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ORIGINAL ARTICLE

Reproductive outcomes and reproductive health care utilization among male survivors of childhood cancer: A DCCSS-LATER study

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Abstract

Background: Treatment-related gonadal dysfunction leading to fertility problems is a frequently encountered late effect in childhood cancer survivors (CCSs). This study evaluated reproductive outcomes and reproductive health care utilization among male CCSs compared with male siblings.

Methods: A nationwide cohort study was conducted as part of the Dutch Childhood Cancer Survivor LATER study part 1, a questionnaire and linkage study. A

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questionnaire addressing reproductive outcomes and reproductive health care was completed by 1317 male CCSs and 407 male siblings. A total of 491 CCSs and 185 siblings had a previous or current desire for children and were included in this study.
Results: Fewer CCSs had biological children compared with siblings (65% vs. 88%; $p < .001$). The type of conception by men who fathered a child was comparable between CCSs and siblings (spontaneous conception of 90% of both groups; $p = .86$). The percentage of men who had consulted a reproductive specialist because of not siring a pregnancy was higher in CCSs compared with siblings (34% vs. 12%; $p < .001$). Following consultation, fewer CCSs underwent assisted reproductive techniques (ART) compared with siblings (41% vs. 77%; $p = .001$). After ART, fewer CCSs fathered a child compared with siblings (49% vs. 94%; $p = .001$).
Conclusions: More male survivors consult a reproductive specialist, but fewer survivors undergo ART and father a child after ART compared with siblings. This insight is important for understanding potential problems faced by survivors regarding family planning and emphasizes the importance of collaboration between oncologists and reproductive specialists.

KEYWORDS
assisted reproductive techniques, childhood cancer survivors, infertility, male, reproductive health services

INTRODUCTION

Advances in treatment for childhood cancer have led to 5-year survival exceeding 80%.[1,2] Unfortunately, many childhood cancer survivors (CCSs) develop late treatment-related morbidity.[3,4] Gonadal dysfunction is a frequently encountered late effect after treatment for childhood cancer.

In the Dutch cohort of CCSs, three-quarters of 1317 male survivors reported to have a desire for children.[5] Because many young adults place great importance on fertility, the potential for infertility can cause significant emotional distress.[6] Ongoing research that focuses on evaluating the toxicity risk of various chemotherapeutic agents and radiotherapy schedules on gonadal function will support personalized infertility risk assessment and guidance on options for fertility preservation at cancer diagnosis.[7]

At cancer diagnosis, it is essential to discuss the risk of gonadotoxicity and offer reproductive counseling by a fertility specialist and discuss options for fertility preservation. After treatment for cancer, it is important to conduct surveillance on gonadal function, discuss reproductive intentions and concerns, and refer survivors in a timely manner to reproductive health services for assessment of fertility potential. Literature addressing reproductive health care utilization among male CCSs is limited. The research published focuses on specific cancer diagnoses or specific assisted reproductive techniques (ART).[8–10] Studies on reproductive outcomes show a decreased likelihood of siring a pregnancy among male CCSs compared with siblings. However, these studies do not report on type of conception and include survivors regardless of their reproductive intentions.[11,12] Although all CCSs should receive reproductive counseling, reporting on reproductive outcomes by focusing on survivors who report a desire for children can further expand knowledge and understanding of potential problems faced by survivors regarding family planning.

Therefore, the aim of this study was to evaluate reproductive outcomes, specified for spontaneous and assisted conception, and reproductive health care utilization among adult male CCSs who had a previous or current desire for children compared with a control group of male siblings.

METHODS

Study design and population

This cross-sectional study is part of the male fertility studies of the Dutch Childhood Cancer Survivor (DCCSS-LATER 1) study, which is a retrospective cohort study among CCSs in the Netherlands. The present study evaluated reproductive outcomes and reproductive health care utilization using a questionnaire survey.

The DCCSS-LATER study cohort ($n = 6165$) includes male and female survivors who were diagnosed with a malignancy according to the third edition of the International Classification of Childhood Cancer or diagnosed with Langerhans cell histiocytosis before the age of 18 years in one of the pediatric oncology/hematology centers in the Netherlands between January 1, 1963, and December 31, 2001, and who survived at least 5 years after their diagnosis.[13] More

details of the cohort have been reported previously.[14] Male CCSs who were aged 18 years or older at time of assessment were eligible for this study ($n = 2616$).

Male siblings of CCSs of the DCCSS-LATER study cohort were included as a control group. Survivors were invited to provide contact information of their sibling(s) if these siblings were willing to participate. A total of 839 male siblings were identified by a survivor, of whom 752 were eligible.

The study protocol was declared exempt from review of medical intervention research by the institutional review boards of participating centers because the CCSs were not subjected to follow rules of behavior and the study was considered to not impact the physical and/or psychological integrity of the subjects, in compliance with Dutch law and regulations for health research involving human beings. Written informed consent was obtained from all participants.

Data collection

Detailed data on prior cancer diagnosis and treatment had been collected under a uniform, standardized protocol in a pseudonymized, web-based central database.[14] Cancer- and treatment-related details of participating survivors were extracted from this database.

During 2013 to 2015, all eligible survivors and siblings were invited to complete a general health questionnaire that addressed a wide variety of topics including sociodemographic characteristics, desire for children, reproductive outcomes, and reproductive health care utilization.

Cohort definition

This study aimed to describe reproductive outcomes and reproductive health care utilization among male CCSs and siblings who had a previous or current desire for children. Not included for this study were: men who indicated having a future desire for children and had no biological children at time of the study; men who did not yet think about fatherhood and had no biological children at time of the study; and men who never had a desire for children. The questions that participants were asked to define the study cohort are shown in Table S1.

Outcome definition

Reproductive outcomes included the number of men who had one or more biological children and the number of men who sired one or more pregnancies that had not led to live birth. Pregnancy was defined as having a positive pregnancy test after a missed period. Details on type of conception (i.e., spontaneous versus assisted conception) were described for each of these outcomes. For the outcome type of conception, in men who reported to have undergone ART and sired a pregnancy or had biological children, we assumed the type of conception to be assisted. In addition, in men who did not report to have undergone ART and sired a pregnancy or had biological children, we assumed the conception to be spontaneous. With regard to reproductive health care utilization, the number of men who consulted a reproductive specialist because of not siring a pregnancy and the number of men who underwent ART were described. In case of assisted conception, details on method of ART were described. If men had undergone more than one method of ART, the most invasive or high technology method was described. This resulted in the following order (from most to least invasive or high-technology method): intracytoplasmic sperm injection (ICSI) combined with surgical sperm retrieval procedure (i.e., testicular sperm extraction [TESE] and/or percutaneous epididymal sperm aspiration [PESA]), ICSI, in vitro fertilization, intrauterine insemination, and ovulation induction only. The number of men who used sperm donation was described separately. The questions that participants were asked to evaluate the study outcomes are shown in Table S2.

Statistical analyses

Descriptive statistics were used to describe details on cancer diagnosis and treatment of survivors. Sociodemographic characteristics, reproductive outcomes, and reproductive health care utilization of male CCSs and siblings were compared using chi-square tests. The Fisher exact test was used in case of small-sized samples.

All tests were two-sided with a .05 significance level. Analyses were conducted using IBM SPSS Statistics for Windows, version 25.0.

RESULTS

Characteristics of survivors and siblings

A total of 1317 of 2616 male CCSs and 407 of 752 male siblings completed the questions addressing the desire for children, reproductive outcomes, and reproductive health care utilization.

The current study cohort included 491 male CCSs and 185 siblings who had a previous or current desire for children (Figure 1). Survivors who had a previous or current desire for children were less likely to have been diagnosed with a central nervous system tumor, to have undergone an allogeneic hematopoietic stem cell transplantation, or to have been treated with surgery only or received no treatment. Those who had a previous or current desire for children were more likely to have received treatment with a combination of radiation therapy and chemotherapy (Table S3).

Sociodemographic characteristics of CCSs and siblings who had a previous or current desire for children, as well as data on prior cancer diagnosis and treatment of the CCSs, are shown in Table 1. Survivors were similar to the siblings with regard to age at assessment (50% and 51% aged between 30 and 40 years, respectively; $p = .85$). Compared with siblings, fewer CCSs were married or living as married (88% vs. 94%; $p = .026$), were employed (91% vs. 98%; $p < .001$),

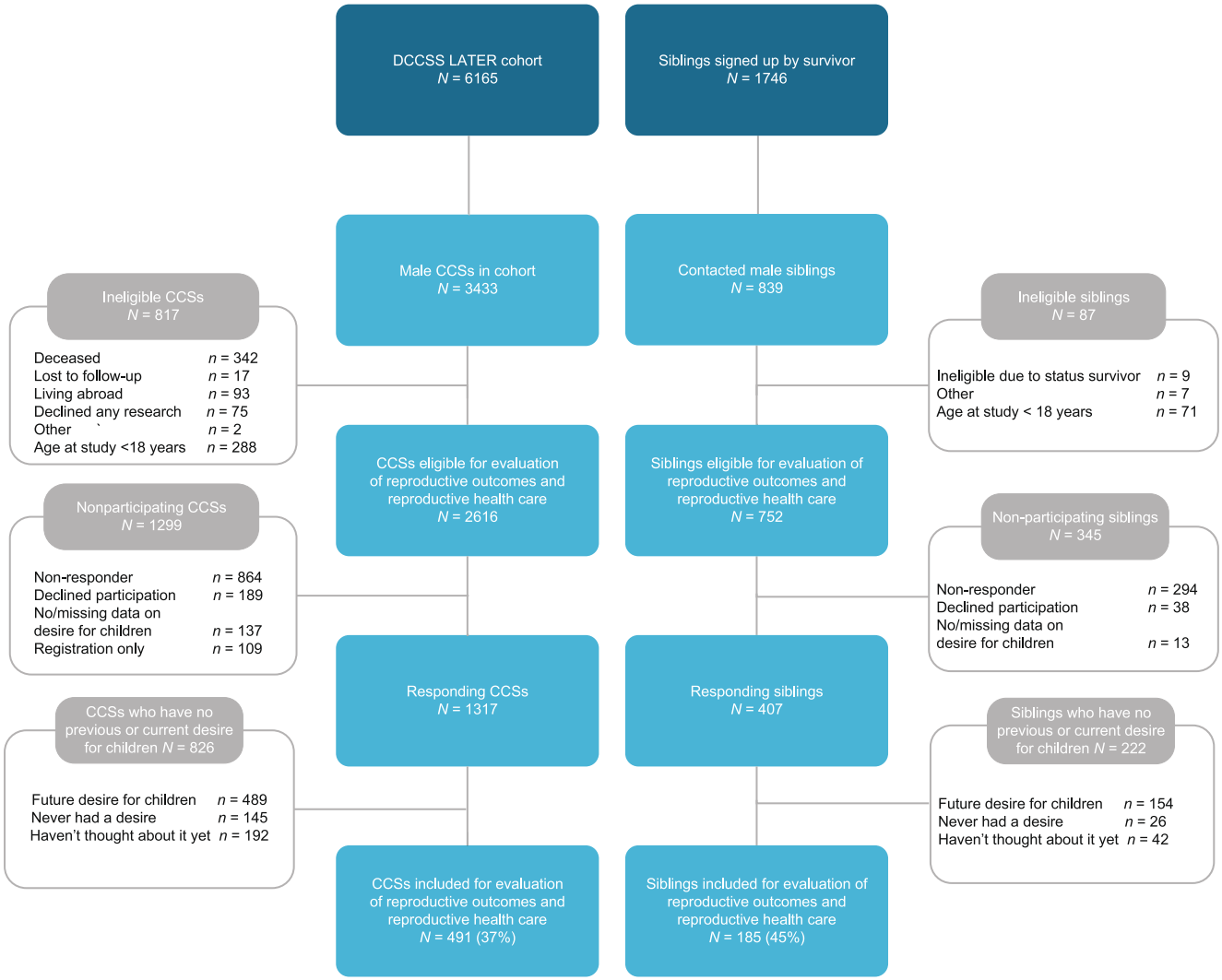

FIGURE 1 Participation of male childhood cancer survivors and male siblings in the Dutch Childhood Cancer Survivor LATER study addressing reproductive outcomes and reproductive health care utilization. CCSs indicates childhood cancer survivors; DCCSS, Dutch Childhood Cancer Survivor Study.

and more had a low level of education (13% vs. 4%; $p = .003$). Lymphoid leukemia was the most common diagnosis (26%). Eighty-five percent of the survivors received chemotherapy and 51% of the survivors received radiotherapy.

Reproductive outcomes

Details on reproductive outcomes are shown in Table 2. Compared with siblings, significantly fewer male CCSs with a previous or current desire for children had one or more biological children (65% vs. 88%; $p < .001$). The type of conception of men who fathered a child was comparable between CCSs and siblings (spontaneous conception in both 90% of CCSs and siblings; $p = .86$).

The percentage of men who sired one or more pregnancies that had not led to live birth was comparable between CCSs and siblings (30% and 29%; $p = .76$). In both CCS and siblings who sired one or more pregnancies that had not led to live birth, the rates of partners who conceived spontaneously was similar as well (83% of CCSs and 79% of siblings; $p = .50$).

Reproductive health care utilization

The percentage of men who consulted a reproductive specialist because of not siring a pregnancy was significantly higher among CCSs compared with siblings (34% vs. 12%; $p < .001$). Following consultation, fewer CCSs underwent ART compared with siblings (41% vs. 77%; $p = .001$). Among CCSs and siblings who underwent ART, the percentage of men who fathered a child was significantly lower in CCSs compared with siblings (49% vs. 94%; $p < .001$). Of men who consulted a reproductive specialist but did not undergo ART, fewer CCSs fathered one or more biological children spontaneously compared with siblings (38% vs. 80%; $p = .07$). Figure 2

TABLE 1 Characteristics of participating male childhood cancer survivors and male siblings with a current or previous desire for children.

	Childhood cancer survivors (*N* = 491)		Siblings (*N* = 185)		
	No.	%	No.	%	*p*
Age at assessment (years)					
18–29	58	11.8	19	10.3	.85
30–39	243	49.5	94	50.8	
≥40	190	38.7	72	38.9	
Marital status					
Married/living as married	429	87.6	173	93.5	.026
Not married/not living as married	61	12.4	12	6.5	
Missing	1		0		
Level of education[a]					
Low	63	12.8	8	4.3	< .001
Middle	244	49.7	80	43.2	
High	184	37.5	97	52.4	
Missing	0				
Employment status					
Employed	442	90.8	182	98.4	.003
Student	5	1.0	0	0	
Unemployed	40	8.2	3	1.6	
Missing	4		0		
Age at cancer diagnosis (years)					
0–4	146	29.7	-	-	
5–9	135	27.5	-	-	
10–17	210	42.8	-	-	
Primary childhood cancer diagnosis[b]					
Lymphoid leukemias	126	25.7	-	-	
Other leukemias, myeloproliferative diseases, and myelodysplastic diseases	13	2.6	-	-	
Non-Hodgkin and other lymphomas and reticuloendothelial neoplasms	82	16.9	-	-	
Hodgkin lymphomas	54	11.0	-	-	
CNS and miscellaneous intracranial and intraspinal neoplasms	35	7.1	-	-	
Renal tumors	50	10.2	-	-	
Malignant bone tumors	43	8.8	-	-	
Soft tissue and other extraosseous sarcomas	47	9.6	-	-	
Other and unspecified malignant neoplasms	40	8.1	-	-	
Time since cancer diagnosis (years)					
5–9	0	0	-	-	
10–19	55	11.2	-	-	
20–29	212	43.2	-	-	
≥30	224	45.6	-	-	

(Continues)

TABLE 1 (Continued)

	Childhood cancer survivors (*N* = 491)		Siblings (*N* = 185)		
	No.	%	No.	%	*p*
Period of cancer diagnosis					
<1970	20	4.1	-	-	
1970–1979	135	27.5	-	-	
1980–1989	231	47.0	-	-	
≥1990	105	21.4	-	-	
Cancer treatment					
Surgery/no treatment[c]	31	6.3	-	-	
Chemotherapy only	211	43.0	-	-	
Radiotherapy only	44	9.0	-	-	
Chemotherapy and radiotherapy combined	205	41.7	-	-	
Allogeneic hematopoietic stem cell transplantation			-	-	
Yes	9	1.9			
No	472	98.1	-	-	
Missing	10				

Abbreviation: CNS, central nervous system.

[a]Level of education: low: primary education, vocational education, special school; middle: preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, preuniversity education; high: higher vocational education, university.

[b]Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3).

[c]Number of survivors who received no treatment = 1.

TABLE 2 Reproductive outcomes after spontaneous and assisted conception among male childhood cancer survivors and male siblings with a previous or current desire for children.[a]

	Childhood cancer survivors (*N* = 491)		Siblings (*N* = 185)		
	n	%	*n*	%	*p*[a]
Men who had one or more biological children	317/491	64.6	162/185	87.6	<.001
Spontaneous conception	284	89.6	146	90.1	.86
Assisted conception	33	10.4	16	9.9	
Men who sired one or more pregnancies that had not led to live birth	102/340[b]	30.0	47/164[b]	28.7	.76
Spontaneous conception	85	83.3	37	78.7	.50
Assisted conception	17	16.7	10	21.3	

[a]Reproductive outcomes of male childhood cancer survivors and siblings were compared using the chi-square test. In addition, *p* values of differences in distribution of method of conception (spontaneous and assisted) of reproductive outcomes between childhood cancer survivors and siblings are shown.

[b]Three childhood cancer survivors and one sibling who reported to have sired a pregnancy but had not answered the question addressing biological children, were not included.

shows the reproductive outcomes, specified for spontaneous and assisted conception, among CCSs and siblings.

Table 3 shows details regarding methods of ART and outcomes of different ART (sperm donation not included). The most frequently applied method of ART was ICSI in CCSs (35%) and intrauterine insemination in siblings (41%). None of the 10 CCSs who underwent ICSI combined with a surgical sperm retrieval procedure sired a pregnancy.

Of men who had a previous of current desire for children, 23 CCSs and no siblings reported to have used sperm donation.

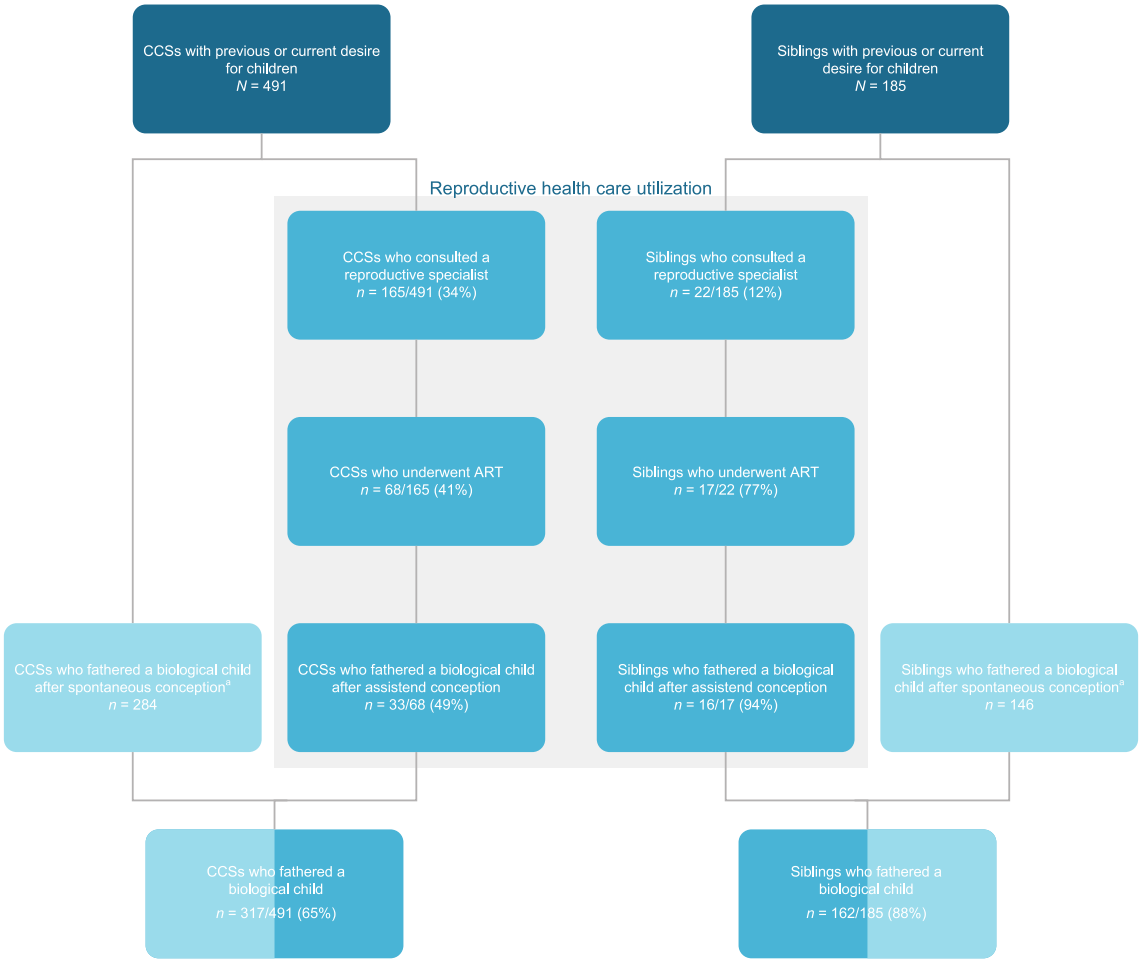

FIGURE 2 Reproductive outcomes, specified for spontaneous and assisted conception, among male childhood cancer survivors and male siblings. ART indicates assisted reproductive techniques; CCSs, childhood cancer survivors. [a]Of men who fathered a biological child after spontaneous conception, 37 of 284 CCSs and four of 146 had consulted a reproductive specialist.

TABLE 3 Methods and outcomes of assisted reproductive techniques applied to male childhood cancer survivors and male siblings.

	Childhood cancer survivors[b] (*N* = 68)			Siblings (*N* = 17)			
Method of assisted reproductive techniques[a]	*n*	%	Survivors with biological child (*n* = 33)	*n*	%	Siblings with biological child (*n* = 16)	*p* (test method of ART)[c]
Ovulation induction	11	16.2	7	4	23.5	4	.49
Intrauterine insemination	4	5.9	3	7	41.2	7	.001
In vitro fertilization	19	27.9	9	4	23.5	4	> .99
ICSI	24	35.3	14	2	11.8	1	.08
ICSI combined with surgical sperm retrieval procedure	10	14.7	0	0	0	-	.20

Abbreviations: ART, assisted reproductive techniques; ICSI, intracytoplasmic sperm injection.

[a]If more than one method of ART was applied, the most invasive or high technology method is described in the following order: ICSI combined with surgical sperm retrieval procedure (i.e., testicular sperm extraction [TESE] and/or percutaneous epididymal sperm aspiration [PESA]), ICSI, in vitro fertilization, intrauterine insemination, and ovulation induction only. Twenty childhood cancer survivors and two siblings underwent more than one method of ART.

[b]Of 68 childhood cancer survivors who had used ART, 15 survivors also used sperm donation.

[c]Methods of ART used for childhood cancer survivors and siblings were compared using the Fisher exact test.

DISCUSSION

This study reports on reproductive outcomes in a nationwide cohort of adult male survivors of childhood cancer, comprising all different cancer diagnoses, in comparison to a control group of male siblings. We extend previous studies addressing reproductive outcomes by providing information regarding utilization of reproductive health care and by focusing on men who had a previous or current desire for children.

In our study, 65% of male CCSs who had a desire for children fathered a biological child. Available literature shows lower percentages of CCSs who sired a pregnancy (15%–30%).[11,15] These studies included CCSs aged between 15 and 44 years and sexually active CCSs, respectively. The current study evaluated fertility in the light of reproductive intentions and focused on men who had a previous or current desire for children. The exclusion of men who had no desire for children (yet) could explain the differences in reproductive outcomes between previous reports and the current study. Furthermore, this study reports on reproductive outcomes specified for type of conception, spontaneous or assisted. Comparable to the siblings, children of 90% of CCSs were conceived spontaneously.

Details regarding reproductive health care utilization showed that, compared with siblings, male CCSs are almost three times more likely to consult a reproductive specialist because of not siring a pregnancy (34% in CCSs vs. 12% in siblings), but the use of ART following consultation was one-half as frequent among CCSs compared with the controls (41% in CCSs vs. 77% in siblings). Reasons for the lower application of ART are unknown. Because 38% of the CCSs who did not undergo ART fathered a biological child after spontaneous conception, fertility assessment that predicted good fertility prospects and counseling for expectant management might explain a part of the lower application of ART of CCSs who consulted a reproductive specialist. Another part of the lower application of ART might be explained by azoospermia. Reproductive concerns addressing fear of cancer recurrence and health of offspring were previously reported by CCSs.[16–18] These concerns and also late effects of cancer treatment could influence a survivor's choice to pursue his desire for children and to undergo ART. Furthermore, in our study, more CCSs had a low level of education and were unemployed. These factors could also influence a choice to undergo ART. In our study, not all CCSs who had to deal with an unfulfilled desire had consulted a reproductive specialist. Reasons for not consulting a reproductive specialist were unknown but might be due to previously mentioned concerns. Future studies could explore these reasons in more detail, in which the medical doctor's point of view on referring/not referring would be informative to study as well.

Details concerning reproductive outcomes of ART showed that birth rates after ART among CCSs were one-half of the rates reported by siblings (49% vs. 94%). Details regarding ART (e.g., sperm retrieval, ovarian stimulation, fertilization rate, embryo development and transfer) could elucidate the potential mechanisms behind this observed difference. For example, in our study, surgical sperm retrieval procedures were performed in 10 CCSs and none of the partners conceived. More details regarding this treatment might have been informative in explaining the low success rate. Because previous studies on TESE reported sperm retrieval rates of 36% in cancer survivors and live birth rates of 42% to 53% achieved with ICSI after successfully retrieved spermatozoa, TESE might be successful in CCSs.[19,20]

Literature addressing miscarriage among partners of male CCSs report a miscarriage rate of 13% and increased rates after treatment with more than 5000 mg/m^2 of procarbazine and after treatment for bone cancer.[16] The present study did not report on miscarriage rates but reported on the percentage of men who (ever) sired a pregnancy that had not led to live birth and showed both 30% of CCSs and siblings had (ever) sired a pregnancy that had not led to live birth. Lifetime risk data on pregnancy loss in men are not available. Lidegraad et al. performed a lifetime analysis in women and reported 23% of women experienced at least one pregnancy loss.[21] Because they did not include pregnancy losses outside hospitals or clinics, the lifetime risk may be even higher. Details concerning type of conception showed that the partners of four-fifths of both the CCSs and siblings who sired a pregnancy that had not led to live birth conceived spontaneously. The interpretation of our data on pregnancy loss is limited by the lack of details regarding information concerning the males' partners and regarding ART.

The present study is a large observational cohort study reporting on reproductive outcomes and use of reproductive health care among male CCSs compared with siblings. However, some limitations need to be discussed. The cohort definition was based on the question addressing desire for children. Information on reasons for not having a desire for children (anymore) or not having decided concerning fatherhood yet was not available. Whether proven infertility or not being in a relationship could have influenced a participant's answer to the question addressing desire for children is therefore not known. Because this study on reproductive outcomes was part of a larger study that addressed a wide variety of topics, this bias may be limited. The differences in cancer diagnosis and treatment between the study cohort and CCSs who had no previous or current desire for children and nonparticipating CCSs could have an affect on the study outcomes. The overrepresentation of treatment with a combination of chemo- and radiotherapy and underrepresentation of treatment with surgery only in the participating CCSs could have negatively influenced the reproductive outcomes. In contrast, the underrepresentation of CCSs who were diagnosed with a central nervous system tumor or who underwent an allogeneic hematopoietic stem cell transplantation could have positively influenced the reproductive outcomes. Information on the male partner's etiology of subfertility, reasons for not using ART and details concerning ART were not available. This information could have partly clarified the observed differences between CCSs and siblings regarding pregnancies and live births after ART. Second, this study analyzed data obtained from a questionnaire survey conducted during 2013 to 2015 in CCSs who were treated before 2002. Because the practice of fertility preservation and reproductive medicine have advanced considerably during the past 15 years, the impact of these developments on reproductive

outcomes needs to be investigated in future studies, including cancer survivors who are treated more recently.[22] Since the introduction of TESE in the Netherlands in 2007, cancer survivors who have azoospermia after treatment can be offered TESE. More data addressing the success rate of TESE and factors associated with successful sperm retrieval are needed to evaluate the impact of this development on achieving biological fatherhood.

CONCLUSIONS

Two-thirds of male survivors of childhood cancer who had a desire for children fathered a biological child. Children of 90% of male CCSs were conceived spontaneously. Compared with male siblings, more male CCSs consult a reproductive specialist because of not siring a pregnancy; however, both the application of and birth rates after ART in survivors are lower. Data on reproductive outcomes and reproductive health care after cancer treatment are important for understanding potential problems faced by survivors regarding family planning and fertility issues and can support counseling of CCSs. At cancer diagnosis, it is essential to discuss the risk of gonadotoxicity and options for fertility preservation. After cancer treatment, it is important to review reproductive intentions and concerns, to conduct evaluation of gonadal function, and to refer for reproductive health services. In case of infertility, it is important to discuss other options to fulfill a desire for children, such as use of donated gametes, adoption, or foster care, and to address grief of unwanted childlessness. Collaboration between oncologists and reproductive specialists is essential for cancer survivorship care at cancer diagnosis and in cancer survivorship care.

AUTHOR CONTRIBUTIONS

Joyce J. M. Claessens: Conceptualization; Methodology; Writing - original draft; Visualization; and Project administration. **Adriaan Penson**: Methodology; Formal analysis; Data curation; and Writing - review & editing. **Ewald M. Bronkhorst**: Methodology; Formal analysis; and Writing - review & editing. **Leontien C. M. Kremer**: Writing - review & editing and Funding acquisition. **Eline van Dulmen-den Broeder**: Writing - review & editing and Funding acquisition. **Margriet van der Heiden-van der Loo**: Funding acquisition; Writing - review & editing; Software; Validation; Investigation; Resources; and Data curation. **Wim J. E. Tissing**: Funding acquisition and Writing - review & editing. **Helena J. H. van der Pal**: Funding acquisition and Writing - review & editing. **Nicole M. A. Blijlevens**: Writing - review & editing. **Marry M. van den Heuvel-Eibrink**: Writing - review & editing and Funding acquisition. **A. Birgitta Versluys**: Writing - review & editing and Funding acquisition. **Dorine Bresters**: Funding acquisition and Writing - review & editing. **Cécile M. Ronckers**: Writing - review & editing and Funding acquisition. **Iris Walraven**: Methodology; Writing - review & editing; Conceptualization; and Formal analysis. **Catharina C. M. Beerendonk**: Conceptualization; Methodology; and Writing - review & editing. **Jacqueline J. Loonen**: Funding acquisition; Writing - review & editing; Supervision; Conceptualization; and Methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

PATIENT CONSENT STATEMENT

All participants gave their written informed consent before their inclusion in the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable. This study did not reproduce material from other sources.

CLINICAL TRIAL REGISTRATION

This study is not registered in a clinical trial register as this study is not a clinical trial. This study is a cross-sectional study that is part of a retrospective cohort study.

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SUPPORTING INFORMATION

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

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