were excluded from the study. The control group consisted of sisters from participating CCSs and women from the general population (van den Berg *et al.*, 2014). Eligible controls were women who had never been diagnosed with cancer, were able to read and speak Dutch, and were at least 18 years of age at study entry. A total of 1749 female CCSs and 1673 controls were eligible and thus invited for participation in the DCOG LATER-VEVO study.

Details about the study design, the study population, data collection methods and comparisons between both types of control groups have been described previously (Overbeek *et al.*, 2012; van den Berg *et al.*, 2014).

## Data collection

For the current study, data from the questionnaire used in the DCOG LATER-VEVO study were used. The questionnaire was an adaption of a well-tested questionnaire used by the Department of Epidemiology of the Netherlands Cancer Institute (de Boer *et al.*, 2005; van Leeuwen *et al.*, 2011).

The questionnaire addressed, amongst other things, sociodemographic characteristics, having children, a current or future desire to have children, reasons for not having a desire for children, consultations with a fertility specialist, causes of subfertility, the use of fertility treatment, ever pregnant, and for each pregnancy, the method of conception. Questions used to address these issues are shown in Supplementary Table SI. Fertility treatment included artificial insemination (both intracervical and intrauterine), IVF, ICSI and ovulation induction (not as part of IVF, ICSI or insemination). Data collection took place between January 2008 and May 2014. Details on prior cancer diagnosis and treatments (given for initial malignancy, recurrences, and any known new primary malignancies until time of study) were collected from original medical files.

## Statistical analyses

Characteristics of survivors and controls were compared using the Chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. Logistic regression analyses were used to compare CCSs and controls regarding overall (previous, current or future) desire to have children, having biological children or being pregnant at time of study, and ever having consulted a fertility specialist. Since the questionnaire addressed current and future desire for children only, the assumption was made that women who had biological children or were pregnant at time of study and indicated to have no current or future desire for additional children, had a desire for children in the past. In addition, for the analyses on overall desire to have children, women without a desire for children were combined with those who indicated not to know yet. These analyses were all corrected for age, BMI, educational level and marital status at time of study.

Additional analyses were performed among the group who had ever consulted a fertility specialist to evaluate whether CCSs who visited a fertility specialist, were different from controls who visited a fertility specialist. Differences between CCSs and controls in age at first consultation with a fertility specialist and number of months of trying to conceive before visiting a fertility specialist were evaluated using the Chi-square test. Logistic regression analyses were performed to investigate in CCSs versus controls the probability of: (i) having been pregnant before consulting a fertility specialist; (ii) becoming pregnant after consulting a fertility specialist; (iii) a female factor being involved in the cause of subfertility; (iv) using fertility treatment; and (v) becoming pregnant by means of fertility treatment. Answer categories for female factors as cause of subfertility included problems with the fallopian tube(s), endometriosis, problems with ovulation, polycystic ovary syndrome (PCOS), hormonal problems, problems with the uterus, problems with the endometrium, premature menopause or vaginal problems. Given the fact that we were predominantly interested in whether cancer and its treatment is more often the cause of subfertility in female CCSs compared to controls, we excluded from analyses 3–5 women who reported a non-cancer related condition, known to affect fertility (i.e. endometriosis or polycystic ovary syndrome). For analyses 4 and 5, women who reported an unexplained or male factor as the cause of their subfertility were subsequently excluded in order to focus on the use and success rate of fertility treatments among CCSs and controls who reported at least a female factor (which was most probably not related to a known non-cancer related condition). These analyses were corrected for age at first consultation with a fertility specialist and BMI at time of study. Linear regression was used to compare age at first consultation with a fertility specialist between CCSs and controls.

To identify possible cancer-related risk factors associated with a reduced desire for children or an increased probability of consulting a fertility specialist, CCSs were categorized by cancer diagnosis, age at diagnosis, time since diagnosis and type of treatment, with the control group as the reference group. Survivors were categorized into four groups based on the presumed gonadotoxicity of their cancer treatment (Lee *et al.*, 2006; Overbeek *et al.*, 2017; van Dorp *et al.*, 2016). Treatment including lower abdominal/pelvic RT, TBI or alkylating chemotherapy (including procarbazine) was considered to be gonadotoxic. The four groups included: no gonadotoxic RT (including no RT at all) and no alkylating chemotherapy (including no CT at all); alkylating chemotherapy without gonadotoxic RT (including no RT at all); gonadotoxic RT without alkylating chemotherapy (including no CT

**Table I Demographic and baseline characteristics of the participating CCSs and controls.**

| | Survivors (*N* = 1106) | Controls (*N* = 818) | *P*-value |
|---|---|---|---|
| Age at time of study (years) | | | |
| Median (IQR) | 28.7 (12.5) | 32.7 (12.6) | <0.001 |
| Education[a] | | | |
| Low | 97 (8.8) | 26 (3.2) | <0.001 |
| Medium | 682 (62.2) | 363 (44.8) | |
| High | 318 (29.0) | 422 (52.0) | |
| Marital status | | | |
| Never married | 312 (28.3) | 146 (17.9) | <0.001[b] |
| Ever married/living as married | 791 (71.7) | 669 (82.1) | |
| BMI | | | |
| Median (IQR) | 23.0 (5.6) | 23.0 (4.9) | 0.91 |
| Biological children or pregnant at time of study | | | |
| Yes | 377 (34.1) | 369 (45.2) | 0.16[b] |
| No | 727 (65.9) | 448 (54.8) | |
| Age at diagnosis (years) | | | |
| Median (IQR) | 6.4 (8.4) | – | |
| Diagnosis | | | |
| Leukaemia | 394 (35.6) | – | |
| Lymphoma | 178 (16.1) | – | |
| Renal tumours | 125 (11.3) | – | |
| CNS | 114 (10.3) | – | |
| Soft tissue sarcoma | 75 (6.8) | – | |
| Bone tumours | 70 (6.3) | – | |
| Neuroblastoma and other peripheral nervous cell tumours | 68 (6.1) | – | |
| Other | 82 (7.4) | – | |
| Treatment[c] | | | |
| Neither gonadotoxic RT nor alkylating CT | 459 (41.6) | – | |
| Alkylating CT, without gonadotoxic RT | 522 (47.3) | – | |
| Gonadotoxic RT, without alkylating CT | 64 (5.8) | – | |
| Alkylating CT and gonadotoxic RT | 58 (5.3) | – | |

[a]Categorized as a low educational level: up to, and including, lower technical and vocational training; medium educational level: up to, and including, secondary technical and vocational training; high educational level: up to, and including, higher technical and vocational training and university.
[b]Corrected for age at time of study.
[c]Alkylating CT: Treatment with busulfan, carmustine, cyclophosphamide, chlorambucil, ifosfamide, lomustine, melphalan, procarbazine, temozolomide, chlormetine, ACNU or thiotepa.
Values represent the number (%) of women, unless indicated otherwise. The subcategories may not add up to the total number of women due to missing values.

at all); or both alkylating chemotherapy and gonadotoxic RT. All tests were two-sided with a 0.05 significance level. All analyses were conducted using Statistical package for Social Sciences version 22.0 (SPSS, Chicago, IL, USA).

### Ethical approval

Approval was obtained from the relevant Medical Ethics Review Committees (METC protocol number 2006/49) and written informed consent was obtained from all participants.

## Results

Of the 1749 CCSs and 1673 controls invited for the study, 1106 (63%) and 818 (49%), respectively, completed the questionnaire. Participating CCSs were similar to non-participating CCSs with regard to age at start of the study, age at diagnosis, and diagnosis, whereas the percentage of survivors within the four broad treatment categories (CT only (±surgery), RT only (±surgery), CT + RT (±surgery), other) differed significantly between participating CCSs and non-participating CCSs (Supplementary Table SII). Sociodemographic characteristics of both participating CCSs and controls, as well as the diagnostic- and treatment-related characteristics of the participating CCSs are shown in Table I. Median (interquartile range (IQR)) age at time of study was 28.7 (12.5) years for survivors and 32.7 (12.6) years for controls ($P < 0.001$). CCSs were less likely to have a high educational level ($P < 0.001$). Moreover, after adjusting for age at time of study, CCSs were less likely to be ever married or to be living as married (OR = 0.6, 95% CI: 0.5–0.8), whereas no difference was found in the likelihood of having biological children or being pregnant at time of study (OR = 0.9, 95% CI: 0.7–1.1). Survivors' median (IQR) age at diagnosis was 6.4 (8.4) years and the majority was diagnosed with leukaemia (36%) or lymphoma (16%). Almost 60% of the CCSs received alkylating chemotherapy and/or gonadotoxic RT.

### Desire to have children

Overall, 86% ($n = 953$) of CCSs reported to have a previous, current or future desire to have children compared to 89% ($n = 726$) of controls. Of these women, 377 (40%) CCSs and 369 (51%) controls had biological children or were pregnant at time of study. After adjusting for age, BMI, educational level and marital status at time of study, no differences were found between CCSs and controls regarding their desire to have children (OR = 1.0, 95% CI: 0.7–1.3) or the proportions of CCSs and controls who had biological children or were pregnant at time of study (OR = 0.9, 95% CI: 0.7–1.2).

No difference was found between CCSs and controls without biological children and not pregnant at time of study ($n = 727$ and $n = 448$, respectively) regarding their current or future wish for children (OR = 1.2, 95% CI: 0.8–1.7) (Table II). Among CCSs and controls without a current or future desire for children or who indicated not to know yet, the reasons for 'not wanting a child' or 'not knowing yet' were evaluated (Table II). Controls more often reported that 'their partner was not ready to have children (yet)' ($P < 0.001$) or that they 'never wanted to have children' ($P < 0.01$), whereas CCSs more often reported that they 'don't know yet because of their medical history' ($P < 0.01$) or that they 'used to desire a child, but that this was not possible due to medical reasons' ($P < 0.01$).

### Reproductive health care use

In total, 12% of CCSs and 10% of controls ever consulted a fertility specialist (OR = 1.7, 95% CI: 1.3–2.4). The characteristics of those who ever consulted a fertility specialist are described in Table III. CCSs were significantly younger at time of their first consultation with a mean (SD) age of 27.7 (4.4) years compared to 29.9 (3.9) years for controls ($P < 0.01$) and significantly more CCSs than controls did so

**Table II Current or future desire for children, and reasons for not wanting children among CCSs and controls without biological children and not pregnant at time of study.**

| | Survivors ($N = 727$) | Controls ($N = 448$) | OR (95% CI)[a] | *P*-value |
|---|---|---|---|---|
| Current or future desire to have children | | | | |
| Yes | 535 (74.0) | 348 (77.9) | 1.2 (0.8–1.7) | 0.32 |
| No/don't know | 188 (26.0) | 99 (22.1) | | |
| Reasons for not having a desire for children or not knowing yet (multiple answers possible) | $N = 188$ | $N = 99$ | | |
| Currently no partner | 54 (30.7) | 29 (29.9) | – | 0.89 |
| Not ready to have children (yet) | 54 (30.7) | 38 (39.2) | – | 0.16 |
| My partner is not ready to have children (yet) | 3 (1.7) | 13 (13.4) | – | <0.001 |
| Never wanted to have children | 30 (17.0) | 32 (33.0) | – | <0.01 |
| Never thought about it properly | 25 (14.2) | 12 (12.4) | – | 0.67 |
| I don't know yet because of my medical history | 25 (14.2) | 2 (2.1) | – | <0.01 |
| My family is complete[b] | 10 (5.7) | 2 (2.1) | – | 0.16 |
| Ever had this wish, but I'm too old now | 14 (7.9) | 5 (5.2) | – | 0.39 |
| Ever had this wish, but it was not possible to have children because of medical reasons | 16 (9.0) | 1 (1.0) | – | <0.01 |

[a]Corrected for age at time of study, BMI at time of study, educational level and marital status.
[b]Completed families because women have adopted children or children conceived through egg donation.
Values represent the number (%) of women. The subcategories may not add up to the total number of women due to missing values.

**Table III Characteristics of women who ever consulted a fertility specialist.**

| | Survivors (*N* = 135) | Controls (*N* = 83) | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Age at first consultation with a fertility specialist (years) | | | | |
| Mean (SD) | 27.7 (4.4) | 29.9 (3.9) | – | <0.01[a] |
| <25 | 30 (25.2) | 7 (9.3) | – | <0.01 |
| ≥25 and <30 | 56 (47.1) | 29 (38.7) | – | |
| ≥30 and <35 | 27 (22.7) | 30 (40.0) | – | |
| ≥35 | 6 (5.0) | 9 (12.0) | – | |
| Number of months trying to conceive before first consultation with a fertility specialist | | | | |
| <6 | 27 (25.0) | 6 (8.1) | – | 0.04 |
| ≥6 and <12 | 19 (17.6) | 14 (18.9) | – | |
| ≥12 and <24 | 42 (38.9) | 36 (48.6) | – | |
| ≥24 | 20 (18.5) | 18 (24.3) | – | |
| Pregnant at least once before consulting a fertility specialist | 15 (11.6) | 23 (29.9) | 0.4 (0.2–0.8)[b] | <0.01 |
| Conceived after having consulted a fertility specialist | 83 (64.8) | 53 (70.7) | 0.8 (0.4–1.5)[b] | 0.45 |
| Cause of subfertility reported[c] | *N* = 120 | *N* = 71 | | <0.001 |
| Female-factor only | 80 (66.7) | 20 (28.2) | – | |
| Male-factor only | 16 (13.3) | 24 (33.8) | – | |
| Both male- and female-factor | 4 (3.3) | 4 (5.6) | – | |
| Unexplained | 20 (16.7) | 23 (32.4) | – | |
| Reported cause of subfertility includes at least a female factor[c] | 84 (70.0) | 24 (33.8) | 4.5 (2.3–8.7)[b] | <0.001 |
| Used some type of fertility treatment[c,d,e] | 46/84 (54.8) | 9/24 (37.5) | 2.9 (1.0–8.2)[b] | 0.05 |
| Ovulation induction | 27 (32.1) | 6 (25.0) | – | |
| Artificial insemination | 12 (14.3) | 3 (12.5) | – | |
| IVF/ICSI | 21 (25.0) | 2 (8.3) | – | |

[a]Corrected for BMI at time of study.
[b]Corrected for age at first consultation with a fertility specialist and BMI.
[c]Women who reported endometriosis or polycystic ovary syndrome as cause of subfertility were excluded.
[d]Women who reported to have unexplained subfertility or a male factor only as the cause of subfertility were excluded
[e]Subcategories are not mutually exclusive.
Values represent the number (%) of women, unless indicated otherwise. Denominators may vary due to missing values or exclusion criteria.

before the age of 30 years. Furthermore, the number of months of trying to conceive before consulting a fertility specialist was significantly lower among CCSs ($P = 0.04$). A quarter of CCSs consulted a fertility specialist within 6 months after they had started trying to achieve a pregnancy, compared to 8% of controls (OR = 3.3, 95% CI: 1.3–8.7). Moreover, CCSs were significantly less likely to have been pregnant before consulting a fertility specialist (OR = 0.4, 95% CI: 0.2–0.8), whereas CCSs and controls were equally likely to become pregnant after having consulted a fertility specialist.

After excluding women with PCOS or endometriosis, CCSs were more likely to report a female factor to be involved in the cause of their subfertility (OR = 4.5, 95% CI: 2.3–8.7). Moreover, among those women who reported at least a female factor to be involved in the cause of their subfertility (thus excluding women with male factor only and unexplained infertility), CCSs seemed more likely to have undergone fertility treatment (OR = 2.9, 95% CI: 1.0–8.2). The largest difference between CCSs and controls was found for the use of IVF/ICSI (25% and 8%, respectively). Finally, 57% of CCSs who have used fertility treatment and who reported a female factor being the reason for their subfertility became pregnant by means of fertility treatment compared to 56% of controls (OR = 1.6, 95% CI: 0.3–7.7).

## Cancer-related risk factors

Cancer-related factors associated with having a previous, current, or future desire for children or consulting a fertility specialist are listed in Table IV. Compared to controls, survivors of CNS tumours were significantly less likely to report a desire for children. Moreover, survivors 15–20 years after diagnosis were more likely to report a desire for children. Age at diagnosis and type of cancer treatment, however, appeared not to influence a survivors' wish to become a parent.

Survivors of renal tumours, leukaemia, lymphoma or CNS tumours were significantly more likely to have ever consulted a fertility specialist regarding their desire to have a child, as well as CCSs diagnosed after the age of four years. Moreover, survivors who were at least 20 years since diagnosis were more likely to have ever consulted a fertility specialist. Finally, treatment with alkylating CT or gonadotoxic RT increased the probability of consulting a fertility specialist compared to

**Table IV Cancer-related factors for having a previous, current, or future desire to have children and consulting a fertility specialist because of a desire for children among CCSs and controls.**

| | Had a previous, current or future desire to have children | OR (95% CI)[a] | Ever consulted a fertility specialist because of a desire for children | OR (95% CI)[a] |
|---|---|---|---|---|
| Diagnosis | | | | |
| Controls | 726/818 (88.8) | Ref. | 83/818 (10.1) | Ref. |
| CNS | 80/114 (70.2) | 0.5 (0.3–0.9) | 10/114 (8.8) | 2.1 (1.0–4.6) |
| Soft tissue sarcoma | 61/75 (81.3) | 0.6 (0.3–1.2) | 4/75 (5.3) | 0.5 (0.2–1.4) |
| Leukaemia | 334/394 (84.8) | 0.8 (0.5–1.2) | 48/394 (12.2) | 2.1 (1.4–3.2) |
| Neuroblastoma and other peripheral nervous cell tumours | 60/68 (88.2) | 0.8 (0.3–1.7) | 10/68 (14.7) | 1.9 (0.9–4.0) |
| Other | 72/82 (87.8) | 1.2 (0.6–2.7) | 12/82 (14.6) | 1.6 (0.8–3.3) |
| Renal tumours | 113/125 (90.4) | 1.5 (0.7–2.9) | 19/125 (15.2) | 2.6 (1.5–4.7) |
| Lymphoma | 166/178 (93.3) | 1.8 (0.9–3.5) | 25/178 (14.0) | 1.8 (1.1–3.0) |
| Bone tumours | 67/70 (95.7) | 4.7 (1.1–20.5) | 7/70 (10.0) | 0.9 (0.4–2.2) |
| Age at diagnosis (years) | | | | |
| Controls | 726/818 (88.8) | Ref. | 83/818 (10.1) | Ref. |
| <4 | 306/357 (85.7) | 0.9 (0.6–1.3) | 34/357 (9.5) | 1.5 (0.9–2.4) |
| ≥4 and <8 | 241/283 (85.2) | 1.0 (0.6–1.6) | 29/283 (10.2) | 2.0 (1.2–3.3) |
| ≥8 and <12 | 179/207 (86.5) | 1.0 (0.6–1.6) | 29/207 (14.0) | 2.0 (1.2–3.2) |
| ≥12 and <19 | 227/259 (87.6) | 1.1 (0.7–1.8) | 43/259 (16.6) | 1.7 (1.1–2.6) |
| Time since diagnosis (years) | | | | |
| Controls | 726/818 (88.8) | Ref. | 83/818 (10.1) | Ref. |
| ≥5 and <15 | 172/208 (82.7) | 0.8 (0.5–1.3) | 7/208 (3.4) | 0.7 (0.3–1.7) |
| ≥15 and <20 | 235/257 (91.4) | 2.2 (1.2–4.0) | 11/257 (4.3) | 0.9 (0.4–1.7) |
| ≥20 and <25 | 193/225 (85.8) | 0.8 (0.5–1.3) | 27/225 (12.0) | 1.7 (1.0–2.8) |
| ≥25 and <30 | 165/197 (83.8) | 0.7 (0.4–1.1) | 37/197 (18.8) | 2.2 (1.4–3.5) |
| ≥30 | 188/219 (85.8) | 1.1 (0.6–1.8) | 53/219 (24.2) | 2.1 (1.4–3.2) |
| Treatment | | | | |
| Controls | 726/818 (88.8) | Ref. | 83/818 (10.1) | Ref. |
| Neither gonadotoxic RT nor alkylating CT | 386/459 (84.1) | 0.8 (0.6–1.2) | 47/459 (10.2) | 1.3 (0.9–2.0) |
| Alkylating CT, without gonadotoxic RT | 463/522 (88.7) | 1.2 (0.8–1.7) | 56/522 (10.7) | 1.6 (1.1–2.4) |
| Gonadotoxic RT, without alkylating CT | 56/64 (87.5) | 1.3 (0.5–3.0) | 16/64 (25.0) | 3.0 (1.6–5.9) |
| Alkylating CT and gonadotoxic RT | 47/58 (81.0) | 0.6 (0.3–1.2) | 15/58 (25.9) | 5.1 (2.5–10.2) |

[a]Corrected for age at time of study, BMI at time of study, educational level and marital status.
Values represent the number (%) of women. The subcategories may not add up to the total number of women due to missing values.

controls, but the risk was highest following a combination of both gonadotoxic RT and alkylating CT (OR = 5.1, 95% CI: 2.5–10.2).

## Discussion

This is one of the first large, quantitative studies evaluating the desire to have children among female CCSs, specifically in comparison to controls. In addition, it is the first to assess reasons for not wanting to pursue parenthood (or not knowing yet), among CCSs without biological children. Our study found that the majority of CCSs reported a previous, current, or future desire to have children, at rates similar to those found in controls (86% and 89%, respectively). This is reassuring in that the experience of cancer, overall, does not seem to influence a survivors' desire for children later in life. However, results imply that, among those without biological children, medical reasons or concerns more often underlie the decision to refrain from having children, while in controls other factors play a role. Reproductive concerns and an unfulfilled desire to have children after cancer diagnosis may substantially impact on well-being, leading to depressive symptoms and a lower quality of life (Wenzel *et al.*, 2005; Nilsson *et al.*, 2014). Timely assessment of reproductive function after cancer, and the provision of detailed information about the risk of infertility and possible options for fertility preservation or treatment, is important to minimize the risk of fertility-related concerns and involuntary childlessness.

Furthermore, female CCSs appeared to be at an almost 2-fold increased risk of consulting a fertility specialist compared to controls.

This is in contrast with a study by Barton *et al.* (2013) showing no differences between CCSs and their siblings, in the likelihood of ever visiting a doctor for clinical infertility, defined as 'ever tried to become pregnant for more than one year without success'. However, the studies are difficult to compare since Barton *et al.* evaluated the likelihood of visiting a reproductive specialist among CCSs and siblings diagnosed with clinical infertility, while our study first evaluated the likelihood of visiting a fertility specialist and identified how long after a first attempt to conceive this happened.

It seems that CCSs and physicians are aware of the potential adverse effects of childhood cancer treatment on fertility. Our study found that CCSs, more often than controls, consulted a fertility specialist, but not per se after being diagnosed with clinical infertility. Overall, 43% of survivors and 27% of controls appeared to visit a fertility specialist within the first year of attempting to become pregnant, 25% of CCSs even within the first 6 months, against 8% of controls. CCSs in our study were more likely to be nulligravidous and were significantly younger than controls at first consultation with a fertility specialist. And, 25% first consulted a fertility specialist before the age of 25 years against 9% of controls. In addition, we found that a female factor was more often included in the cause of subfertility of CCSs, whereas controls more often reported that their subfertility was caused by a male factor only. This finding is in line with previous studies showing that reproductive function is reduced in CCSs, particularly after treatment with alkylating chemotherapy, TBI or lower abdominal/pelvic irradiation (Green *et al.*, 2009b; Thomas-Teinturier *et al.*, 2015). Among those women who reported a female factor to be involved in the cause of their subfertility, CCSs seemed more likely to receive fertility treatment. So it appears that an increased awareness nowadays results in CCSs being younger when starting trying to conceive, while physicians refer sooner and fertility specialists appear more likely to initiate fertility treatments.

This study is unique in that it evaluated cancer-related risk factors associated with a desire for having children and for consulting a fertility specialist among CCSs. Mancini *et al.* (2011) reported that cancer-related factors were not associated with reproductive intentions among survivors of adult cancer. In contrast, we found that survivors of a CNS tumour appeared less likely to pursue parenthood, possibly due to the fact that survivors of a CNS tumour are at high risk for several severe adverse physical and mental sequelae (Ellenberg *et al.*, 2009; Brinkman *et al.*, 2016). Therefore, they might not be capable or cannot imagine themselves having children. Furthermore, our analyses showed that the probability of visiting a fertility specialist was higher following a diagnosis of renal tumours, leukaemia, CNS tumours or lymphoma, and after treatment with alkylating CT and/or gonadotoxic RT. A quarter of CCSs whose treatment included gonadotoxic RT visited a fertility specialist, whereas 11% of CCSs who were treated with alkylating CT only did so. This may indicate that the majority of CCSs receiving gonadotoxic treatment either conceived naturally or have not pursued pregnancy yet. In any case, women treated with alkylating agents, TBI, and/or lower abdominal/pelvic irradiation are at risk of a shorter than expected window of fertility (Chemaitilly *et al.*, 2006; Green *et al.*, 2009a, 2009b). Thus, they may represent an important target population for reproductive health care. Improved education for both CCSs and physicians about the risk of fertility impairment after gonadotoxic cancer treatment could further increase early referrals. This may contribute to lower rates of CCSs with an unfulfilled wish for children and less reproductive concerns.

Despite several strengths of this study, including its large sample size, the inclusion of a large control group, and the linkage to former childhood cancer treatment, some limitations also need to be considered. First, the assumption that all women who had biological children or were pregnant at time of study, had a previous desire to have children, may not apply to all survivors. Moreover, because of the relatively young age (median 28.7 years) as well as the rather low marriage rate in our CCSs group, the results may be an underestimation of the use of reproductive health care in this group during their total life span. Another limitation, although reassuring, is the low number of survivors who actually used fertility treatments. Therefore, we were not able to look at cancer-related factors associated with the use of fertility treatments. Nevertheless, we were able to evaluate diagnostic- and treatment-related risk factors for consulting a fertility specialist. Finally, details regarding consultations with a fertility specialist and fertility treatment were based on self-report and may therefore be subject to recall bias.

In conclusion, the majority of female CCSs report a desire to have children. However, CCSs without biological children are more likely to report an unfulfilled wish to have children due to their medical history compared to controls. Furthermore, CCSs, particularly those diagnosed with a renal tumour, leukaemia, lymphoma, or a CNS tumour, or those treated with alkylating chemotherapy, gonadotoxic RT or both, have a higher probability to ever consult a fertility specialist. They do this at a younger age, sooner after attempting to become pregnant, and they are more likely to be nulligravidous. CCSs with a female factor included in their cause of subfertility seemed more likely to receive fertility treatments. Timely evaluation of reproductive intentions and function after cancer treatment is important so survivors can be adequately counselled regarding family planning and fertility treatment. Close collaboration between oncologists and fertility specialists may result in a more speedy access to fertility treatments for CCSs with reproductive intentions.

## Supplementary data

Supplementary data are available at *Human Reproduction* online.

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## Authors' roles

Mv.D. was responsible for data cleaning, data analysis, interpretation and discussion, and the drafting of the article. Ev.D.dB., M.Hv.dB., G.J.L.K., C.B.L. and F.Ev.L. initiated and designed the DCOG LATER-VEVO study, were involved in data interpretation and discussion, and critically revised the article. A.O., M.Hv.dB., M.Mv.dH.E., W.J.T.,L.C.K., H.Jv.dP., J.J.L., B.V. and D.B. contributed to data collection. All authors critically reviewed and approved the article.

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## Conflict of interest

All authors declare that they have no conflict of interest.

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