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Female Survivors of Childhood Cancer: Preterm Birth and Low Birth Weight Among Their Children

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Abstract

Background—Improved survival after childhood cancer raises concerns over the possible long-term reproductive health effects of cancer therapies. We investigated whether children of female childhood cancer survivors are at elevated risk of being born preterm or exhibiting restricted fetal growth and evaluated the associations of different cancer treatments on these outcomes.

Methods—Using data from the Childhood Cancer Survivor Study, a large multicenter cohort of childhood cancer survivors, we studied the singleton live births of female cohort members from 1968 to 2002. Included were 2201 children of 1264 survivors and 1175 children of a comparison group of 601 female siblings. Data from medical records were used to determine cumulative prepregnancy exposures to chemotherapy and radiotherapy. Logistic regression was used to estimate odds ratios (ORs) for the association between quantitative therapy exposures and preterm (<37 weeks) birth, low birth weight (<2.5 kg), and small-for-gestational-age (SGA) (lowest 10th percentile) births. All statistical tests were two-sided.

Results—Survivors' children were more likely to be born preterm than the siblings' children (21.1% versus 12.6%; OR = 1.9, 95% confidence interval [CI] = 1.4 to 2.4; $P<.001$). Compared with the children of survivors who did not receive any radiotherapy, the children of survivors treated with high-dose radiotherapy to the uterus (>500 cGy) had increased risks of being born preterm (50.0% versus 19.6%; OR = 3.5, 95% CI = 1.5 to 8.0; $P = .003$), low birth weight (36.2% versus 7.6%; OR = 6.8, 95% CI = 2.1 to 22.2; $P = .001$), and SGA (18.2% versus 7.8%; OR = 4.0, 95% CI = 1.6 to 9.8; $P = .003$). Increased risks were also apparent at lower uterine radiotherapy doses (starting at 50 cGy for preterm birth and at 250 cGy for low birth weight).

Conclusions—Late effects of treatment for female childhood cancer patients may include restricted fetal growth and early births among their offspring, with risks concentrated among women who receive pelvic irradiation.

As progress in improving the survival of childhood cancer patients is achieved, there is a concomitant concern about long-term health effects among survivors, particularly effects among those exposed to intensive radiotherapy and chemotherapy. Concerns have emerged, for example, about the effects of these therapies on the reproductive capacity of the survivors, including implications for fertility, pregnancy outcomes, and health problems in the offspring (1-3). Some patients who are exposed to high-dose chemotherapy or gonadal irradiation experience permanent infertility (depending on the dosages and their age when treated) (4), but many survivors retain reproductive function and wish to have children (5). With regard to pregnancy outcomes, some studies have documented an increased risk of fetal death (either spontaneous abortion or perinatal death) for female survivors of childhood cancer (6-10). These findings were primarily reported among Wilms tumor survivors or were related to treatment involving high-dose abdominal irradiation (6-9). However, in a recent analysis of a much larger study population of childhood cancer survivors than in previous studies (11,12), we found little convincing evidence that rates of fetal loss were elevated for female survivors of childhood cancer or for the partners of male survivors of childhood cancer.

Previous investigators have also noted an increased risk of preterm birth and/or low birth weight for the offspring of female survivors of Wilms tumor who received irradiation to the flank, pelvis, or abdomen (6,8,9,13,14). An additional recent study found an excess of low birth weight among the children of women who received direct abdominal—pelvic irradiation,

irrespective of cancer type (7). Information on the risk of preterm birth or low birth weight for survivors of cancers other than Wilms tumor or for survivors who received treatments other than pelvic or abdominal irradiation is limited (10,15). Moreover, most of the previous studies addressing these pregnancy outcomes were small and included fewer than 100 childhood cancer survivors (8-10,13,15).

To better evaluate the potential risk of preterm birth and diminished fetal growth among the offspring of female childhood cancer survivors and to examine this risk in relation to different cancer therapies (using quantified treatment exposures), we studied the pregnancies of female members of the ongoing Childhood Cancer Survivor Study (CCSS) (16). This study includes a large number of childhood cancer survivors who were treated for a wide array of cancers and who underwent a wide range of treatments.

Subjects and Methods

Study Setting

Design details of the CCSS have been presented elsewhere (16). Briefly, members of the CCSS cohort were less than 21 years old at initial diagnosis of an eligible cancer (leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, bone sarcoma, soft tissue sarcoma, central nervous system cancer, cancer of the kidney [primarily Wilms tumor], and neuroblastoma) between January 1, 1970, and December 31, 1986, at one of 25 participating institutions in the United States and Canada. To be eligible for the study, patients must also have survived at least 5 years after the date at which their initial (i.e., index) cancer was diagnosed. This study was approved by the institutional review board at each participating institution, and written informed consent was obtained from all subjects who were 18 years old and older or from their parents if they were younger than 18 years.

Data were collected from CCSS participants using a baseline questionnaire administered beginning in 1994. One section of this baseline questionnaire elicited a report of pregnancies (either their own, for females, or those of female partners, for males). In addition, a random sample of CCSS participants was asked permission to contact their nearest-age full sibling. These siblings were then sent the baseline questionnaire. If any pregnancy was reported in the baseline questionnaire, the cohort member or sibling was mailed a detailed pregnancy questionnaire that elicited information about each pregnancy, including numerous maternal and paternal exposures, duration of the pregnancy, outcome of the pregnancy, and, for live births, the sex, birth weight, and any health problems of the offspring. The present analysis is restricted to females who completed the pregnancy questionnaire.

Study Population

From the pregnancy questionnaire, 2335 female childhood cancer survivors (hereafter referred to as survivors) reported 3529 total pregnancies. We excluded 1220 (35%) reported pregnancies that did not result in a live birth. Of the remaining 2309 live births, we excluded 55 because they were part of multiple births (which are strongly associated with the outcomes in question) and 53 because they occurred concurrent with or before the cancer diagnosis. The exclusions left 1264 survivors reporting 2201 singleton live births for analysis.

From the pregnancy questionnaire, 1170 female siblings reported 1700 pregnancies. We excluded 491 (29%) reported pregnancies that did not result in a live birth. Of the remaining 1209 live births, 34 were excluded because they were part of multiple births, leaving 601 siblings reporting on 1175 singleton live births for analysis.

The births included in this analysis occurred from 1972 to 2002 for survivors and from 1968 to 2002 for siblings. The median year of the births for each group was 1991.

The survivors and siblings are not matched pairs. Because of the random recruitment of siblings (described above), the female siblings need not have their corresponding survivor be female nor in any case be eligible for this study by reporting a pregnancy, and vice versa. Only 64 sister pairs were included in the analysis.

Exposure and Outcome Assessment

The survivors' medical records were abstracted to obtain data on cancer treatment, including the dates of treatment, types of treatment (i.e., surgery, radiotherapy, and/or chemotherapy), types and doses of chemotherapeutic agents used, and anatomic sites exposed during radiotherapy. We collected treatment data for the index cancer, as well as for any recurrences. If dates of treatment indicated that a particular treatment was given after a pregnancy, then that treatment was not considered as an exposure for that pregnancy.

For each survivor, photocopies of radiotherapy records were obtained from the treating institutions and forwarded to the collaborating medical physicist. Doses from all relevant radiation treatments were summed to determine the total dose for each survivor before each pregnancy. Absorbed doses to the ovaries, uterus, and pituitary gland, including the contribution of radiation scatter, were estimated by the method described by Stovall et al. (17). Gonadal shielding, ovarian pinning (oophoropexy), and field blocking were taken into account (17). Doses to the two ovaries were estimated separately. We used the maximum dose to either ovary as the treatment exposure in our analyses. Using the minimum ovarian dose led to similar results. None of the women included in this analysis received total body irradiation.

For analyses of chemotherapeutic agents, alkylating agents were defined as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, methyl-CCNU, mitomycin-C, prednimustine, procarbazine, thiotepa, and uracil mustard. Alkylating scores were calculated as a means for combining different alkylating agents for dose—response evaluations. For each aklylating 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 1–3 and a value of 0 indicating that the drug was not administered. These tertile scores for all alkylating agents were summed, and the cumulative score was then divided into tertiles, resulting in alkylating score values of 1–3 (with 0 meaning no exposure to alkylating agents).

Birth weight was reported by survivors and siblings in pounds and ounces, which was converted to grams. Low birth weight was defined as less than 2500 g, per the standard international definition (18). Gestational age at the time of delivery was reported in single weeks, and preterm birth was defined as a birth occurring at less than 37 weeks gestation (18). Small-for-gestational-age (SGA) was defined as having a birth weight in the bottom 10th percentile of infants of the same sex born during the same gestational week, using an external standard of US births published by Alexander et al. (19). This widely used standard is based on data from more than 3 million singleton live births in the United States in 1991.

Statistical Analysis

Logistic regression modeling was used to calculate odds ratios (ORs) as measures of relative risk for the dichotomous outcomes of low birth weight, preterm birth, and SGA. Being the offspring of a survivor was considered to be the exposure in models that compared outcomes between the survivors' and siblings' children. The potential effect of different treatments on low birth weight, preterm birth, and SGA was evaluated in analyses restricted to the survivors' children, with the various treatments modeled as the exposures. Unless otherwise noted, all regression models were adjusted for the following core group of variables that we considered a priori to be potential confounding factors: maternal age (as a continuous variable), birth order

(as a continuous variable), sex of the child (male or female), maternal drinking of alcohol during the pregnancy (yes or no), maternal smoking of cigarettes during the pregnancy (yes or no), and the use of assisted reproductive technology (yes or no). Analyses of low birth weight were further adjusted for gestational week at delivery (as a continuous variable). Analyses of treatment exposures were also adjusted for the index cancer diagnosis. All *P* values reported are two-sided, and $P<.05$ was considered to be statistically significant.

Multiple pregnancies per subject were included in the analyses. To assess the effect of the dependent nature of the data for children born to the same subject, we compared the results of models that used generalized estimating equations (GEE) to produce standard errors and test statistics with the results of models that did not use GEE. In the models that used GEE, we used an exchangeable working correlation structure, meaning that a common covariance was assumed among all children born to the same mother regardless of birth order. The standard errors produced in the models using GEE were negligibly different from those produced in models without the use of GEE. Nevertheless, we used models using GEE to minimize the chances of underestimating the standard errors and of producing biased results.

Results

We first identified characteristics of the survivors' and siblings' pregnancies that could potentially act as confounders in our analyses (Table 1). With few exceptions, the survivors and siblings were alike with respect to these factors. The maternal age at the time of pregnancy was slightly higher for siblings than survivors (mean ± standard deviation, 25.1 ± 4.9 years versus 24.4 ± 4.7 years; $P<.001$). Survivors were also more likely than siblings to report diabetes during pregnancy ($P = .001$). None of the other variables in Table 1 (aside from birth order, which is a reflection of the siblings having had more children than the survivors) were statistically significantly associated with survivor or siblingstatus.

Approximately 21% of the children of survivors were reported to be born earlier than 37 weeks gestation, compared with 12.6% of the children of the siblings (Table 2). Of the children born preterm in this study, the median gestational week at birth was 35 weeks. We estimated that the children of survivors were nearly twice as likely as the children of the siblings to be born preterm (OR = 1.9, 95% confidence interval [CI] = 1.4 to 2.4; $P<.001$).

The mean birth weight among the children of survivors (3312 g, 95% CI = 3284 to 3340 g) was also statistically significantly ($P<.001$) less than that of the children of the siblings (3447 g, 95% CI = 3414 to 3480 g). The crude risks of low birth weight among the children of survivors and siblings were 9.0% and 4.2%, respectively (Table 2). However, the higher risk of low birth weight among the children of survivors could be attributed to their birth at earlier gestational ages. Adjusting for the core set of confounders only (maternal age, birth order, sex of the child, maternal alcohol drinking, maternal smoking, and use of assisted reproductive technology), we observed a statistically significant doubling of risk for low birth weight (OR = 2.1, 95% CI = 1.5 to 2.9; $P<.001$); however, after further adjustment for gestational week at birth, the association was no longer apparent (OR = 1.3, 95% CI = 0.9 to 1.9; $P = .23$). The SGA results further confirmed that the children of survivors were not born smaller than the siblings' children of equivalent gestational age (OR = 1.0, 95% CI = 0.8 to 1.4; $P = .84$).

We calculated the crude risks of preterm birth, low birth weight, and SGA among the survivors' children after stratification for the index cancer diagnosis (Table 3). Nearly half of the survivors had been treated for Hodgkin lymphoma or leukemia. Survivors with kidney cancer were substantially more likely to have children born preterm (with associated low birth weight), but they did not have an excess of SGA births. The treatment-related analyses (Tables 4-7) are adjusted for the index cancer diagnosis.

The majority of the survivors in this analysis (65%) underwent chemotherapy, and we examined whether the type of chemotherapeutic agent used (i.e., alkylating or nonalkylating) was related to risk of the studied outcomes (Table 4). Compared with the children of survivors who did not undergo chemotherapy, those whose mothers were treated only with nonalkylating agents had no increased risk of preterm birth. Exposure to any alkylating agent versus none showed little association with preterm birth (core variable—adjusted OR = 1.3, 95% CI = 0.9 to 2.0; $P = .18$; data not shown in table), but survivors with the highest alkylating score exhibited a somewhat larger increase in risk (OR = 1.6, 95% CI = 0.9 to 2.7; $P = .09$). Chemotherapy with nonalkylating or alkylating agents did not appear to be associated with an increase in the risk of low birth weight or SGA births.

We next examined the association between radiotherapy dose (to the uterus, ovaries, and pituitary gland) and the risk of preterm, low birth weight, and SGA births (Tables 5-7). We observed increasing risk of preterm birth with increasing cumulative dose to the uterus. In contrast to the children of survivors who did not receive any radiotherapy (among whom 19.6% were born preterm), preterm birth was reported for 26.1% of the children of survivors who received uterine doses in the range of 50–250 cGy (OR = 1.8, 95% CI = 1.1 to 3.0; $P = .03$), for 39.6% of the children of survivors who received uterine doses in the range of 250–500 cGy (OR = 2.3, 95% CI = 1.0 to 5.1; $P = .04$), and for 50.0% of the children of survivors who received uterine doses higher than 500 cGy (OR = 3.5, 95% CI = 1.5 to 8.0; $P = .003$). With the hypothesis that an immature uterus would be more susceptible to the effects of radiation, we also stratified by whether the treatment occurred pre- or postmenarche. Data on age at menarche were available for 79% of the survivors. Within this subgroup, we found the association between uterine irradiation and preterm birth to be stronger for survivors exposed before menarche (for >250 cGy, OR = 4.9, 95% CI = 1.7 to 13.9; $P = .003$) than those exposed after menarche (for >250 cGy, OR = 1.9, 95% CI = 0.7 to 4.9; $P = .21$); however, the interaction was not statistically significant based on the likelihood ratio test comparing models with and without the interaction terms for menarche status by uterine dose ($P = .44$).

Due to the close proximity of the uterus and the ovaries, radiation doses to these organs were highly related. For analyses of ovarian exposure, therefore, to minimize confounding by high-dose uterine exposure, we calculated the effect of ovarian irradiation only among women who had a dose of less than 100 cGy to the uterus. Using this restrictive strategy still allowed us to examine doses to the ovary over a wide range, as well as those that constituted relatively high exposure for that organ. We found no convincing associations with ovarian or pituitary exposure and preterm birth (Table 5).

High-dose radiation to the uterus was statistically significantly related to the risk of low birth weight. In contrast to the children of survivors who did not receive any radiotherapy (among whom 7.6% were of low birth weight), low birth weight was reported for 25.5% of the children of survivors who received uterine doses in the range of 250–500 cGy (OR = 4.3, 95% CI = 1.4 to 12.8; $P = .01$) and for 36.2% of the children of survivors who received uterine doses greater than 500 cGy (OR = 6.8, 95% CI = 2.1 to 22.2; $P = .001$) (Table 6). We did not observe strong evidence of effect modification for treatment pre- versus postmenarche (>250 cGy: premenarche OR = 4.7, 95% CI = 1.2 to 18.6; $P = .03$ and postmenarche OR = 3.8, 95% CI = 1.3 to 11.2; $P = .02$, data not shown in table). Although many of the odds ratios for various levels of ovarian dose and pituitary dose were also elevated, none reached statistical significance and there was no evidence of a dose response (Table 6). Similarly, uterine irradiation at cumulative doses greater than 500 cGy was also associated with an elevated risk of SGA births (18.2% versus 7.8% among the children of survivors who did not undergo radiotherapy; OR = 4.0, 95% CI = 1.6 to 9.8; $P = .003$), but ovarian and pituitary doses appeared unrelated to this outcome (Table 7). Data were too sparse to evaluate the interaction between menarche status and uterine irradiation dose on the risk of SGA births.

Discussion

In this study, the offspring of female survivors of childhood cancer had a moderately higher risk of being born preterm than a comparison group of offspring of female siblings. They did not, however, have an increased risk of being born small for their gestational age, and the elevated risk of low birth weight seen in the survivors' children was a consequence of their being born early rather than an independent outcome. The rates of preterm birth and low birth weight in the sibling group were fairly comparable to those among singleton live births in the general US population during the time period covered by the study (20,21), and the proportion of SGA births in the sibling group (between 9% and 10%) was also consistent with the general US population data used as our standard (by definition, the bottom 10th percentile).

In an attempt to identify aspects of treatment that would preferentially affect the risk of these adverse pregnancy outcomes among the survivors, we found that uterine exposure to radiotherapy was associated with increased risk of preterm birth. Our results also suggested that the effect of uterine irradiation may be greater, and the threshold lower, for girls treated before menarche. This would be consistent with observations noting the vulnerability of the prepubertal uterus to irradiation (22) and may be related to the documented relationship between age at irradiation and final (adult) uterine volume (23,24). We observed that high-dose uterine irradiation was also associated with children born small when compared with others of the same gestational age and, furthermore, with low birth weight. Increased risk for low birth weight was seen at lower radiation doses (>250 cGy) than for SGA births (>500 cGy).

Thus, radiotherapy to the pelvis may raise the risks of both preterm birth and restricted fetal growth. Previous investigators have hypothesized that radiation-induced damage to abdomino-pelvic structures, tissue, or vasculature could interfere with fetal growth by constraining the developing pregnancy or by restricting vascular support to the pregnancy, leading to low birth weight or SGA infants (7-9,13,14). The etiology of preterm birth is largely unknown, but most established risk factors [extremes of maternal age, infection, gestational hypertension, lack of prenatal care, multiple births, heavy physical workload, and demographic factors (25-29)] are not likely candidates to explain the associations we observed. The mechanisms by which radiotherapy could cause preterm birth are speculative, but several possibilities exist. First, it is possible that physical constraint of the pregnancy induced by somatic effects including decreased uterine volume, as described above, could influence the risk of preterm birth. Also, uterine fibrosis might impair cervical competence or placentation (leading to abruptio placentae), both factors that are linked to preterm birth (13,28,30-32). A recent investigation also demonstrated an excess of fetal malpresentation among female cancer survivors treated with flank irradiation (14), and malpresentation is a risk factor for preterm birth (25,26). Emotional stress is also believed to increase the risk of preterm birth (25,27,33), and it is possible that female childhood cancer survivors experience a greater degree of stress during pregnancy, merely because they are concerned about their risk for adverse pregnancy outcomes.

This study confirms previously reported findings with respect to elevated rates of preterm birth (and associated low birth weight) among children born to mothers treated for Wilms tumor (8,9,13,14). In our study, the children born to mothers treated for kidney cancer (mostly Wilms tumor) exhibited the highest rates of these outcomes. Possible explanations include the mechanisms we hypothesize above in response to radiation treatment to the pelvis, as well as the potential result of congenital malformations of the genitourinary tract seen in Wilms tumor complex (2,7,13).

Our finding that female survivors who were treated with the highest tertile dose of alkylating agents had a higher risk of preterm birth is somewhat novel, but it should be interpreted

cautiously given its lack of statistical significance and lack of dose—response trend ($P = .13$) across the tertiles. Chiarelli et al. (7) assessed the risk of low birth weight in a study of 340 female childhood cancer survivors and found no excess risk among women exposed to alkylating agents, although their analysis relied on only two cases of low birth weight among the alkylating agent—treated survivors. Sanders et al. (10) reported on 24 women who received treatment with the alkylating agent cyclophosphamide for aplastic anemia or hematologic malignancy. Eighteen percent of those pregnancies ended in preterm labor and birth, which is higher than expected in the general population (20).

It is important to predict whether some treatment subgroups of survivors are at higher risk than others for adverse pregnancy outcomes, but such analyses suffer from limitations that are difficult to overcome. We believe that other childhood cancer survivors are a more appropriate control group for treatment-related evaluations than are siblings, who differ importantly from survivors in that they did not have the underlying disease. Consequently, we restricted the treatment-related analyses to survivors only. With the intention of having these analyses reflect the effect of treatment, as opposed to reflecting the underlying type of disease, we attempted to control for cancer type. However, thorough statistical adjustment is hindered when imbalances in cancer type and treatment are large, as they were in our sample. More straightforward attempts to calculate the risk of low birth weight, preterm birth, and SGA by treatment regimens, separately for each cancer type, were too finely stratified to produce reliable statistics. Thus, there could be some residual effect of cancer type in the analyses we present regarding treatment effects.

Other limitations in the data should also be discussed. First, although the total number of childhood cancer survivors and siblings included in this study is among the largest to date, the number of adverse outcomes available for analysis was often small, and adjustment for several confounders further added to the difficulty in generating precise results. Thus, the confidence intervals for many results allow for the possibility of a wide range of effects and often include the null value, hindering interpretation. Also, the large number of relative risks we calculated using numerous exposures and three different outcomes also leads to the problem of multiple comparisons (34), making it possible that some of our findings arose out of chance.

Data on the studied outcomes and some nontreatment exposures were self-reported, and the period of recall for reporting these data was sometimes substantial. Thus, we expect some amount of misclassification in these data. It is possible that survivors recalled events of preterm birth more accurately than did the comparison group of siblings, perhaps contributing to the differences observed for this outcome. However, this could not explain the associations observed between different cancer treatments and the risk of the studied outcomes, when the analyses were restricted only to survivors.

We were missing treatment dates for a substantial number of chemotherapy records (43%), and in the event of a missing treatment date we made the assumption that the treatment preceded the pregnancy, as we knew that the cancer diagnosis did. When evaluating radiation treatment records, where we had essentially 100% complete dates of treatment, we found that only two children were born before their mothers' radiation treatments and thus needed to be reclassified. Therefore, we expect the problem of misclassifying the temporal sequence of chemotherapy and pregnancy to be equally small and not a basis for concern in interpreting the results regarding chemotherapy. Overall, we were able to abstract a large amount of detailed treatment data from the treating institutions. We were able to formulate alkylator scores for 85% of the survivors who were known to have had chemotherapy. Similarly, we were able to calculate cumulative ovarian and uterine radiation doses for 89% and pituitary radiation doses for 88% of the survivors known to have had radiotherapy.

In conclusion, our data indicate that female survivors of childhood cancer who are able to become pregnant have a moderately elevated risk of having a preterm birth. Certain cancer therapies are associated with an increase in the risk of preterm birth and fetal growth restriction (manifested as SGA or low birth weight), namely those involving radiotherapy in high doses to the uterus. If the associations observed between high-dose uterine irradiation and these adverse pregnancy outcomes are causal, the mechanism is likely multifactorial. Our findings also suggest that the adverse association between uterine irradiation and the risk of future preterm birth might be especially important for girls who receive such treatment before menarche. Although gonadal irradiation can induce irreversible premature menopause (4), doses to the ovary at levels that allowed for future fertility were not found to increase the risk for the adverse pregnancy outcomes studied. Furthermore, no or little convincing effect on these outcomes was apparent for radiation exposure to the pituitary gland or for treatment with alkylating agents.

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Table 1

Descriptive characteristics of the pregnancies of the female childhood cancer survivors and female siblings

Characteristic	No. of live-born children of		*P**
	Survivors (N = 2201), N (%)	Siblings (N = 1175), N (%)	
Maternal age, y			.01
<20	355 (16.1)	168 (14.3)	
20–24	787 (35.8)	379 (32.3)	
25–29	729 (33.2)	403 (34.4)	
30–34	278 (12.6)	178 (15.2)	
≥35	50 (2.3)	45 (3.8)	
Missing	2	2	
Live birth order			.002
1	1264 (57.4)	601 (51.2)	
2	706 (32.1)	400 (34.0)	
3	186 (8.5)	137 (11.7)	
4	37 (1.7)	31 (2.6)	
5	7 (0.3)	5 (0.4)	
6	1 (0.1)	1 (0.1)	
Infant sex			.99
Male	1136 (51.9)	599 (51.9)	
Female	1054 (48.1)	556 (48.1)	
Missing	11	20	
Use of assisted reproductive technology†			.78
Yes	75 (3.5)	43 (3.7)	
No	2076 (96.5)	1127 (96.3)	
Missing	50	5	
Maternal high blood pressure during pregnancy			.07
Yes	272 (12.5)	121 (10.4)	
No	1907 (87.5)	1046 (89.6)	
Missing	22	8	
Maternal toxemia during pregnancy			.39
Yes	141 (6.5)	67 (5.7)	
No	2031 (93.5)	1102 (94.3)	
Missing	29	6	
Maternal diabetes during pregnancy			.001
Yes	93 (4.3)	24 (2.1)	
No	2076 (95.7)	1143 (97.9)	
Missing	32	8	
Maternal smoking of cigarettes during pregnancy			.09

Characteristic	No. of live-born children of		*P*[*]
	Survivors (N = 2201), N (%)	Siblings (N = 1175), N (%)	
Yes	369 (16.9)	225 (19.2)	
No	1821 (83.2)	945 (80.8)	
Missing	11	5	
Maternal drinking of alcohol during pregnancy			.57
Yes	331 (15.1)	185 (15.9)	
No	1858 (84.9)	981 (84.1)	
Missing	12	9	
Maternal use of recreational drugs during pregnancy			.74
Yes	50 (2.3)	29 (2.5)	
No	2124 (97.7)	1140 (97.5)	
Missing	27	6	
Maternal use of vitamin supplements during pregnancy			.13
Yes	1988 (90.8)	1082 (92.3)	
No	202 (9.2)	90 (7.7)	
Missing	11	3	

[*] Chi-square *P* values (two-sided).

[†] Reported maternal use of fertility drugs, in vitro fertilization, or use of some other technology to assist in getting pregnant.

Table 2

Duration of gestation and infant birth weight for the live-born children of female childhood cancer survivors and female siblings*

Outcome	No. of live-born children of		OR (95% CI)	P†
	Survivors (N = 2201), N (%)	Siblings (N = 1175), N (%)		
Duration of gestation				
Preterm‡	441 (21.1)	145 (12.6)	1.9 (1.4 to 2.4)	<.001
Full term‡	1653 (78.9)	1007 (87.4)	Referent	
Unknown	107	23		
Birth weight, g§				
<1500	37 (1.8)	9 (0.8)		
1500–1999	37 (1.8)	9 (0.8)		
2000–2499	115 (5.5)	30 (2.6)		
2500–2999	354 (16.8)	170 (14.9)		
3000–3499	751 (35.6)	371 (32.5)		
3500–3999	581 (27.6)	390 (34.2)		
≥4000	233 (11.1)	163 (14.3)		
Unknown	93	33		
LBW‖	189 (9.0)	48 (4.2)	1.3 (0.9 to 1.9)¶	.23
Non-LBW‖	1919 (91.0)	1094 (95.8)	Referent	
SGA#				
Yes	191 (9.5)	101 (9.2)	1.0 (0.8 to 1.4)	.84
No	1815 (90.5)	1002 (90.8)	Referent	
Unknown	195	72		

*Odds ratios were adjusted for maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy, and the use of assisted reproductive technology. Odds ratios for low birth weight were further adjusted for gestational week at birth. OR = odds ratio; CI = confidence interval.

†*P* values (two-sided) were calculated based on a *z* score using empirical standard error estimates derived from a logistic regression model using generalized estimating equations.

‡Preterm birth = less than 37 weeks gestation; full-term birth = 37 weeks gestation or longer.

§Birth weight of survivors versus siblings, *P* <.001 (chi-square, two-sided test).

‖LBW = low birth weight = birth weight less than 2.5 kg; Non-LBW = birth weight 2.5 kg and greater.

¶The odds ratio adjusting for all listed confounders except gestational week at birth was 2.1 (95% CI = 1.5 to 2.9).

#SGA = small-for-gestational-age, defined as birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, using the standard of Alexander et al. (19).

Table 3

Distribution of index cancer diagnosis among female childhood cancer survivors, and the crude risk of preterm birth, low birth weight (LBW), and small-for-gestational-age (SGA) among the children of survivors, by maternal index diagnosis

Index diagnosis of childhood cancer survivor (N = 1264 survivors)	N (%)	Proportion preterm birth(%)*†	Proportion LBW (%)*‡	Proportion SGA (%)*§
Hodgkin lymphoma	337 (26.7)	19.2	5.9	9.0
Leukemia	291 (23.0)	18.8	9.4	9.8
Bone sarcoma	207 (16.4)	20.3	9.4	10.5
Soft tissue sarcoma	154 (12.2)	28.9	10.3	9.5
Non-Hodgkin lymphoma	87 (6.9)	20.9	10.1	9.7
Central nervous system	87 (6.9)	16.2	7.5	7.3
Kidney cancer	61 (4.8)	41.5	25.6	9.3
Neuroblastoma	40 (3.2)	9.5	6.3	11.1

*Risks were calculated in the population of children whose mother had the same cancer type.

†Preterm birth = less than 37 weeks gestation; full-term birth = 37 weeks gestation or longer.

‡LBW = birth weight less than 2.5 kg; Non-LBW = birth weight 2.5 kg or greater.

§SGA = birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, using the standard of Alexander et al. (19).

Table 4

Risk of preterm birth, low birth weight, and small-for-gestational-age among the live born children of female cancer survivors, in relation to alkylating score*

Chemotherapy	Preterm, N (%)†	Full term, N (%)†	OR (95% CI)	P‡	LBW, N (%)§	Non-LBW, N (%)§	OR (95% CI)	P‡	SGA, N (%)//	Non-SGA, N (%)//	OR (95% CI)	P‡
Alkylating score												
No chemo treatment	92 (18.4)	409 (81.6)	1.0 (referent)		31 (6.1)	476 (93.4)	1.0 (referent)		39 (8.0)	448 (92.0)	1.0 (referent)	
0 (nonalkylator only)	84 (20.3)	330 (79.7)	1.1 (0.6 to 1.9)	.85	48 (11.5)	371 (88.5)	1.5 (0.6 to 4.1)	.42	41 (10.4)	353 (89.6)	1.1 (0.5 to 2.2)	.83
1	73 (22.5)	252 (77.5)	1.3 (0.8 to 2.2)	.33	30 (9.1)	299 (90.9)	1.3 (0.5 to 3.1)	.60	24 (7.8)	284 (92.2)	0.9 (0.5 to 1.9)	.87
2	48 (21.2)	178 (78.8)	1.1 (0.6 to 1.8)	.82	18 (8.0)	207 (92.0)	0.7 (0.2 to 2.0)	.46	19 (8.8)	198 (91.2)	0.8 (0.4 to 1.9)	.67
3	51 (25.4)	150 (74.6)	1.6 (0.9 to 2.7)	.09	21 (10.2)	184 (89.8)	1.0 (0.4 to 2.9)	.96	18 (9.2)	178 (90.8)	1.1 (0.5 to 2.4)	.74

*Odds ratios were adjusted for index cancer diagnosis, radiation dose to uterus, maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy, and the use of assisted reproductive technology. Odds ratios for low birth weight were further adjusted for gestational week at birth. OR = odds ratio; CI = confidence interval; LBW = low birth weight; SGA = small-for-gestational-age.

†Preterm birth = less than 37 weeks gestation; full-term birth = 37 weeks gestation or longer. Children (N = 534) were excluded from the preterm birth analysis due to missing data regarding gestational age (N = 90), chemotherapy treatment of their mother (N = 427), or both (N = 17).

‡*P* values (two-sided) were calculated based on a z score using empirical standard error estimates derived from a logistic regression model using generalized estimating equations.

§LBW = birth weight less than 2.5 kg; Non-LBW = birth weight 2.5 kg or greater. Children (N = 516) were excluded from the LBW analysis due to missing data regarding birth weight (N = 72), chemotherapy treatment of their mother (N = 423), or both (N = 21).

//SGA = birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, using the standard of Alexander et al. (19). Children (N = 599) were excluded from the SGA analysis due to missing data regarding birth weight or gestational age (N = 155), chemotherapy treatment of their mother (N = 404), or both (N = 40).

Table 5

Risk of preterm birth among live born children of female childhood cancer survivors, by radiation treatment and organ dose*

	Preterm birth, N (%)†	Full-term birth, N (%)†	OR (95% CI)	P‡
Not treated with any radiation	121 (19.6)	496 (80.4)	1.0 (referent)	
Radiation dose to uterus, cGy (treatment at all ages)				
0–10	81 (17.3)	386 (82.7)	0.9 (0.6 to 1.4)	.72
10–50	53 (19.9)	214 (80.1)	1.2 (0.7 to 2.0)	.53
50–250§	74 (26.1)	209 (73.9)	1.8 (1.1 to 3.0)	.03
250–500	21 (39.6)	32 (60.4)	2.3 (1.0 to 5.1)	.04
>500	23 (50.0)	23 (50.0)	3.5 (1.5 to 8.0)	.003
Radiation dose to uterus, cGy (treatment premenarche)‖				
0–10	29 (16.9)	143 (83.1)	0.9 (0.5 to 1.9)	.85
10–50	23 (27.4)	61 (72.6)	2.2 (1.0 to 4.8)	.05
50–250	21 (26.3)	59 (73.8)	2.1 (1.0 to 4.6)	.05
>250	15 (48.4)	16 (51.6)	4.9 (1.7 to 13.9)	.003
Radiation dose to uterus, cGy (treatment postmenarche)‖				
0–10	39 (21.2)	145 (78.8)	1.2 (0.6 to 2.4)	.69
10–50	20 (15.4)	110 (84.6)	0.8 (0.3 to 1.7)	.52
50–250	39 (27.5)	103 (72.5)	1.8 (0.8 to 4.3)	.18
>250	24 (40.7)	35 (59.3)	1.9 (0.7 to 4.9)	.21
Radiation dose to ovary, cGy¶				
0–10	75 (17.7)	349 (82.3)	0.9 (0.6 to 1.5)	.81
10–20	25 (21.2)	93 (78.8)	1.2 (0.7 to 2.4)	.51
20–50	27 (17.1)	131 (82.9)	0.9 (0.4 to 1.7)	.66
50–100	36 (26.3)	101 (73.7)	1.5 (0.8 to 3.0)	.22
>100	9 (25.0)	27 (75.0)	1.2 (0.4 to 3.8)	.76
Radiation dose to pituitary, cGy				
0–50	74 (30.5)	169 (69.5)	1.6 (1.0 to 2.7)	.05
50–250	96 (21.1)	360 (78.9)	1.0 (0.6 to 1.9)	.90
250–2000	27 (23.9)	86 (76.1)	1.4 (0.7 to 2.7)	.34
>2000	54 (18.7)	235 (81.3)	1.0 (0.6 to 1.6)	.96

* Odds ratios were adjusted for index cancer diagnosis, alkylating score category, maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy, and the use of assisted reproductive technology. OR = odds ratio; CI = confidence interval.

† Preterm birth = less than 37 weeks gestation; full-term birth = 37 weeks gestation or longer. Children missing data regarding gestational age (N = 107) were excluded from the analysis, as were an additional 361 children missing data to calculate uterine dose, 361 children missing data to calculate ovarian dose, and 376 children missing data to calculate pituitary dose (from those site-specific analyses).

‡ *P* values (two-sided) were calculated based on a *z* score using empirical standard error estimates derived from a logistic regression model using generalized estimating equations.

§ This category includes survivors exposed to 50–100 cGy (49%) and 100–250 cGy (51%).

‖ Referent group for the stratified analyses included children whose mothers received cancer treatment, but not radiotherapy, in the same pre- or postmenarche period. Sparse numbers compelled us to combine the two highest dose categories (250–500 and >500 cGy) for this analysis.

¶ Maximum radiation dose to either ovary. Analysis limited to female survivors with a uterine radiation dose of <100 cGy.

Table 6

Risk of low birth weight (LBW) among the live born children of female childhood cancer survivors, by radiation treatment and organ dose*

	LBW, N (%)†	Non-LBW, N (%)†	OR (95% CI)	P‡
Not treated with any radiation	47 (7.6)	575 (92.4)	1.0 (referent)	
Radiation dose to uterus, cGy				
0–10	31 (6.5)	443 (93.5)	1.5 (0.7 to 3.4)	.35
10–50	19 (7.1)	250 (92.9)	1.2 (0.5 to 3.2)	.66
50–250§	25 (8.7)	262 (91.3)	1.2 (0.5 to 3.2)	.66
250–500	14 (25.5)	41 (74.5)	4.3 (1.4 to 12.8)	.01
>500	17 (36.2)	30 (63.8)	6.8 (2.1 to 22.2)	.001
Radiation dose to ovary, cGy‖				
0–10	30 (7.0)	401 (93.0)	1.6 (0.7 to 3.6)	.30
10–20	6 (5.2)	109 (94.8)	0.5 (0.1 to 2.1)	.37
20–50	12 (7.4)	151 (92.6)	2.3 (0.7 to 7.0)	.15
50–100	12 (8.8)	124 (91.2)	0.9 (0.2 to 3.1)	.81
>100	5 (14.7)	29 (85.3)	1.7 (0.3 to 9.6)	.52
Radiation dose to pituitary, cGy				
0–50	38 (15.6)	205 (84.4)	1.7 (0.7 to 3.9)	.23
50–250	28 (6.1)	434 (93.9)	2.1 (0.8 to 5.9)	.15
250–2000	10 (8.7)	105 (91.3)	1.4 (0.4 to 4.7)	.62
>2000	30 (10.1)	266 (89.9)	1.5 (0.6 to 3.8)	.36

*Odds ratios were adjusted for index cancer diagnosis, alkylating score category, gestational week at birth, maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy, and the use of assisted reproductive technology. OR = odds ratio; CI = confidence interval.

†LBW = birth weight less than 2.5 kg; Non-LBW = birth weight 2.5 kg or greater. Children missing data regarding birth weight (N = 93) were excluded from the analysis, as were an additional 354 children missing data to calculate uterine dose, 354 children missing data to calculate ovarian dose, and 370 children missing data to calculate pituitary dose (from those site-specific analyses).

‡*P* values (two-sided) were calculated based on a *z* score using empirical standard error estimates derived from a logistic regression model using generalized estimating equations.

§This category includes survivors exposed to 50–100 cGy (49%) and 100–250 cGy (51%).

‖Maximum radiation dose to either ovary. Analysis limited to female survivors with a uterine radiation dose of <100 cGy.

Table 7

Risk of a small-for-gestational-age (SGA) birth among the live-born children of female childhood cancer survivors, by radiation treatment and organ dose*

	SGA, N (%)†	Non-SGA, N (%)†	OR (95% CI)	P‡
Not treated with any radiation	46 (7.8)	547 (92.2)	1.0 (referent)	
Radiation dose to uterus, cGy				
0–10	39 (8.7)	409 (91.3)	1.1 (0.6 to 2.1)	.66
10–50	21 (8.2)	236 (91.8)	1.3 (0.6 to 2.8)	.46
50–250§	20 (7.3)	256 (92.8)	1.0 (0.4 to 2.2)	.92
250–500	3 (5.7)	50 (94.3)	1.3 (0.3 to 4.8)	.70
>500	8 (18.2)	36 (81.8)	4.0 (1.6 to 9.8)	.003
Radiation dose to ovary, cGy‖				
0–10	36 (8.9)	369 (91.1)	1.2 (0.6 to 2.2)	.61
10–20	8 (7.0)	106 (93.0)	0.8 (0.3 to 2.5)	.75
20–50	14 (9.2)	138 (90.8)	1.4 (0.6 to 3.3)	.46
50–100	7 (5.2)	127 (94.8)	0.7 (0.2 to 2.2)	.57
>100	3 (8.8)	31 (91.2)	1.2 (0.2 to 6.7)	.81
Radiation dose to pituitary, cGy				
0–50	20 (8.6)	213 (91.4)	1.7 (0.8 to 3.4)	.14
50–250	35 (7.9)	408 (92.1)	1.7 (0.7 to 4.7)	.27
250–2000	5 (4.7)	101 (95.3)	0.3 (0.1 to 1.4)	.12
>2000	30 (10.6)	252 (89.4)	1.1 (0.6 to 2.1)	.69

*Odds ratios were adjusted for index cancer diagnosis, alkylating score category, maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy, and the use of assisted reproductive technology. OR = odds ratio; CI = confidence interval.

†SGA = birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, using the standard of Alexander et al. (19). Children missing data regarding gestational age or birth weight (N = 195) were excluded from the analysis, as were an additional 335 children missing data to calculate uterine dose, 337 children missing data to calculate ovarian dose, and 349 children missing data to calculate pituitary dose (from those site-specific analyses).

‡*P* values (two-sided) were calculated based on a *z* score using empirical standard error estimates derived from a logistic regression model using generalized estimating equations.

§This category includes survivors exposed to 50–100 cGy (49%) and 100 –250 cGy (51%).

‖Maximum radiation dose to either ovary. Analyses limited to female survivors with a uterine radiation dose of <100 cGy.