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ORIGINAL REPORT

Congenital Anomalies in the Children of Cancer Survivors: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Children with cancer receive mutagenic treatments, which raises concern about the potential transmissibility of germline damage to their offspring. This question has been inadequately studied to date because of a lack of detailed individual treatment exposure assessment such as gonadal radiation doses.

Methods
Within the Childhood Cancer Survivor Study, we performed a retrospective cohort analysis of validated cases of congenital anomalies among 4,699 children of 1,128 male and 1,627 female childhood cancer survivors. We quantified chemotherapy with alkylating agents and radiotherapy doses to the testes and ovaries and related these exposures to risk of congenital anomalies using logistic regression.

Results
One hundred twenty-nine children had at least one anomaly (prevalence = 2.7%). For children whose mothers were exposed to radiation or alkylating agents versus neither, the prevalence of anomalies was 3.0% versus 3.5% (P = .51); corresponding figures were 1.9% versus 1.7% (P = .79) for the children of male survivors. Neither ovarian radiation dose (mean, 1.19 Gy; odds ratio [OR] = 0.59; 95% CI, 0.20 to 1.75 for 2.50+ Gy) nor testicular radiation dose (mean, 0.48 Gy; OR = 1.01; 95% CI, 0.36 to 2.83 for 0.50+ Gy) was related to risk of congenital anomalies. Treatment with alkylating agents also was not significantly associated with anomalies in the children of male or female survivors.

Conclusion
Our findings offer strong evidence that the children of cancer survivors are not at significantly increased risk for congenital anomalies stemming from their parent's exposure to mutagenic cancer treatments. This information is important for counseling cancer survivors planning to have children.

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INTRODUCTION

Childhood patients with cancer receive aggressive, though life-saving, treatments that can impair their future reproductive experience.[1] Infertility may result, and women who retain fertility have increased risks for miscarriage, stillbirth, low birthweight, and preterm birth, generally related to pelvic irradiation and associated uterine damage.[1,2] Radiotherapy and chemotherapy with alkylating agents are DNA-damaging treatments; indeed they are capable of causing cancer in treated patients through their mutagenic actions on somatic cells.[3] Whether such treatments can also result in genetic damage being transmitted to the offspring (via a mutated germ cell) is a question of longstanding interest to patients. How sensitive or tolerant the human germ cell is to these kinds of insults is unclear,[4] as are the mechanisms of transgenerational instability in the germ line.[5] Only in animal studies have radiation-induced germline mutations been conclusively shown to result in offspring with genetic defects.[6]

Determining whether treatment imparts genetic risks to the future children of cancer survivors is challenging. Given the rarity of individual genetic disorders and lack of detailed data on treatment exposures, prior studies of childhood cancer survivors have provided limited information on which to base conclusions. To our knowledge, no large study has robustly assessed offspring risk of congenital

anomalies in relation to quantified gonadal radiation doses. Thus, although existing studies are generally reassuring,[1,2] concerns about the potential for inherited effects persist.[7]

The Childhood Cancer Survivor Study (CCSS), a large multicenter cohort investigation, provided the opportunity to relate quantified treatment exposures (cumulative gonadal radiation and alkylating agent doses) to congenital anomaly outcomes in the offspring of cancer survivors. We recently reported on stillbirth and neonatal death among the children of CCSS participants as one potential indicator of transmitted germline damage.[8] In follow-up, we now report on validated outcomes of unambiguous genetic origin (single-gene defects, cytogenetic abnormalities) and of frequent genetic origin (congenital malformations) with the aim of providing critical data to inform late-effects follow-up for cancer survivors.

METHODS

Study Population

Details of the CCSS have been published.[9-11] Briefly, participants were younger than 21 years of age at initial diagnosis of an eligible cancer (Table 1) from January 1, 1970, through December 31, 1986, at 25 US and one Canadian institution and had survived at least 5 years after diagnosis. The study was approved by institutional review boards at each participating institution and in accord with an assurance filed with and approved by the Department of Health and Human Services, where appropriate. Informed consent was obtained from all subjects who were ≥ 18 years of age or from their parents if they were younger than 18 years.

Data were collected from participants using a baseline questionnaire beginning in 1994 and from follow-up questionnaires completed periodically thereafter. The baseline questionnaire response rate was 81.2% for subjects successfully contacted (69% for the total eligible population identified), and response rates to the follow-up questionnaires generally ranged from 77% to 81%.[9,10] These questionnaires (available at http://ccss.stjude.org/documents/questionnaires) included a pregnancy history for both men and women as well as a section to report on medical conditions for their biologic children. For the present study, we identified all livebirths or stillbirths (fetal loss after 20 gestational weeks) occurring at least 5 years after diagnosis for the calendar years 1971 to 2002 (N = 5,725). This figure excludes known in vitro fertilization–assisted conceptions, because the use of donor eggs/sperm could not be conclusively determined. Nonsingleton pregnancies were excluded because this group was too small (n = 180) to examine separately. Pregnancies were also excluded if the child was in utero during cancer treatment (n = 1) or if complete treatment details were unavailable (n = 845, largely as a result of participant refusal to sign a release allowing access to their medical records). As noted earlier, children born before their parent achieved 5-year survivorship (and thus eligibility for the CCSS) were not included, however, the number of such children was small (n = 247), and adding them to our study analyses did not change the results (not shown).

Participants who reported a pregnancy (their own for female patients, sired for male patients) on the baseline questionnaire received a more detailed pregnancy questionnaire eliciting further information on pregnancy exposures (eg, maternal smoking) that may affect pregnancy outcomes and thus be potential confounders. Among our study population, 61% completed the pregnancy questionnaire.

Congenital Anomalies in the Offspring

Congenital anomalies were defined as cytogenetic abnormalities (eg, trisomy 21, Down syndrome), single-gene defects (eg, achondroplasia), and congenital malformations (eg, cleft lip). Nearly 200 such outcomes were reported on either the baseline or routine follow-up questionnaires, which provided lists of examples of hereditary conditions and abnormalities present at birth and collected the data in an open-ended manner so as not to limit reporting (Table 2). The children's medical records were sought, and a validation approach was followed as previously described.[10] If consent was unavailable for medical record review, calls were placed to participants to seek the necessary medical details to confirm the diagnosis. All available information was reviewed by a three-person panel consisting of a geneticist-dysmorphologist, pediatrician, and epidemiologist (J.J.M., D.M.G., and J.D.B.) who reached a consensus decision. Examples of rejected outcomes included certain birthmarks (ie, "stork bites") and cerebral palsy. We also excluded self-reported outcomes for which there was evidence of a familial or alternate explanation not involving cancer therapy (see Appendix, online only). After validation and other exclusions (Table 2), we identified 129 offspring with congenital anomalies among the 4,699 final offspring included in this study. Nine offspring had multiple malformations, and these children were counted only once each in the analysis.

Table 1. Descriptive Characteristics of the Male and Female Cancer Survivors (N = 2,755) With Offspring Included in the Current Study

Characteristic	Female Patients (n = 1,627) No.	%	Male Patients (n = 1,128) No.	%
Index cancer diagnosis				
Leukemia	441	27	311	28
Hodgkin's lymphoma	351	22	190	17
Non-Hodgkin's lymphoma	119	7	156	14
Bone sarcoma	235	14	153	14
Soft tissue sarcoma	178	11	125	11
Central nervous system cancer	116	7	98	9
Kidney cancer/Wilms tumor	104	6	64	6
Neuroblastoma	83	5	31	3
Age at cancer diagnosis, years				
0-4	314	19	193	17
5-9	315	19	217	19
10-14	524	32	325	29
15-20	469	29	390	35
Missing	5	0.3	3	0.3
Age of survivor at birth of first child, years				
< 20	301	19	79	7
20-24	599	37	349	31
25-29	511	31	435	39
30+	214	13	260	23
Missing	2	0.1	5	0.4
No. of included children born after diagnosis				
1	757	47	554	49
2	653	40	412	37
3	174	11	120	11
4+	43	3	42	4
Treated with radiotherapy				
Yes	1020	63	716	63
No	607	37	412	37
Treated with alkylating agents				
Yes	810	50	496	44
No	783	48	603	53
Missing	34	2	29	3

Radiation Dosimetry

The participants' medical records were abstracted (blinded to the children's outcomes) to obtain treatment data for the index cancer and recurrences. Photocopied radiotherapy records were obtained from the treating institutions, and absorbed doses to the testes and ovaries, including the contribution of radiation scatter, were estimated on the basis of measurements in water and applied to age-specific three-dimensional mathematical phantoms

Table 2. Identification and Exclusions of Congenital Anomalies Among the Offspring of 1,627 Female and 1,128 Male Cancer Survivors

Offspring	Congenital Malformations	Single-Gene Defects	Cytogenetic Abnormalities	Total Offspring With Anomalies
Identified through self-report	161	25	9	196*
Exclusions				
Validation study rejected	44	10	0	54
Missing treatment information	10	2	1	13
Final number of offspring with anomalies	107	13	8	129*
Among female survivors	77	11	4	93*
Among male survivors	30	2	4	36

*Total includes one offspring with reported mental retardation who, although included in the total count of children with anomalies, could not be definitively classified in one of the three categories because of the lack of detail on the child's condition.

as has been described by Stovall et al.[12] Gonadal shielding, oophoropexy, and field blocking were taken into account. Doses from all radiation treatments were summed to determine the total dose received before each pregnancy. Doses to the two ovaries were estimated separately. We used the minimum dose to either ovary as the treatment exposure in our analyses, because for cancers that generally involve unilateral treatment (eg, Wilms tumor), we reasoned that the less exposed ovary was more likely to be the functioning one. However, analyses that used the maximum ovarian dose gave similar results.

Alkylating Agent Dose Scores

Alkylating agents were defined as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, and thiotepa. Technically, the platinum compounds are not alkylating agents, but they were included because of their DNA-damaging capability. For each alkylating agent, we divided the distribution of cumulative dose in milligrams per square meter (among the entire CCSS cohort) into tertiles with a corresponding value of 1 to 3, with a value of 0 indicating that the drug was not administered. These tertile scores for individual alkylating agents were summed, and this cumulative score was then itself divided into tertiles, resulting in alkylating agent dose (AAD) score values of 1 to 3.

Statistical Methods

Logistic regression was used to estimate odds ratios (OR) for congenital anomalies associated with radiation dose to the parent's ovaries or testes, with the children of survivors who did not receive radiotherapy serving as the referent group. We also estimated ORs associated with increasing AAD scores, using the children of survivors with no chemotherapy exposure as the referent group. Calendar year of birth was included as a covariate in all adjusted models, along with maternal age (in female models) and paternal age (in male models). AAD score was also tested as a covariate in models estimating the effect of radiotherapy, and vice versa, with no impact on the findings. Other factors were considered as potential confounders (including age of the partner, maternal smoking, alcohol drinking, and vitamin supplement use during pregnancy), but among subjects with complete data on these factors (the 61% who completed the more detailed pregnancy questionnaire; see Methods), such adjustment did not affect the results.

Multiple pregnancies per subject were included. To account for dependency between children born to the same subject, we used generalized estimating equations to produce effect estimates and SEs using an exchangeable working correlation structure. Only five female cancer survivors (two exposed to radiation and three not exposed) and one male cancer survivor (not exposed to radiation) had multiple children with anomalies.

RESULTS

Characteristics of the cancer survivors are provided in Table 1. The most common diagnoses were leukemia and lymphoma (57%). Survivors had a wide range of age at cancer diagnosis as well as age at first birth. More than 60% had been exposed to radiotherapy, and approximately half (47%) were exposed to alkylating agents.

Table 3 shows the distribution of anomalies identified among the offspring and suggests no association between radiotherapy and risk of malformations, single-gene defects, or cytogenetic abnormalities. Overall, 129 children had at least one reported anomaly, for a prevalence of 2.7%. Among the children of women exposed to radiation or alkylating agents versus neither, the prevalence of congenital anomalies was 3.0% versus 3.5% ($P = .51$), with corresponding figures of 1.9% versus 1.7% ($P = .79$) for the offspring of the men (data not shown).

Radiation doses to the ovaries (mean, 1.19 Gy among women who received radiotherapy) and testes (mean, 0.48 Gy among men who received radiotherapy) were not associated with risk of anomalies in the children (Table 4). The proportion of children with anomalies born to women treated with radiation was 3.1% versus 3.7% for those with unexposed mothers, and ORs for all categories of ovarian radiation exposure were less than 1.0. Children with fathers who underwent radiation were also not at increased risk for congenital anomalies, with the OR for the highest testicular dose category (0.50+ Gy) being 1.01 (95% CI, 0.36 to 2.83).

Exposure to alkylating agents (yes/no) was not associated with increased risk of congenital anomalies among the children of female (adjusted OR = 1.03; 95% CI, 0.65 to 1.64) or male (adjusted OR = 0.99; 95% CI, 0.49 to 2.01) cancer survivors (not shown), nor was exposure to nonalkylating agents only (Table 5). For male survivors, an evaluation of dose response using AAD scores did not suggest increasing risk with increasing exposure (Table 5). Similarly, for female survivors, the ORs for AAD scores 1, 2, and 3 were 0.63, 1.00, and 1.13, respectively ($P_{trend} = .69$).

The small number of cytogenetic abnormalities and single-gene defects was insufficient to support an analysis of these outcomes separately. For congenital malformations, adjusted ORs for ovarian radiation dose categories ranged from 0.84 to 1.14 and for testicular radiation dose categories from 0.62 to 0.84 (not shown), suggesting no adverse effects. The AAD score analysis for malformations among female survivors showed a nonsignificantly decreased risk (OR = 0.62; 95% CI, 0.26 to 1.47) for the lowest tertile exposure and nonsignificantly increased risks for the middle and top tertile (OR = 1.15, 95% CI, 0.54 to 2.43; and OR = 1.30, 95% CI, 0.62 to 2.70, respectively). AAD score also showed no consistent or significant association with malformations in the children of male survivors: OR = 1.47 (95% CI,

Table 3. Distribution of Congenital Anomalies Among 4,699 Offspring of 1,627 Female and 1,128 Male Cancer Survivors, Stratified by the Parent's Exposure to Radiotherapy

	Offspring of Female Survivors				Offspring of Male Survivors			
	Mother Irradiated (n = 1,753)		Mother Not Irradiated (n = 1,021)		Father Irradiated (n = 1,218)		Father Not Irradiated (n = 707)	
Congenital Anomaly	No.	%	No.	%	No.	%	No.	%
Congenital malformations, total*	50	2.9	27	2.6	16	1.3	14	2.0
Nervous system	3	0.2	3	0.3	1	0.1	2	0.3
Eye, ear, face, and neck	7	0.4	7	0.7	1	0.1	1	0.1
Heart and blood vessels	13	0.7	6	0.6	3	0.2	2	0.3
Respiratory organs	0	0	0	0	0	0	0	0
Lip and palate	4	0.2	1	0.1	2	0.2	3	0.4
Digestive system	3	0.2	1	0.1	0	0	2	0.3
Genitalia	4	0.2	3	0.3	2	0.2	0	0
Urinary organs	2	0.1	0	0	0	0	1	0.1
Extremities	1	0.1	3	0.3	2	0.2	0	0
Musculoskeletal system	9	0.5	2	0.2	3	0.2	0	0
Skin, hair, nails	9	0.5	4	0.4	3	0.2	2	0.3
Endocrine disorder	0	0	0	0	0	0	1	0.1
Multiple simple malformations†	5	0.3	3	0.3	1	0.1	0	0
Single-gene defects, total	5	0.3	6	0.6	2	0.2	0	0
Polydactyly/syndactyly/hypodactyly	3	0.2	1	0.1	2	0.2	0	0
Neurofibromatosis	0	0	1	0.1	0	0	0	0
Tourette syndrome	1	0.1	0	0	0	0	0	0
Goldenhar syndrome	0	0	1	0.1	0	0	0	0
Wolfe-Parkinson-White syndrome	0	0	1	0.1	0	0	0	0
Achondroplasia	0	0	1	0.1	0	0	0	0
Deafness	0	0	1	0.1	0	0	0	0
Congenital megacolon	1	0.1	0	0	0	0	0	0
Cytogenetic abnormalities, total	0	0	4	0.4	3	0.2	1	0.1
Down syndrome (trisomy 21)	0	0	3	0.3	1	0.1	0	0
Shone syndrome	0	0	1	0.1	0	0	0	0
Angelman syndrome	0	0	0	0	1	0.1	0	0
13q deletion syndrome	0	0	0	0	0	0	1	0.1
Edwards syndrome (trisomy 18)	0	0	0	0	1	0.1	0	0

NOTE. One offspring with reported mental retardation, although included in the analyses of total anomalies, is not included in Table 3, because the lack of detail on the child's condition prevented definitive classification in one of the three categories.

*Total reflects the total number of offspring with malformations (n = 107), although the individual malformations sum to 116 because nine children had multiple malformations.

†Nine children had multiple malformations, and these children were counted only once each in the regression analyses.

0.53 to 4.08) for the lowest tertile exposure and OR = 0.83 (95% CI, 0.25 to 2.71) for the highest two tertiles.

DISCUSSION

This is among the largest investigations of congenital anomalies in the offspring of childhood cancer survivors and, importantly, among the first to evaluate these outcomes using carefully reconstructed gonadal radiation and chemotherapy doses. With subjects from 26 institutions, the study was well powered (80%) to detect ORs of 1.7 to 2.2 for the effect of ovarian radiation dose more than 1.00 Gy, testicular radiation dose more than 0.10 Gy, and the highest cumulative exposure to alkylating agents. Yet over a wide range of exposures, we found no significant associations between these therapies and congenital anomalies in the offspring, providing evidence against adverse transgenerational effects. These findings have relevance for both male and female survivors and were supported by rigorous validation of self-reported outcomes.

For alkylating agents, there were no consistent associations with overall anomaly risk in relation to dose, although we noted a modestly elevated malformation risk with the lowest tertile exposure for men (OR = 1.47) and the highest tertile exposure for women (OR = 1.30), both nonsignificant. The former finding makes little intuitive sense and was likely a chance finding. The latter finding was based on malformations in 12 unrelated offspring, among whom there was no clear pattern of malformation type, which included those of the heart (n = 5), eye (n = 3), extremities (n = 1), skin (n = 1), genitalia (n = 1), and musculoskeletal system (n = 1). With few exceptions,[13] alkylating agents have not been linked to malformations in the children of patients with cancer.[14-18] Our findings should be interpreted cautiously given that malformations can also be of environmental origin, that ever use of alkylating agents showed no effect, and that the CIs for the AAD ORs were compatible with a null effect.

Table 4. ORs and 95% CIs for the Association Between Gonad-Specific Radiotherapy Doses and Risk of Congenital Anomalies in the Offspring of Female and Male Childhood Cancer Survivors

Treatment Group	Congenital Anomaly Outcome (n)	All Offspring (n)	Proportion With Anomalies (%)	Crude OR	95% CI	OR*	95% CI
Females							
Not treated with radiation	38	1,021	3.7	1.0	Referent	1.0	Referent
Ovarian radiation dose, Gy							
0.01-0.99	44	1,332	3.3	0.89	0.57 to 1.40	0.87	0.55 to 1.38
1.00-2.50	6	196	3.1	0.83	0.35 to 1.99	0.80	0.33 to 1.92
2.50+	5	225	2.2	0.59	0.20 to 1.75	0.59	0.20 to 1.75
P_{trend}				.52		.53	
Males							
Not treated with radiation	15	707	2.1	1.0	Referent	1.0	Referent
Testicular radiation dose, Gy							
0.01-0.09	10	677	1.5	0.70	0.31 to 1.58	0.71	0.31 to 1.63
0.10-0.50	6	317	1.9	0.91	0.35 to 2.42	0.88	0.33 to 2.36
0.50+	5	224	2.2	1.07	0.38 to 2.98	1.01	0.36 to 2.83
P_{trend}				.99		.90	

Abbreviation: OR, odds ratio.
*ORs adjusted for calendar year of birth and maternal age (for the female analyses) and for calendar year of birth and paternal age (for the male analyses).

Our investigation follows earlier CCSS analyses, which found similar genetic disease occurrence for survivors' children and those of a sibling control group.[19] Now with treatment dosimetry, we can focus specifically on individual exposure to mutagenic therapy, conduct dose-response evaluations, and thus confirm that even high-doses of gonadal irradiation are unassociated with future genetic disease risk. Our results strengthen the conclusions of at least a dozen studies that reported no increased risk of congenital anomalies in the children of cancer survivors.[13-17,20-26] In contrast, two Scandinavian studies reported some positive associations, comparing offspring outcomes of cancer survivors with those of the general Norwegian[27] and Swedish/Danish[28] populations. In these studies, differential clinical surveillance of cancer survivors' children compared with that of the general population may account for more defects being diagnosed in the former group.[29] We believe our use of nonexposed cancer survivors as a referent resulted in groups with similar impetus to report offspring health problems and with similar health surveillance for their children.

Overall we found a congenital anomaly prevalence of 2.7% in the offspring, within the range of previous reports of childhood cancer survivors and their siblings,[13,16,17,20-24,27,28] and consistent with US population estimates of approximately 3%.[30] Our prevalence is slightly underestimated because we excluded defects related to known (eg, familial) causes, given the hypotheses being tested. Although heritable defects are present at birth, not all are diagnosed immediately. The average age of the children at the time when their parent provided data for this study was 4.6 years, which should have provided opportunity for most anomalies to be diagnosed. Moreover, the parents of children with and without anomalies had a comparable time period for potential diagnoses (average, 5.0 and 4.5 years, respectively). We noted a higher reported prevalence of anomalies among

Table 5. ORs and 95% CIs for the Association Between Chemotherapy With Alkylating and Nonalkylating Agents and Risk of Congenital Anomalies in the Offspring of Female and Male Childhood Cancer Survivors

Treatment Group	Congenital Anomaly Outcome (n)	All Offspring (n)	Proportion With Anomalies (%)	Crude OR	95% CI	OR*	95% CI
Females, AAD score†							
No chemo treatment	24	696	3.4	1.0	Referent	1.0	Referent
0 (nonalkylator only)	18	668	2.7	0.77	0.40 to 1.48	0.73	0.37 to 1.44
1	10	441	2.3	0.66	0.31 to 1.39	0.63	0.29 to 1.37
2	13	370	3.5	1.03	0.52 to 2.03	1.00	0.49 to 2.03
3	13	330	3.9	1.15	0.58 to 2.26	1.13	0.57 to 2.25
P_{trend}				.68		.69	
Males, AAD score†							
No chemo treatment	12	574	2.1	1.0	Referent	1.0	Referent
0 (nonalkylator only)	8	455	1.8	0.83	0.32 to 2.16	0.92	0.32 to 2.59
1	10	398	2.5	1.16	0.50 to 2.70	1.29	0.52 to 3.22
2 or 3‡	4	335	1.2	0.57	0.18 to 1.79	0.59	0.19 to 1.86
P_{trend}				.55		.62	

Abbreviation: OR, odds ratio.
*ORs adjusted for calendar year of birth and maternal age (for the female analyses) and for calendar year of birth and paternal age (for the male analyses).
†Alkylating agent dose score, see Methods for definition.
‡Scores 2 and 3 were grouped because of small numbers.

the children of female versus male survivors for reasons that are unclear but could involve underreporting by the fathers.

Sperm can be damaged by the therapies used for many cancers, resulting in abnormal numbers of chromosomes (aneuploidy) that underlie certain types of genetic disorders, such as Down syndrome, which were rare outcomes in our study.[31-34] Although sperm DNA damage has been shown to persist for as long as 2 years after treatment,[31] the effect generally seems to be transient without lasting damage to the spermatogonial stem cells.[31-35] In our study, the children were born an average of 15.5 years after paternal irradiation. However, in a separate analysis (not shown, and including children not part of our main analysis because they were born before their parent achieved 5-year survivorship), no children born within 3 years after diagnosis to fathers exposed to testicular irradiation (mean dose, 1.35 Gy) had a reported congenital anomaly, although these results were based on a small number of children (n = 14). Similarly, there were no congenital anomalies reported among children born within 3 years after diagnosis to fathers exposed to alkylating agents.

We cannot rule out the possibility that cancer treatment resulted in inherited mutations, albeit ones not resulting in a recognized anomaly in the offspring. However, the search for such genetic damage has not been fruitful to date. Two recent studies in Denmark that included adult survivors of childhood cancer, their nonaffected partners, and their offspring demonstrated no indication of transmissible genomic instability in the offspring using chromosomal analysis[36] and no evidence of germline minisatellite mutation rates being associated with radiotherapy.[37] Our ability to fully evaluate this issue is likely to improve as genomic technologies improve,[6] but given the current body of evidence, important increases in the risk of treatment-related genetic disease seem unlikely. As we reported previously in this population,[8] induced abortions were not more frequently reported by male and female survivors with a history of high gonadal irradiation, limiting the possibility that pregnancy terminations of adversely affected fetuses obscured our results.

Our findings were based on 5-year childhood cancer survivors and thus are limited in their generalization outside this group. However, given the young ages of these patients, pregnancies would be unusual before 5-year survivorship, thus our findings should be relevant to the majority of childhood cancer survivors. Nonresponse to the questionnaires limited our inclusion of all potential offspring, and it is possible that nonresponse was related to the probability of offspring medical problems (either more likely if it provided impetus to respond, or less likely if competing parental responsibilities interfered with participation). Approximately 15% of the identified offspring also could not be included in our analyses because of missing treatment details for their parent. These exclusions, however, are unlikely to have affected our dose-response evaluations performed within the responder group with complete data. Finally, although our analyses were based on relatively complete treatment exposure data, information on behavioral confounders such as cigarette smoking or alcohol drinking were available for only approximately 60% of the subjects; although analyses on this subset suggested these factors were not necessary for our final models, we cannot rule out the possibility that uncontrolled confounding influenced our findings.

In conclusion, our findings offer strong evidence that the children of 5-year cancer survivors are not at increased risk for congenital anomalies stemming from their parent's exposure to mutagenic cancer treatments. Whether humans have the capacity to repair damage to germ cell DNA or whether the various processes of reproduction filter out such insults (eg, through early pregnancy losses or infertility) merit exploration. It is nevertheless reassuring that potential damage is not manifesting as recognized, genetic disease in the offspring. Such information is important for counseling cancer survivors planning to have children.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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