VOLUME 27 · NUMBER 16 · JUNE 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Fertility of Female Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, and Leslie L. Robison

From the Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, Memphis, TN; Clinical Statistics and Cancer Prevention Programs, Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX; Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Pediatrics, Emory University, Atlanta, GA; Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA and Boyne Research Foundation, Washington, DC.

Submitted September 15, 2008; accepted December 16, 2008; published online ahead of print at www.jco.org on April 13, 2009.

Supported by the National Institutes of Health, National Cancer Institute Grant No. U24 CA55727 (L.L.R.); by the Children's Cancer Research Fund to the University of Minnesota Cancer Center; and by the American Lebanese Syrian Associated Charities.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Daniel M. Green, MD, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 735, Memphis, TN 38105-2794; e-mail: daniel.green@stjude.org.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2716-2677/$20.00

DOI: 10.1200/JCO.2008.20.1541

ABSTRACT

Purpose
This study was undertaken to determine the effect, if any, of treatment for cancer diagnosed during childhood or adolescence on fertility.

Patients and Methods
We reviewed the fertility of female participants in the Childhood Cancer Survivor Study (CCSS), which consisted of 5-year survivors, and a cohort of randomly selected siblings who responded to a questionnaire. Medical records of all members of the cohort were abstracted to obtain chemotherapeutic agents administered; the cumulative dose of drug administered for several drugs of interest; and the doses, volumes, and dates of administration of all radiation therapy.

Results
There were 5,149 female CCSS participants, and there were 1,441 female siblings of CCSS participants who were age 15 to 44 years. The relative risk (RR) for survivors of ever being pregnant was 0.81 (95% CI, 0.73 to 0.90; $P < .001$) compared with female siblings. In multivariate models among survivors only, those who received a hypothalamic/pituitary radiation dose $\geq$ 30 Gy (RR, 0.61; 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant (RR, 0.56 for 5 to 10 Gy; 95% CI, 0.37 to 0.85; RR, 0.18 for $>$ 10 Gy; 95% CI, 0.13 to 0.26). Those with a summed alkylating agent dose (AAD) score of three or four or who were treated with lomustine or cyclophosphamide were less likely to have ever been pregnant.

Conclusion
This large study demonstrated that fertility is decreased among female CCSS participants. The risk factors identified may be utilized for pretreatment counseling of patients and their parents.

J Clin Oncol 27:2677-2685. © 2009 by American Society of Clinical Oncology

INTRODUCTION

The treatment of children and adolescents who have cancer has become increasingly successful. Approximately 78% of all patients diagnosed before 15 years of age will survive for 5 years.[1] The majority are expected to survive for many years after diagnosis.

The treatment that these patients receive may affect germ cell survival. Ovarian damage results in both sterilization and loss of hormone production. High-dose radiation to the hypothalamic-pituitary axis can produce secondary hypogonadism as a result of gonadotropin deficiency.[2]

There are limited epidemiologic data that assess fertility in exposed populations. Byrne et al[3] evaluated the fertility of 2,283 childhood cancer survivors diagnosed between 1945 and 1975, excluding women who had never married; who married before their diagnosis of cancer; who became pregnant before their first marriage; who had never menstruated; or who had undergone sterilizing surgery. The adjusted relative fertility of female survivors was 0.93 (95% CI, 0.83 to 1.04). The absence of a significant difference in the relative fertility for female survivors in that report may be partly explained by the exclusion criteria employed and/or the exposure of few of those studied to potentially gonadal toxic therapy.[3]

This study was undertaken to evaluate fertility in the female participants in the Childhood Cancer Survivor Study (CCSS) and to determine risk factors for decreased fertility.

PATIENTS AND METHODS

A cohort of 20,720 previously untreated patients who were younger than 21 years of age at diagnosis, who survived for at least 5 years after the date of diagnosis, and who were diagnosed with an eligible cancer between January 1, 1970

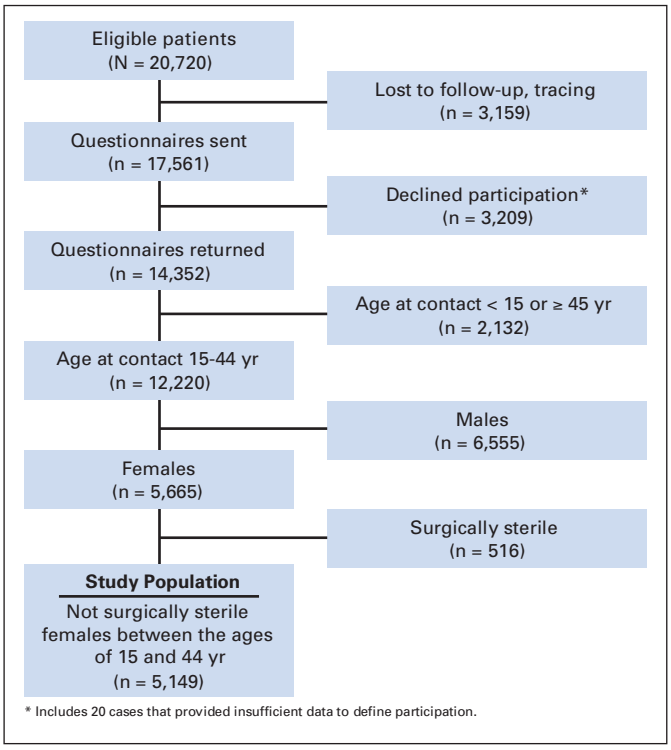

Fig 1. Flowchart of cohort subgroups for female fertility analysis.

and December 31, 1986, was identified at the 26 participating institutions of the CCSS (Fig 1). The study design, cohort characteristics, and baseline data collection are presented in detail elsewhere. Age at pregnancy, marital status, educational level, and smoking status were self reported.[4]

The CCSS collected data for all surgical procedures performed for cancer treatment. In addition, participants and siblings were asked about additional surgical procedures performed and the methods employed for contraception, including tubal ligation and vasectomy. Those participants or their partners who underwent an operation that resulted in sterilization (eg, tubal ligation, hysterectomy, vasectomy) were classified as surgically sterile as a result of contraceptive or noncontraceptive reasons and were excluded from this analysis.[5] On the basis of these definitions, 516 female CCSS participants and/or their partners who were age 15 to 44 years at follow-up were categorized as surgically sterile (contraceptive reasons, n = 474; noncontraceptive reasons, n = 42). This analysis focused on the 5,149 female survivors who were not surgically sterile (Fig 1).

Permission was requested from a random sample of the cohort to contact their nearest-age siblings.[4] Three thousand forty eight (80.5%) participated among 4,782 eligible siblings, of whom 1,441 were women between the ages of 15 to 44 years who were not surgically sterile. These siblings were used as controls for comparisons to survivors in the CCSS cohort. Two hundred ninety-four female siblings of CCSS participants and/or their partners who were age 15 to 44 years at follow-up were categorized as surgically sterile (contraceptive reasons, n = 288; noncontraceptive reasons, n = 6).

This study was approved by the institutional review board at each participating institution, and informed consent for participation was obtained from all participants who were 18 years of age or older, or from their parents if the participants were younger than 18 years of age.

Exposure Assessment

Detailed data regarding the chemotherapeutic agents administered to the patient for treatment of the original cancer; any recurrences of the cancer; the cumulative dose of drug administered for several drugs of interest; and the doses, volumes, and dates of administration of all radiation therapy were recorded on the Medical Record Abstract Form for 12,492 of those who completed the baseline questionnaire.

The cumulative doses of a number of chemotherapeutic agents were obtained. The distribution of cumulative doses for each of the agents was divided into tertiles (Table 1). Among patients exposed to an alkylating agent, the alkylating agent dose (AAD) score was calculated by adding the tertile score (1, 2, or 3) for each of the alkylating agents given to a particular patient.[6] An AAD score of 0 was assigned to nonexposed patients.

Radiation doses to the ovaries, uterus, and hypothalamus/pituitary[7] were estimated for each patient by reviewing and abstracting details of the radiation therapy from records submitted by the treating institutions. For organs in a beam, standard radiotherapy depth dose data were used to estimate dose. For organs outside a treatment beam, measurements in a water phantom were applied to a three-dimensional mathematical phantom that simulated the size and shape of patients of various ages. Any field blocking used during treatment was accounted for in estimating doses. Details of the dosimetry methods were described by Stovall et al.[8,9]

Statistical Methods

Cox proportional hazard models that used age as the time scale were used to compare hazards of a pregnancy, as previously described by Yasui et al.[10] Participants entered the risk set for regression analyses at the age at which they entered the CCSS cohort (ie, 5 years after date of diagnosis of primary cancer) or at age 15 years, whichever was older, and were observed until the minimum

Table 1. Tertile Distribution of Alkylating Agents in Cumulative Dose

Alkylating Agent	Cumulative Dose by Tertile		
	First	Second	Third
BCNU, mg/m^2	1-300	301-529	530-5,370
Busulfan, mg/m^2	1-317	318-509	510-6,845
CCNU, mg/m^2	1-361	362-610	611-3,139
Chlorambucil, mg/m^2	1-165	166-634	635-3,349
Parenteral cyclophosphamide, mg/m^2	1-3,704	3,705-9,200	9,201-58,648
Oral cyclophosphamide, mg/m^2	1-4,722	4,723-10,636	10,637-143,802
Ifosfamide, mg/m^2	1-16,771	16,772-55,758	55,759-192,391
Melphalan, mg/m^2	1-39	40-137	138-574
Nitrogen mustard, mg/m^2	1-44	45-64	65-336
Procarbazine, mg/m^2	1-4,200	4,201-7,000	7,001-58,680
Intrathecal thiotepa, mg	1-80	81-320	321-914
Thiotepa, mg/m^2	1-77	78-220	221-3,749

NOTE. First tertile score is 1; second is 2; and third is 3.
Abbreviations: BCNU, carmustine; CCNU, lomustine.

Table 2. Demographic and Treatment Characteristics of Female Survivors of Childhood Cancer and of Siblings Who Were Not Surgically Sterile

Characteristic	No. of Missing Data	Survivors		Siblings		*P*
		No.	%	No.	%	
Ethnicity	72*					
Non-Hispanic white		4,266	83.2	1,248	89.7	< .001
Hispanic		131	2.6	18	1.3	
Non-Hispanic black		223	4.3	40	2.9	
Other		507	9.9	85	6.1	
Smoking status	121*					
Never smoked		3,907	77.5	930	65.2	< .001
Current smoker		687	13.6	290	20.3	
Former smoker		449	8.9	206	14.4	
Marital status	265*					
Never married		2,993	60.3	614	45.0	< .001
Currently married		1,648	33.2	663	48.6	
Formerly married		319	6.4	88	6.4	
Education level	332*					
No high school or GED		1,197	24.6	231	16.6	< .001
High school or GED		880	18.1	199	14.3	
Some college, no bachelor's degree		1,542	31.7	436	31.3	
Bachelor's degree or higher		1,244	25.6	529	37.9	
Age at baseline, years						
15-19		1,443	28.0	301	20.9	< .001
20-24		1,416	27.5	342	23.7	
25-29		1,109	21.5	355	24.6	
30-34		755	14.7	250	17.3	
35-39		339	6.6	147	10.2	
40-44		87	1.7	46	3.2	
Age at diagnosis, years						
0-4		1,798	34.9			
5-9		1,245	24.2			
10-14		1,181	22.9			
15-19		807	15.7			
≥ 20		118	2.3			
Primary diagnosis						
Leukemia		1758	34.1			
CNS		663	12.9			
HD		707	13.7			
NHL		269	5.2			
Kidney (Wilm's)		498	9.7			
Neuroblastoma		317	6.2			
Soft tissue sarcoma		460	8.9			
Bone cancer		477	9.3			
Radiation dose						
Ovarian	737					
No		1,435	32.5			
Yes		2,977	67.5			
Uterine	733					
No		1,428	32.3			
Yes		2,988	67.7			
Ovarian/uterine	738					
No		1,428	32.4			
Yes		2,983	67.6			
Hypothalamic/pituitary	743					
No		1,429	32.4			
Yes		2,977	67.6			
Oophoropexy						
No		4,979	96.7			
Yes		170	3.3			

(continued on following page)

Table 2. Demographic and Treatment Characteristics of Female Survivors of Childhood Cancer and of Siblings Who Were Not Surgically Sterile (continued)

Characteristic	No. of Missing Data	Survivors		Siblings		*P*
		No.	%	No.	%	
Summed AAD	1,092†					
0		2,223	54.8			
1		415	10.2			
2		455	11.2			
3		587	14.5			
4		161	4.0			
5		117	2.9			
6-11		99	2.4			
CCNU	597					
No		4,399	96.6			
Yes		153	3.4			
Cisplatin	597					
No		4,329	95.1			
Yes		223	4.9			
Cyclophosphamide	597					
No		2,617	57.5			
Yes		1,935	42.5			
Cytosine arabinoside	597					
No		3,594	79.0			
Yes		958	21.0			
Doxorubicin	597					
No		3,129	68.7			
Yes		1,423	31.3			
Nitrogen mustard	597					
No		4,283	94.1			
Yes		269	5.9			
Procarbazine	597					
No		4,093	89.9			
Yes		459	10.1			
Vinblastine	597					
No		4,346	95.5			
Yes		206	4.5			
VM26	597					
No		4,372	96.0			
Yes		180	4.0			
VP16	597					
No		4,325	95.0			
Yes		227	5.0			

NOTE. Age of siblings at time of baseline questionnaire ranged from 15 to 44 years.
Abbreviations: GED, general education development; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; AAD, alkylating agent dose; CCNU, lomustine; VM26, teniposide; VP16, etoposide.
*Number missing is that of both survivors and siblings.
†Those patients with alkylating agents but without dose information were set as missing.

age of first pregnancy, death, completion of baseline questionnaire, or age of 44 years, whichever came first. To create a similar age-based follow-up period, siblings were assigned a pseudo-diagnosis date that corresponded to the age of their survivor sibling at diagnosis of their primary cancer, and identical methods were used to define their time-to-event variables. Within-family correlation was accounted for with the use of sandwich standard-error estimates.[11] Multiple-imputation methodology for event-time imputations[12,13] was employed for those who reported one or more pregnancies but who did not report age at first pregnancy. Age at first pregnancy was available for 81.0% (1,111 of 1,372) of survivors and for 86.6% (479 of 553) of siblings, and the age was imputed for the remaining 19.0% (261 of 1,372) of female survivors and for the remaining 13.4% (74 of 553) of female siblings. Analyses of treatment (exposure) variables were restricted to those female survivors for whom medical record abstraction was completed (n = 4,317), whereas those analyses that required only demographic data (eg, age at questionnaire, diagnosis) included all women age 15 to 44 years who had completed the baseline questionnaire.

Two sets of models were evaluated. The first compared fertility for survivors versus siblings and controlled for education level, marital status, age at diagnosis (or age at pseudo-diagnosis), ethnicity, and smoking status. A second set of models, among survivors only, evaluated the impact of treatment variables and adjusted for the same variables as the first set. Candidate treatment variables that were evaluated included summed AAD score, ovarian/uterine radiation dose, hypothalamic/pituitary radiation dose, and the following individual chemotherapy agents: dactinomycin, carmustine (BCNU), lomustine (CCNU), cyclophosphamide, cisplatin, cytarabine, daunorubicin, doxorubicin, dacarbazine (DTIC), nitrogen mustard, procarbazine, vinblastine, vincristine, teniposide (VM26), etoposide (VP16), thiotepa, ifosfamide, and melphalan. Univariate and multivariate analyses were carried out, and final treatment variables that were included in the multivariate model were significant at the .05 level or were those that markedly influenced (> 10% change) the effect of another factor in the model (ie, a confounder). Two separate, multivariate models were fit to evaluate the

impact of separate chemotherapy agents and combined alkylating agents by using the previously described AAD score. Interactive effects between the two radiation volumes (ie, ovary/uterus and hypothalamus/pituitary) were evaluated to the extent possible, and they were not significant. Cut points for radiation categories were selected on the basis of both biologic plausibility[2,14-19] and statistical separation of groups. The referent group for ovarian/uterine radiation was selected to include those with ≤ 2.5 Gy and no radiation exposure to this region. Similarly, for the hypothalamic/pituitary radiation, the referent group consisted of those without radiation exposure to this region and those with ≤ 10 Gy exposure.

RESULTS

Six thousand six hundred forty-three women returned a baseline questionnaire, 5,149 of whom were between the ages of 15 and 44 years at the time of completion of the questionnaire and were not surgically sterile. One thousand three hundred seventy-two women indicated that they had ever been pregnant 5 or more years after the date of the primary cancer diagnosis.

The CCSS participants were younger ($P < .001$), more likely to be of minority ethnicity ($P < .001$), less likely to have a bachelor's degree or higher ($P < .001$), more likely to have never been married ($P < .001$), and more likely to have never smoked ($P < .001$) than the sibling cohort (Table 2). The distributions listed in Table 3 are those of calculated, organ-specific radiation exposure to each ovary, uterus, ovaries/uterus combination, and hypothalamus/pituitary.

When analysis was adjusted for age at diagnosis, marital status, educational attainment, ethnicity, and smoking status, the relative risk (RR) of a survivor ever being pregnant was 0.81 (95% CI, 0.73 to 0.90; $P < .001$), compared with the sibling cohort. Multivariate models among survivors were developed (Table 4). A dose-response relationship was present for decreased risk of pregnancy with increasing dose of ovarian/uterine radiation. The RR of pregnancy was 0.56 (95% CI, 0.37 to 0.85) for exposure of 5 to 10 Gy and was 0.18 (95% CI, 0.13 to 0.26) for exposure of greater than 10 Gy to the ovaries/uterus (Table 4). The risk of pregnancy was decreased for hypothalamic/pituitary doses greater than 30 Gy (RR, 0.61; 95% CI, 0.44 to 0.83). In the multivariate model that assessed the summed AAD score, a score of three (RR, 0.72; 95% CI, 0.58 to 0.90; $P = .003$) or four (RR, 0.65; 95% CI, 0.45 to 0.96; $P = .03$) was associated with lower observed risk of pregnancy compared with those who had no alkylating agent exposure. Increasing AAD score was statistically significantly associated with the risk of not having been pregnant ($P = .004$). Multivariate models that evaluated individual chemotherapeutic agents demonstrated lower risk of pregnancy for those who were treated with CCNU (RR, 0.44; 95% CI, 0.24 to 0.80; $P = .008$) or cyclophosphamide (RR, 0.8; 95% CI, 0.68 to 0.93; $P = .005$). The impacts of these single drugs were dose related, and fertility decreased with increasing dose (CCNU first tertile RR, 0.76; 95% CI, 0.30 to 1.93; $P = .57$; CCNU second or third tertile RR, 0.31; 95% CI, 0.11 to 0.88; $P = .028$; cyclophosphamide first tertile RR, 0.83; 95% CI, 0.65 to 1.06; $P = .13$; cyclophosphamide second tertile RR, 1.06; 95% CI, 0.84 to 1.33; $P = .63$; cyclophosphamide third tertile RR, 0.72; 95% CI, 0.58 to 0.90; $P = .003$). Although both were statistically significant in univariate analyses, neither oophoropexy nor treatment with nitrogen mustard, cytarabine, cisplatin, procarbazine, vinblastine, VM26, or VP16 remained significant in the multivariate models. In both multivariate models, treatment that included doxorubicin was associated with a statistically significant increased risk of pregnancy (RR, 1.21; 95% CI, 1.01 to 1.45; and RR, 1.22; 95% CI, 1.04 to 1.45). The models yielded qualitatively identical results whether constructed with or without inclusion of those participants for whom age at first pregnancy was imputed.

DISCUSSION

We undertook these analyses to determine the demographic and treatment factors that predicted the likelihood of pregnancy among female long-term survivors of childhood cancer. Overall, female survivors among the CCSS cohort were less likely to become pregnant compared with the participants in the sibling cohort. In contrast to previously published analyses,[3] women with ovarian failure produced by either ovarian irradiation or specific chemotherapeutic exposures were included in our analyses, which thus provided a truer picture of overall fertility among long-term survivors. Those who had completed less than a high school education, were African American, were married, or were in the youngest age group at diagnosis were more likely to

Table 3. Distribution of Radiation Dose Exposure of Female Survivors of Childhood Cancer Who Were Not Surgically Sterile

Radiation Dose, Gy	Patients per Radiation Dose Group*							
	Ovarian		Uterine		Ovarian/Uterine		Hypothalamic/Pituitary	
	No.	%	No.	%	No.	%	No.	%
0	1,435	32.5	1,428	32.3	1,428	32.4	1,429	32.4
0.001-2.5	2,295	52.0	2,374	53.8	2,256	51.1	1,316	29.9
2.51-5.00	226	5.1	166	3.8	209	4.7	74	1.7
5.01-10.00	144	3.3	104	2.4	140	3.2	43	1.0
10.01-15.00	95	2.2	115	2.6	105	2.4	49	1.1
15.01-20.00	49	1.1	42	1.0	49	1.1	436	9.9
20.01-25.00	49	1.1	59	1.3	72	1.6	536	12.2
25.01-30.00	30	0.7	37	0.8	41	0.9	86	2.0
30.01-35.00	33	0.7	33	0.7	41	0.9	75	1.7
35.01-40.00	21	0.5	14	0.3	22	0.5	76	1.7
> 40.00	35	0.8	44	1.0	48	1.1	286	6.5

NOTE. Age of survivors at time of baseline questionnaire ranged from 15 to 44 years.
*Numbers missing per group are as follows: ovarian, 737; uterine, 733; ovarian/uterine, 738; and hypothalamic/pituitary, 743.

Table 4. Relative Risk of Pregnancy Among Female Childhood Cancer Survivors in Two Separate Multivariate Models

Characteristic	Multivariate Analysis by Model					
	Individual Chemotherapy Agent			Summed AAD Score		
	RR	95% CI	*P*	RR	95% CI	*P*
Age at diagnosis, years						
0-4	1.85	1.44 to 2.38	< .001	1.95	1.51 to 2.54	< .001
5-9	1.25	1.03 to 1.51	.022	1.27	1.04 to 1.56	.02
10-14	1.25	1.00 to 1.57	.055	1.29	1.01 to 1.63	.039
15-20	1.00			1.00		
Education						
No high school/GED	1.00			1.00		
High school/GED	0.78	0.60 to 1.03	.082	0.71	0.54 to 0.94	.018
Some college	0.63	0.49 to 0.81	< .001	0.58	0.45 to 0.75	< .001
Bachelor's or higher	0.36	0.28 to 0.47	< .001	0.37	0.28 to 0.48	< .001
Ethnicity						
White	1.00			1.00		
Hispanic	0.88	0.57 to 1.35	.56	0.98	0.63 to 1.53	.94
Black	1.69	1.22 to 2.36	.002	1.73	1.24 to 2.42	.001
Other	0.98	0.77 to 1.23	.83	0.97	0.76 to 1.24	.81
Marital status						
Never married	1.00			1.00		
Currently married	5.14	4.28 to 6.18	< .001	5.03	4.15 to 6.09	< .001
Formerly married	3.92	3.04 to 5.05	< .001	3.96	3.04 to 5.15	< .001
Smoking status						
Never smoked	1.00			1.00		
Current smoker	0.78	0.62 to 0.97	.025	0.76	0.60 to 0.96	.02
Former smoker	0.68	0.57 to 0.80	< .001	0.64	0.54 to 0.76	< .001
Radiation dose, Gy						
Ovarian/uterine						
≤ 2.50	1.00			1.00		
2.50-5.00	0.80	0.57 to 1.11	.18	0.82	0.58 to 1.17	.27
5.00-10.00	0.56	0.37 to 0.85	.007	0.67	0.43 to 1.04	.075
> 10.00	0.18	0.13 to 0.26	< .001	0.20	0.14 to 0.29	< .001
Hypothalamic/pituitary						
≤ 10.00	1.00			1.00		
10.00-30.00	0.85	0.72 to 1.01	.067	0.86	0.72 to 1.02	.088
> 30.00	0.61	0.44 to 0.83	.002	0.61	0.44 to 0.85	.003
Oophoropexy						
Yes	0.80	0.58 to 1.09	.16	0.81	0.57 to 1.13	.21
No	1.00			1.00		
Summed AAD score						
0				1.00		
1				0.90	0.69 to 1.18	.44
2				0.91	0.72 to 1.16	.44
3				0.72	0.58 to 0.90	.003
4				0.65	0.45 to 0.96	.03
5				0.82	0.55 to 1.24	.35
6-11				0.76	0.49 to 1.19	.23
Cisplatin						
Yes	1.04	0.74 to 1.46	.83	1.07	0.74 to 1.55	.73
No	1.00			1.00		
Cytosine arabinoside						
Yes	1.08	0.88 to 1.33	.48	1.05	0.84 to 1.32	.67
No	1.00			1.00		
Doxorubicin						
Yes	1.22	1.04 to 1.45	.018	1.21	1.01 to 1.45	.034
No	1.00			1.00		
Vinblastine						
Yes	0.83	0.57 to 1.22	.34	0.86	0.52 to 1.41	.54
No	1.00			1.00		

(continued on following page)

Table 4. Relative Risk of Pregnancy Among Female Childhood Cancer Survivors in Two Separate Multivariate Models (continued)

Characteristic	Multivariate Analysis by Model					
	Individual Chemotherapy Agent			Summed AAD Score		
	RR	95% CI	*P*	RR	95% CI	*P*
VP16						
Yes	1.39	0.94 to 2.08	.1	1.50	0.97 to 2.30	.066
No	1.00			1.00		
VM26						
Yes	1.30	0.81 to 2.08	.28	1.32	0.81 to 2.17	.27
No	1.00			1.00		
CCNU						
Yes	0.44	0.24 to 0.80	.008			
No	1.00					
Cyclophosphamide						
Yes	0.80	0.68 to 0.93	.005			
No	1.00					
Nitrogen mustard						
Yes	0.82	0.57 to 1.19	.3			
No	1.00					
Procarbazine						
Yes	0.94	0.68 to 1.31	.73			
No	1.00					

NOTE. All factors that display estimates for a specific column are included together in that multivariate model.
Abbreviations: AAD, alkylating agent dose; RR, relative risk; GED, general education development; VP16, etoposide; VM26, teniposide; CCNU, lomustine.

have become pregnant. The findings with regard to marital status, ethnicity, and educational attainment reflected general population trends.[5] Those in the youngest age group at diagnosis (ie, 0 to 4 years) had an increased risk of pregnancy, which possibly reflected the greater number of ova present.[20,21]

In our treatment models, a hypothalamic/pituitary radiation dose greater than 30 Gy or an ovarian/uterine radiation dose greater than 5 Gy was a significant risk factor among female survivors for not having a pregnancy. Previous studies reported an increased risk of ovarian failure after whole-abdomen[22-24] or craniospinal irradiation[25,26] during childhood. Direct irradiation of the hypothalamus and/or pituitary may produce impaired secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), especially when the dose is greater than 35 Gy.[2,16-19] Lower-dose exposures (18 to 24 Gy), such as those employed for prophylactic cranial irradiation of children with acute lymphoblastic leukemia (ALL), did not appear to produce major abnormalities in FSH or LH release to luteinizing hormone–releasing hormone[27] or in 12-hour urinary excretion of FSH and LH,[28] although Bath et al[29] reported that LH excretion was decreased in patients with ALL compared with controls.

Abdominal radiation may damage the ovaries and/or uterus. Stillman et al[30] reported ovarian failure in none of 34 women who received abdominal irradiation to a volume that did not include both ovaries, in 14% of 35 women whose ovaries were at the edge of the abdominal treatment volume, and in 68% of 25 women whose ovaries were entirely within the treatment volume. Chemaitilly et al[14] demonstrated that ovarian doses greater than 10 Gy were associated with a high risk of acute ovarian failure among female CCSS participants.[14] Lower doses rarely produced sterilization.[15] Critchley et al[31,32] reported that uterine length was significantly less, endometrial thickness did not increase in response to hormone replacement therapy, and blood flow was undetectable in women after abdominal irradiation. Similar changes were reported after total-body irradiation.[33,34]

Ovarian function may be impaired after treatment with chemotherapy that includes an alkylating agent (eg, nitrogen mustard, procarbazine, chlorambucil, and cyclophosphamide).[14,35-43] Six cycles of the combination of nitrogen mustard, vincristine, procarbazine, and prednisone, as originally reported by DeVita et al,[44] exposes a patient to 8,400 mg/m^2 (1,400 mg/m^2/d $\times$ 14 days $\times$ six courses) of procarbazine and 72 mg/m^2 (12 mg/m^2/wk $\times$ 2 weeks $\times$ six courses) of nitrogen mustard and has an AAD score of six (Table 1). The risk of ovarian failure appeared to be directly correlated with cumulative dose but inversely correlated with age at exposure.[40,43]

Cumulative cyclophosphamide doses used in contemporary regimens for Hodgkin's disease (3.2 g/m^2 to 4.8 g/m^2)[45] and rhabdomyosarcoma (4.8 g/m^2 to 16.8 g/m^2; S. Spunt, personal communication, 2008) correspond to AAD scores of one to three. Current regimens for Ewing sarcoma include cyclophosphamide (8.4 g/m^2) and ifosfamide (63 g/m^2) in combination, which results in an AAD score of six.[46]

This study demonstrated a statistically significant reduction in the likelihood of pregnancy to be associated with ovarian/uterine radiation in a dose-dependent fashion. Moreover, we found that alkylating agent exposure was independently associated with reduced risk of pregnancy in a dose-dependent manner. Chiarelli et al[47] did not demonstrate a significant reduction in fertility among childhood cancer survivors who were treated with abdominal-pelvic irradiation and/or alkylating agents. Byrne et al[48] reported that the unadjusted fertility rate for female survivors of ALL was significantly lower than that of their siblings, but they were unable to demonstrate an effect of treatment with an alkylating agent or spinal irradiation on the fertility rates.

Unexpectedly, the risk of pregnancy was increased among those who had been treated with doxorubicin, independent of exposure to other potentially sterilizing modalities. There is no known mechanism whereby doxorubicin may enhance fertility; therefore, we consider this a spurious association.

This study has a number of strengths. The CCSS is the largest, most thoroughly characterized cohort of survivors of cancer diagnosed during childhood or adolescence, and it utilizes a sibling comparison group. Thus, important questions regarding the frequency of outcomes that may be modified by treatment exposures, as well as the relationship of these exposures to significant, though uncommon, late events, can be evaluated with substantial statistical power.

There are certain limitations that must be taken into account when interpreting this data. The participants were ascertained retrospectively; 15% of the eligible participants were lost to follow-up, and 16% declined participation. Participants, however, did not differ from nonparticipants with regard to demographics or cancer characteristics.[4] Radiation dosimetry was estimated by using the paper records supplied by the participating institutions without review of port films.

The CCSS utilized self-administered questionnaires for ascertainment of outcomes. In the general population, the frequency of pregnancies is under-reported by women, as approximately 22% of pregnancies detected by a transient increase in the serum level of human chorionic gonadotropin are not recognized clinically.[49] Information relating to adjustment variables (eg, smoking, education) should be considered surrogate measures, because they are derived from a single point in time (ie, at baseline questionnaire). Thus, these factors do not directly measure their influence over time.

We did not evaluate fertility in light of personal choices regarding pregnancy. Women may have chosen not to attempt pregnancy on the basis of concerns that they might transmit a trait that would predispose their children to cancer, concerns that they thought or were told that they are or might be infertile, or concerns that their appearance, sexual preference, socioeconomic status, or neurocognitive function interfered with their abilities to form or maintain an intimate heterosexual relationship.[50-52] Some of these factors may be related to the therapeutic exposures considered in this analysis. We cannot determine how these factors may have confounded the results of this study.

We have demonstrated that fertility is impaired in female childhood cancer survivors, and we have provided treatment-specific and dose-specific risk estimates. Women age 15 to 44 years who received a hypothalamic/pituitary radiation dose greater than 30 Gy; an ovarian/uterine radiation dose greater than 5 Gy; or CCNU, cyclophosphamide, or any AAD summed score of three or four were less likely to ever become pregnant. These data may be utilized to counsel patients and their parents before initiation of treatment and to identify those at exceptionally high risk for impaired fertility who may benefit from assisted reproduction techniques.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, Leslie L. Robison
Financial support: Leslie L. Robison
Administrative support: Ann C. Mertens, Leslie L. Robison
Collection and assembly of data: Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Ann C. Mertens
Data analysis and interpretation: Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Sarah S. Donaldson, Leslie L. Robison
Manuscript writing: Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, Leslie L. Robison
Final approval of manuscript: Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, Leslie L. Robison

REFERENCES

1. Ries LA, Melbert D, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2005. Bethesda, MD, National Cancer Institute, 2008
2. Sklar CA, Constine LS: Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113-1121, 1995
3. Byrne J, Mulvihill JJ, Myers MH, et al: Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317:1315-1321, 1987
4. Robison LL, Mertens AC, Boice JD, et al: Study design and cohort characteristics of the childhood cancer survivor study: A multi-institutional collaborative project. Med Pediatr Oncol 38:229-239, 2002
5. Abma J, Chandra A, Mosher W, et al: Fertility, family planning, and women's health: New data from the 1995 National Survey of Family Growth. National Center for Health Statistics. Vital Health Stat 23:1-114, 1997
6. Tucker MA, Medows AT, Boice JD Jr, et al: Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 78:459-464, 1987
7. Packer RJ, Gurney JG, Punyko JA, et al: Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood cancer survivor study. J Clin Oncol 21:3255-3261, 2003
8. Stovall M, Donaldson SS, Weathers RE, et al: Genetic effects of radiotherapy for childhood cancer: Gonadal dose reconstruction. Int J Radiat Oncol Biol Phys 60:542-552, 2004
9. Stovall M, Weathers R, Kasper C, et al: Dose reconstruction for therapeutic and diagnostic radiation exposures: Use in epidemiological studies. Radiat Res 166:141-157, 2006
10. Yasui Y, Liu Y, Neglia JP, et al: A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancers. Am J Epidemiol 158:1108-1113, 2003
11. Therneau TM, Grambsch PM. Modeling survival data: Extending the Cox model. New York, NY, Springer-Verlag, 2000
12. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY, John Wiley and Sons Inc, 1987
13. Taylor JMG, Munoz A, Bass SM, Saah AJ, Chmiel JS, Kinglsey LA: Estimating the distribution of times for HIV seroconversion to AIDS using multiple imputation. Stat Med 9:505-514, 1990
14. Chemaitilly W, Mertens AC, Mitby P, et al: Acute ovarian failure in the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 91:1723-1728, 2006
15. Le Floch O, Donaldson SS, Kaplan HS: Pregnancy following oophoropexy and total nodal irradiation in women with Hodgkin's disease. Cancer 38:2263-2268, 1976
16. Bajorunas DR, Ghavimi F, Jereb F, et al: Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. J Clin Endocrinol Metab 50:329-335, 1980
17. Shalet S, Beardwell C, MacFarlane I, et al: Endocrine morbidity in adults treated with cerebral irradiation for brain tumours during childhood. Acta Endocrinol 84:673-680, 1977
18. Rappaport R, Brauner R, Czernichow P, et al: Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. J Clin Endocrinol Metab 54:1164-1168, 1982
19. Brauner R, Rappaport R: Precocious puberty secondary to cranial irradiation for tumors distant from the hypothalamo-pituitary area. Horm Res 22: 78-82, 1985
20. Hansen KR, Knowlton NS, Thyer AC, et al: A new model of reproductive aging: The decline in ovarian non-growing follicle number from birth to menopause. Hum Reprod 23:699-708, 2008

21. Faddy MJ, Gosden RG, Gougeon A, et al: Accelerated disappearance of ovarian follicles in mid-life: Implications for forecasting menopause. Hum Reprod 7:1342-1346, 1992

22. Wallace WHB, Shalet SM, Crowne EC, et al: Ovarian failure following abdominal irradiation in childhood: Natural history and prognosis. Clin Oncol (R Coll Radiol) 1:75-79, 1989

23. Scott JES: Pubertal development in children treated for nephroblastoma. J Pediatr Surg 16:122-125, 1981

24. Shalet SM, Beardwell CG, Morris Jones PH, et al: Ovarian failure following abdominal irradiation in childhood. Br J Cancer 33:655-658, 1976

25. Hamre MR, Robison LL, Nesbit ME, et al: Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukemia: A report from the Children's Cancer Study Group. J Clin Oncol 5:1759-1765, 1987

26. Wallace WHB, Shalet SM, Tetlow LJ, et al: Ovarian function following the treatment of childhood acute lymphoblastic leukemia. Med Pediatr Oncol 21:333-339, 1993

27. Swift PGF, Kearney PJ, Dalton RG, et al: Growth and hormonal status of children treated for acute lymphoblastic leukemia. Arch Dis Child 53: 890-894, 1978

28. Voorhess ML, Brecher ML, Glicksman AS, et al: Hypothalamic-pituitary function of children with acute lymphocytic leukemia after three forms of central nervous system prophylaxis: A retrospective study. Cancer 57:1287-1291, 1986

29. Bath LE, Anderson RA, Critchley HO, et al: Hypothalamic-pituitary-ovarian dysfunction after prepubertal chemotherapy and cranial irradiation for acute leukaemia. Hum Reprod 16:1838-1844, 2001

30. Stillman RJ, Schinfeld JS, Schiff I, et al: Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 139:62-66, 1981

31. Critchley HO, Wallace WH, Shalet SM, et al: Abdominal irradiation in childhood: The potential for pregnancy. Br J Obstet Gynecol 99:392-394, 1992

32. Critchley HOD: Factors of importance for implantation and problems after treatment for childhood cancer. Med Pediatr Oncol 33:9-14, 1999

33. Bath LE, Critchley HOD, Chambers SE, et al: Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: Response to sex steroid replacement. Br J Obstet Gynaecol 106:1265-1272, 1999

34. Holm K, Nysom K, Brocks V, Hertz H, Jacobsen N, Muller J: Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. Bone Marrow Transplant 23:259-263, 1999

35. Hudson MM, Greenwald C, Thompson E, et al: Efficacy and toxicity of multiagent chemotherapy and low-dose involved-field radiotherapy in children and adolescents with Hodgkin's disease. J Clin Oncol 11:100-108, 1993

36. Papadakis V, Vlachopapadopoulou E, Van Cyckle K, et al: Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 32:366-372, 1999

37. Mackie EJ, Radford M, Shalet SS: Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 27:74-78, 1996

38. Ortin TT, Shostak CA, Donaldson SS: Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: The Stanford experience. Int J Radiat Oncol Biol Phys 19:873-880, 1990

39. Chapman RM, Sutcliffe SB, Malpas JS: Cytotoxic-induced ovarian failure in women with Hodgkin's disease: Hormone function. JAMA 242: 1877-1881, 1979

40. Schilsky RL, Sherins RJ, Hubbard SM, et al: Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 71:552-556, 1981

41. Waxman JHX, Terry Y, Wrigley PFM, et al: Gonadal function in Hodgkin's disease: Long-term follow-up of chemotherapy. BMJ 285:1612-1613, 1982

42. Santoro A, Bonadonna G, Valagussa P, et al: Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: Superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 5:27-37, 1987

43. Andrieu JM, Ochoa-Molina ME: Menstrual cycle, pregnancies and offspring before and after MOPP therapy for Hodgkin's disease. Cancer 52: 435-438, 1983

44. Devita VTJ, Serpick AA, Carbone PP: Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 73:881-895, 1970

45. Schwartz CL, Constine LS: Current protocol and concepts for classical Hodgkin disease (HD) in the USA: A Children's Oncology Group (COG) report. Presented at the 7th International Symposium on Hodgkin Lymphoma, Cologne, Germany, November 3-7, 2007, p 6

46. Womer RB, West DC, Krailo MD, et al. Randomized comparison of every-two-week versus every-three-week chemotherapy in Ewing sarcoma family tumors (ESFTs). J Clin Oncol 26:554s, 2008 (suppl; abstr 10504)

47. Chiarelli AM, Marrett LD, Darlington GA: Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada. Am J Epidemiol 150:245-254, 1999

48. Byrne J, Fears TR, Mills JL, et al: Fertility in women treated with cranial radiotherapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 42:589-597, 2004

49. Wilcox AJ, Weinberg CR, O'Connor JF, et al: Incidence of early loss of pregnancy. N Engl J Med 319:189-194, 1988

50. Schover LR, Rybicki LA, Martin BA, et al: Having children after cancer: A pilot survey of survivors' attitudes and experiences. Cancer 86:697-709, 1999

51. Zebrack BJ, Casillas J, Nohr L, et al: Fertility issues for young adult survivors of childhood cancer. Psychooncology 13:689-699, 2004

52. Oosterhuis BE, Goodwin T, Kiernan M, et al: Concerns about infertility risks among pediatric oncology patients and their parents. Pediatr Blood Cancer 50:85-89, 2008

