

Pregnancy Outcomes in Female Childhood and Adolescent Cancer Survivors

A Linked Cancer-Birth Registry Analysis

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Objective: To compare birth outcomes among female survivors of childhood and adolescent cancer who subsequently bear children, relative to those of women without a history of cancer.

Design: Retrospective cohort study.

Setting: Four US regions.

Participants: Cancer registries identified girls younger than 20 years who were diagnosed as having cancer from 1973 through 2000. Linked birth records identified the first live births after diagnosis (n=1898). Comparison subjects were selected from birth records (n=14 278). Survivors of genital tract carcinomas underwent separate analysis.

Main Exposure: Cancer diagnosis at younger than 20 years.

Main Outcome Measures: Infant low birth weight, preterm delivery, sex ratio, malformations, mortality, and delivery method, and maternal diabetes, anemia, and preeclampsia.

Results: Infants born to childhood cancer survivors were more likely to be preterm (relative risk [RR], 1.54; 95% confidence interval [CI], 1.30-1.83) and to weigh less than 2500 g (1.31; 1.10-1.57). For the offspring of genital tract carcinoma survivors, RRs were 1.33 (95% CI, 1.13-1.56) and 1.29 (1.10-1.53), respectively. There were no increased risks of malformations, infant death, or altered sex ratio, suggesting no increased germ cell mutagenicity. In exploratory analysis, bone cancer survivors had an increased risk of diabetes (RR, 4.92; 95% CI, 1.60-15.13), and anemia was more common among brain tumor survivors (3.05; 1.16-7.98) and childhood cancer survivors whose initial treatment was chemotherapy only (2.45; 1.16-5.17).

Conclusions: Infants born to female survivors of childhood and adolescent cancer were not at increased risk of malformations or death. Increased occurrence of preterm delivery and low birth weight suggest that close monitoring is warranted. Increased diabetes and anemia among subgroups have not been reported, suggesting areas for study.

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CANCER THERAPIES MAY affect future reproductive potential. One concern of female survivors of childhood and adolescent cancer is the possibility of adverse outcomes among offspring.¹ Given the increasing number of young cancer survivors, it is important to evaluate their pregnancy outcomes. Linked birth-cancer registry data offer an opportunity

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to provide additional information to reports from large follow-up studies. Using data from 4 US regions, we conducted an exploratory, population-based study to compare the occurrence of outcomes among infant offspring and selected preg-

nancy conditions among female cancer survivors with those of a comparison group identified from birth records.

METHODS

SUBJECT IDENTIFICATION AND DATA LINKAGE

Human subject protection committee approval was received by the relevant institutions and state health departments before the study. Data from the following 4 population-based cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute were used to identify cancer patients: the Cancer Surveillance System of Western Washington in Seattle; the Karmanos Cancer Institute of Wayne State University in Detroit,

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Michigan; the Utah Cancer Registry at the University of Utah in Salt Lake City; and the SEER registry in Atlanta, Georgia. These registries perform active surveillance and follow-up of incident cancer cases in each region. Aside from Utah, the regions are not statewide but encompass the named metropolitan region plus surrounding counties (registry details may be found at <http://seer.cancer.gov/registries/index.html>).

Records of girls younger than 20 years and newly diagnosed as having cancer were identified from each registry for the following periods: 1974 through 1995 in Seattle; 1973 through 1998 in Utah; 1973 through 2000 in Detroit; and 1975 through 2000 in Atlanta. The available data included demographic information (birth date, age at diagnosis, and race/ethnicity), tumor characteristics (date of diagnosis, primary site, histologic type per the second edition of the *International Classification of Diseases for Oncology*,² and SEER summary stage), and initial course of treatment (chemotherapy, surgical treatment, radiation, and combinations). Childhood cancer diagnoses were categorized using the International Classification of Childhood Cancer.³ Because of small numbers, categories corresponding to neuroblastoma and related tumors, embryonal renal and hepatic tumors, and retinoblastoma were collapsed into a single embryonal tumor category.⁴ The anatomical primary cancer site also was categorized as to whether it occurred within the abdomen and further subcategorized as occurring within the pelvis. Initial course of treatment was examined as a yes/no variable for each modality (any chemotherapy, any surgical treatment, etc) and by nonoverlapping combinations of therapies. Cancer relapse information was unavailable.

Records of potential subjects were linked in each region to state birth records to identify the first live-born infant after the subject's cancer diagnosis for the following available years: 1974 through 2001 in Seattle, 1973 through 2001 in Utah, 1975 through 2001 in Detroit, and 1980 through 2000 in Atlanta. Live-born infants delivered before a subject's cancer diagnosis were not included in this analysis. Linkage strategies varied by state and included probabilistic and deterministic strategies used for routine data linkages within each health department or agency.^{5,6} Variables available for linkage included the patient's maiden and married names, birth dates, sex, birthplace (Utah only), race/ethnicity (Atlanta only), and Social Security number (Utah, Detroit, and Atlanta). Comparison subjects were randomly selected from remaining birth records at a comparison to case ratio of 10:1 in Seattle, Utah, and Atlanta and of 4:1 in Detroit. Women were frequency matched by delivery year, age (<20, 20-24, 25-29, 30-34, and ≥35 years), and race/ethnicity (white, African American, Asian, Native American, and other; as recorded by cancer registries and birth records).

On examination of the merged file, we determined that the following potential cases were ineligible, and these were subsequently excluded: 74 cases with benign/possibly benign lesions, 1 with squamous cell and 1 basal cell skin lesion, and 2 with only deliveries identified before their cancer diagnosis. Three fetal death records were identified among the cases and 22 among the controls. These also were excluded because the analyses focused on live births only. This resulted in 1898 cancer survivors and 14 278 women for comparison. Analyses were conducted separately for the 1006 cases with genital tract carcinomas (SEER topography codes 51.0-57.9), of whom 96% had in situ cervical lesions diagnosed at 15 to 19 years of age. The remaining 892 cases involved survivors of childhood cancer.

OUTCOMES EVALUATED

Infant outcomes included birth weight (<2500, 2500-3999, and ≥4000 g), gestational age (<37, 37-41, and ≥42 weeks), being small for gestational age (SGA) (defined as <10% birth weight

for gestational age and sex based on a representative national sample⁷), presence of any malformation, 5-minute Apgar score of less than 7 (yes/no; unavailable in Detroit), and infant death before 12 months of age (unavailable in Atlanta). Maternal outcomes that could be evaluated using birth records included delivery type (cesarean section or vaginal) and anemia. Because birth records in all states did not distinguish gestational from established diabetes or preeclampsia from eclampsia, these were collapsed into any diabetes (yes/no) and any preeclampsia (yes/no). Other available information included maternal prenatal smoking (yes/no), marital status, number of prior pregnancies and births, and time of prenatal care initiation. No information on assisted reproductive techniques was available.

STATISTICAL ANALYSES

The number of cancer survivors in each region who linked with birth records and the total number of cases ascertained in each SEER region during the same period (using SEER*Stat, version 6.1.4, 2005) were used to calculate the proportions identified with subsequent live births. The distribution of maternal and infant outcomes was described separately for comparison subjects and girls with childhood cancer and genital tract carcinoma. Because many outcomes were relatively common, we determined that odds ratio estimates of the relative risk (RR) from logistic regression overestimated the RR, and instead we used stratified analyses with Mantel-Haenszel methods. The results were similar to those produced by log-binomial or Poisson models.⁸ We adjusted all RRs for state, frequency-matched variables (delivery year, maternal age, and race/ethnicity), and parity. Gestational age also was adjusted for in estimates of low birth weight. Other variables considered for their possible role in the associations included maternal prenatal smoking, marital status, and infant sex. Except where noted, adjustment by these variables did not meaningfully alter the RR estimates, and only those variables for which inclusion resulted in such change were retained in the analyses. Sensitivity analyses in which deliveries occurring within 9 months of diagnosis, multiple-gestation births, and multiparous mothers were excluded showed similar results. Subanalyses were conducted that stratified by cancer type, primary cancer site, year of and age at diagnosis, time interval between the diagnosis and subsequent delivery, and initial course of cancer treatment. Analyses were conducted using Stata statistical software, (version 9; StataCorp, College Station, Texas). Data are presented as mean (SD) or median (range).

RESULTS

CHARACTERISTICS OF CANCER SURVIVORS AND COMPARISON SUBJECTS

The proportion of childhood cancer survivors identified with live births ranged from 13.1% to 17.2% across the 4 regions, with an overall median time from diagnosis to delivery of 7 (0-27) years (**Table 1**). Among genital tract carcinoma survivors, the proportions with subsequent live deliveries identified ranged from 28.2% to 54.8%, and the overall median time from diagnosis to delivery was 3 (0-19) years.

This difference in elapsed time between cancer diagnosis and subsequent live birth between the 2 cohorts reflected the younger median age at diagnosis of the childhood cancer survivors (16 [0-19] years) compared with genital tract carcinoma survivors (18 [14-19] years). How-

Table 1. Female Survivors of Childhood Cancer and Adolescent Genital Tract Carcinoma With Subsequent Live Birth Identified^a

	Seattle	Utah	Detroit	Atlanta	Total
No. of childhood cancer cases ^b	1393	1249	2414	1039	6095
Identified with subsequent live births, No. (%)	183 (13.1)	215 (17.2)	345 (14.3)	149 (14.3)	892 (14.6)
Years from diagnosis to delivery, median [range]	9 [0-25]	7 [0-24]	7 [0-27]	6 [0-22]	7 [0-27]
No. of genital tract carcinoma cases ^c	746	176	766	305	1993
Identified with subsequent live births, No. (%)	210 (28.2)	89 (50.6)	397 (51.8) ^d	167 (54.8) ^e	863 (43.3)
Years from diagnosis to delivery, median [range]	4 [0-18]	2 [0-8]	3 [0-17]	3 [0-19]	3 [0-19]

^aRegions are described in the "Subject Identification and Data Linkage" subsection of the "Methods" section.

^bIncludes in situ and malignant lesions except for female genital tract carcinomas (using SEER*Stat, version 6.1.4, 2005).

^cIncludes in situ and malignant lesions reported through 1995 (using SEER*Stat). Beginning in 1996, SEER no longer routinely reported cervical in situ lesions.

^dDoes not include 142 cases diagnosed from 1996 through 2000 and included in subsequent tables.

^eDoes not include 1 case diagnosed in 1997 and included in subsequent tables.

ever, most childhood cancer survivors (84.0%) were 10 years or older at diagnosis (**Table 2**). The most common childhood cancer diagnoses were lymphoma (22.6%), thyroid carcinoma (13.2%), central nervous system tumors (10.0%), leukemia (9.8%), and skin tumors (8.7%). Because SEER does not report on basal or squamous cell skin tumors, 77 of 78 skin tumors were melanomas. Seventy survivors had other carcinomas, most commonly malignant carcinoid tumors (n=20). Among the genital tract carcinoma cohort, 98.3% had in situ lesions, with involvement of the cervix in 96.1%. The distribution of childhood cancer types across regions generally was similar (data not shown), except Atlanta had fewer thyroid carcinomas (6.7%) compared with the other 3 regions (14.5%), and Utah and Atlanta had more skin tumors (13.2%) compared with Seattle and Detroit (5.7%). The distribution of any chemotherapy, surgical treatment, and radiotherapy exposure was similar across regions.

Compared with all childhood cancer cases ascertained by SEER in the 4 regions during the study period (using the SEER*Stat software), the subset of cases linked in this study were more likely to be diagnosed in an earlier era (before 1990, 81.8% vs 61.1%) and at an older age (≥ 10 years, 84.0% vs 52.6%). Similarly, the distribution of cancer diagnoses more likely included cancers associated with older age at diagnosis (lymphoma, 22.7% vs 13.6%, and non-genital tract carcinomas, 29.8% vs 12.9%). The genital tract carcinoma cases linked in this study were similar to the overall genital tract carcinoma cohort ascertained by SEER with respect to diagnosis age and diagnosis year distributions.

Age at and year of delivery and race/ethnicity were similar across cohorts except for a slightly greater proportion of African Americans (26.1%) among the genital tract carcinoma cohort compared with the childhood cancer (18.2%) and comparison (20.1%) groups (**Table 3**). Genital tract carcinoma survivors were more likely to have smoked prenatally (36.9%) than were comparison subjects (19.4%) and childhood cancer survivors (11.6%). A greater proportion of genital tract carcinoma survivors were unmarried at delivery (48.9%) compared with childhood cancer survivors (32.5%) and comparison women (34.1%). Childhood cancer survivors were less likely to have had a prior pregnancy or birth compared with the genital tract carcinoma survivors or the comparison group, but the proportion of multiple gestation

births was similar in all groups (1%-2%; data not shown).

OVERALL PREGNANCY AND INFANT OUTCOMES

Maternal diabetes, preeclampsia, and anemia occurred in similar proportions in all groups (**Table 4**). Childhood cancer survivors had a borderline increased risk of cesarean section delivery relative to comparison women (RR, 1.15; 95% confidence interval [CI], 0.99-1.33; overall; 1.14 [0.97-1.33] among those without prior deliveries). Cesarean section deliveries were not more common among the genital tract carcinoma cohort. The male to female ratio among infants born to the 2 cancer cohorts and the comparison group were similar, ranging from 0.98 to 1.02 (corresponding to RRs ranging from 0.97-1.00).

Both cancer cohorts were more likely to deliver infants before 37 weeks' gestation or weighing less than 2500 g relative to the comparison group, although the risks of having an SGA infant were not increased (Table 4). Only childhood cancer survivors had an increased risk of very preterm delivery (< 32 weeks: RR, 1.77; 95% CI, 1.18-2.66 [data not shown]). When analyses of low birth weight were restricted to infants of at least 37 weeks' gestational age, the RR remained significantly increased for childhood cancer cases (RR, 1.56; 95% CI, 1.12-2.16), but not for genital tract carcinoma cases (1.27; 0.90-1.79 [data not shown]). These estimates were unchanged when adjusted for maternal anemia, diabetes, and preeclampsia. Neither cohort was more likely than the comparison subjects to have infants with birth weights of less than 1500 g or malformations or who died before 12 months of age.

OUTCOMES STRATIFIED BY DIAGNOSTIC AND TREATMENT CHARACTERISTICS

When pregnancy outcomes were analyzed among childhood cancer survivors by diagnostic and treatment characteristics, bone cancer survivors were twice as likely to undergo a cesarean section delivery, relative to comparison women (**Table 5**). However, cesarean section was not significantly more common among women who had childhood cancers primarily located in the abdomen or

Table 2. Diagnostic Characteristics of Female Survivors of Childhood Cancer and Adolescent Genital Tract Carcinoma With Subsequent Live Births

Characteristic	Cohort, No. (%) ^a	
	Childhood Cancer (n=892)	Genital Tract Carcinoma (n=1006)
Year of diagnosis		
1973-1979	309 (34.6)	144 (14.3)
1980-1989	420 (47.1)	303 (30.1)
1990-2000	163 (18.3)	559 (55.6)
Age at diagnosis, y		
<5	66 (7.4)	
5-9	77 (8.6)	
10-14	186 (20.9)	9 (0.9)
15-19	563 (63.1)	997 (99.1)
Elapsed years until delivery		
<2	71 (8.0)	308 (30.6)
2-5	263 (29.5)	474 (47.1)
6-10	263 (29.5)	175 (17.4)
11-30	295 (33.1)	49 (4.9)
Cancer type ^b		
Leukemia	87 (9.8)	
Lymphoma	202 (22.6)	
Central nervous system	89 (10.0)	
Embryonal ^c	47 (5.3)	
Malignant bone	53 (5.9)	
Soft-tissue sarcoma	65 (7.3)	
Germ cell, gonadal, trophoblastic	66 (7.4)	
Thyroid carcinoma	118 (13.2)	
Non-basal/squamous cell skin	78 (8.7)	
Other carcinoma	70 (7.8)	1006 (100.0)
Other tumors	17 (1.9)	
Primary cancer site		
Abdomen	185 (20.7)	1006 (100.0)
Pelvis only	115 (12.9)	1006 (100.0)
Cancer treatment		
Chemotherapy only	112 (12.6)	2 (0.2)
Surgical treatment only	328 (36.8)	789 (78.4)
Radiotherapy only	87 (9.8)	0
Chemotherapy + surgical treatment	83 (9.3)	0
Chemotherapy + radiotherapy	86 (9.6)	1 (0.1)
Surgical treatment + radiotherapy	111 (12.4)	2 (0.2)
Chemotherapy + surgical treatment + radiotherapy	48 (5.4)	0
Other/unknown	37 (4.1)	212 (21.1)
Any chemotherapy	329 (36.9)	3 (0.3)
Any surgical treatment	570 (63.9)	791 (78.6)
Any radiotherapy	332 (37.2)	3 (0.3)

^aBecause of rounding, percentages may not total 100.

^bBased on International Classification of Childhood Cancers.³ Includes in situ lesions consisting of 989 genital tract carcinomas, 4 non-genital tract carcinomas, and 7 skin lesions.

^cIncludes neuroblastoma and related tumors, embryonal renal and hepatic tumors, and retinoblastoma.

pelvis. The risk of diabetes also was increased among bone cancer survivors (RR, 4.92; 95% CI, 1.60-15.13) but not for other diagnostic/treatment characteristics. Anemia was increased significantly among those with central nervous system tumors (RR, 3.05; 95% CI, 1.16-7.98) and childhood cancer survivors treated with chemotherapy only (2.45; 1.16-5.17); these estimates remained significant if deliveries within 2 years of diagnosis were excluded (data not shown). No increased risk of preeclampsia was observed except for a borderline estimate among

Table 3. Prenatal Characteristics of Female Survivors of Childhood and Adolescent Cancer at Time of First Subsequent Birth vs a Comparison Group^a

Characteristic	Cohort, No. (%)		
	Childhood Cancer (n=892)	Genital Tract Carcinoma (n=1006)	Comparison (n=14 278)
Race/ethnicity			
White	702 (80.0)	711 (71.8)	10 729 (76.8)
African American	160 (18.2)	258 (26.1)	2811 (20.1)
Asian	11 (1.3)	10 (1.0)	203 (1.5)
Native American	2 (0.2)	8 (0.8)	127 (0.9)
Other	3 (0.3)	3 (0.3)	94 (0.7)
Age at delivery, y			
<20	240 (26.9)	241 (26.8)	3918 (27.5)
20-24	382 (42.8)	389 (43.2)	6801 (47.7)
25-29	180 (20.2)	181 (20.1)	2498 (17.5)
30-34	75 (8.4)	75 (8.3)	909 (6.4)
35-39	15 (1.7)	14 (1.6)	141 (1.0)
Year of delivery			
1973-1979	28 (3.1)	29 (2.9)	450 (3.2)
1980-1989	271 (30.4)	264 (26.2)	4418 (30.9)
1990-1999	522 (58.5)	599 (59.5)	8368 (58.6)
2000-2001	71 (8.0)	114 (11.3)	1042 (7.3)
Prenatal smoking ^b	72 (11.6)	280 (36.9)	1994 (19.4)
Unmarried at time of delivery ^c	178 (32.5)	228 (48.9)	3615 (34.1)
No. of prior pregnancies			
0	596 (67.9)	409 (41.4)	6074 (43.7)
1	202 (23.0)	354 (35.8)	4251 (30.6)
≥2	80 (9.1)	225 (22.8)	3571 (25.7)
No. of prior births			
0	767 (87.2)	588 (59.5)	7240 (52.0)
1	92 (10.5)	303 (30.7)	4299 (30.9)
≥2	21 (2.4)	97 (9.8)	2392 (17.2)
Trimester prenatal care began			
First	721 (82.9)	771 (79.2)	10 472 (75.4)
Second	118 (13.6)	148 (15.2)	2631 (18.9)
Third or no care	31 (3.6)	55 (5.6)	783 (5.6)

^aNumbers may not add up to totals because of missing data. Percentages are based on category totals and, because of rounding, may not total 100.

^bNot available all years.

^cUnavailable in Detroit area.

women who had received a combination of chemotherapy, surgical treatment, and radiotherapy (RR, 2.57; 95% CI, 0.99-6.68 [data not shown]).

Having an infant delivered before 37 weeks' gestation or weighing less than 2500 g occurred more commonly among childhood cancer survivors than comparison women for many of the cancer types, sites, and treatment categories examined (Table 5). Risk of preterm delivery was greatest after leukemia (RR, 2.55; 95% CI, 1.78-3.64) but also was associated with lymphoma, bone tumors, soft-tissue sarcomas, and an abdominal primary cancer site. Among treatment exposures, chemotherapy was associated with a 2-fold increased risk of preterm delivery, but RRs were significantly increased for most other modalities as well. Risk of preterm delivery also was increased across almost all categories of age at diagnosis and elapsed time since diagnosis. After adjusting for gestational length, modest increased risks of birth weight less than 2500 g were observed for women with

Table 4. Pregnancy Outcomes Associated With First Subsequent Birth Among Childhood Cancer and Adolescent Genital Tract Carcinoma Survivors vs a Comparison Group^a

Outcome	Cohort, No. (%)			RR (95% CI) ^b	
	Childhood Cancer (n=892)	Genital Tract Carcinoma (n=1006)	Comparison (n=14 278)	Childhood Cancer Cohort	Genital Tract Carcinoma Cohort
Maternal conditions					
Any cesarean section ^c	163 (21.5)	154 (17.2)	2212 (17.1)	1.15 (0.99-1.33)	0.97 (0.83-1.13)
Primary cesarean section ^d	145 (21.8)	110 (20.8)	1216 (18.4)	1.14 (0.97-1.33)	1.11 (0.92-1.32)
Diabetes ^c	11 (1.6)	13 (1.5)	174 (1.4)	1.02 (0.53-1.95)	0.86 (0.49-1.53)
Preeclampsia ^c	37 (5.4)	34 (3.9)	452 (3.7)	1.01 (0.73-1.42)	0.99 (0.70-1.41)
Anemia ^c	18 (2.7)	12 (1.4)	269 (2.3)	1.30 (0.81-2.08)	0.65 (0.36-1.17)
Infant outcomes					
Female	444 (49.8)	507 (50.4)	7058 (49.4)	1 [Reference]	1 [Reference]
Male	448 (50.2)	499 (49.6)	7220 (50.6)	1.00 (0.93-1.07)	0.97 (0.90-1.03)
Gestational age, wk					
<37	130 (14.9)	145 (14.8)	1423 (10.3)	1.54 (1.30-1.83)	1.33 (1.13-1.56)
37-41	677 (77.4)	747 (76.1)	11 088 (79.9)	1 [Reference]	1 [Reference]
≥42	68 (7.8)	89 (9.1)	1371 (9.9)	0.86 (0.68-1.08)	0.91 (0.74-1.11)
Birth weight, g^e					
<2500	103 (11.6)	122 (12.2)	1081 (7.6)	1.31 (1.10-1.57)	1.29 (1.10-1.53)
2500-3999	708 (79.5)	813 (81.1)	11 917 (83.6)	1 [Reference]	1 [Reference]
≥4000	80 (9.0)	68 (6.8)	1256 (8.8)	1.18 (0.94-1.48)	0.89 (0.70-1.14)
Small for gestational age ^f	96 (11.1)	149 (15.3)	1549 (11.3)	0.87 (0.67-1.12)	1.09 (0.90-1.33)
Malformation ^c	10 (1.3)	14 (1.6)	220 (1.7)	0.92 (0.48-1.75)	1.16 (0.66-2.04)
5-min Apgar score <7 ^g	13 (2.4)	15 (3.3)	172 (1.7)	1.30 (0.72-2.35)	2.01 (1.15-3.50)
Infant death ^h	7 (1.0)	6 (0.7)	93 (0.9)	1.08 (0.47-2.48)	0.83 (0.36-1.89)

Abbreviations: CI, confidence interval; RR, relative risk.

^aNumbers may not add up to totals because of missing data.

^bAdjusted for region, maternal age, year of delivery, race/ethnicity, and parity.

^cNot available for all years.

^dAmong women without prior deliveries.

^eAlso adjusted by gestational age (<32, 32-36, 37-41, or ≥42 weeks).

^fAlso adjusted for maternal prenatal smoking.

^gNot available for all years, and unavailable in Detroit area.

^hNot available for all years, and unavailable in Atlanta area.

a history of leukemia, central nervous system tumors, and germ cell and related tumors, as well as those with primary abdominal and pelvic tumors. Increased risk of low birth weight also was seen after chemotherapy or any radiotherapy exposure. No significantly increased RRs for SGA, malformations, 5-minute Apgar score of less than 7, or infant death were observed across diagnostic and treatment categories (data not shown).

Among genital tract carcinoma survivors, risks of having preterm or low-birth-weight infants generally were increased, although not always significantly, for most categories of diagnosis year and time since diagnosis (data not shown). However, no obvious pattern or trend with respect to these variables was observed.

COMMENT

In this population-based study, 14.6% of female childhood cancer survivors and 43.3% of genital tract carcinoma survivors identified within the registry in each region had a live birth recorded within the same state during the study period (≤28 years of follow-up). The childhood cancer survivors we identified with subsequent live births differed somewhat from all childhood cancer cases diagnosed in the study regions in that they were more often older at diagnosis (likely at least in part because more of

them were of childbearing age during the years of data linkage). Genital tract carcinoma survivors with subsequent deliveries were generally similar to all patients with the same diagnosis in the registries. Out-of-state migration of survivors after diagnosis may lead to underestimation of the true proportion of young cancer patients who delivered infants. However, a separate linkage of Washington State birth certificates indicated that 17% of all girls born in that state in 1966 had a subsequent live birth in Washington from 1987 through 2006 (data not shown). Although this latter linkage included only women aged 21 to 37 years at delivery, it suggests that any possible loss to follow-up because of out-of-state migration among childhood cancer survivors is similar to that of the general population. Finally, many of our cases were treated decades ago, so it also is possible that childbearing rates in more recent cohorts are greater owing to development of therapies more likely to conserve fertility and to increased assisted fertilization options for survivors.

Approximately 30% of 6494 female childhood cancer survivors in the Childhood Cancer Survivor Study reported that they became pregnant after diagnosis,⁹ and 47% of 719 childhood and adolescent cancer survivors at risk of pregnancy (still menstruating) reported becoming pregnant in a province-wide cohort study in Ontario, Canada.¹⁰ Although most childless individuals with

Table 5. Selected Pregnancy Outcomes Associated With First Subsequent Birth Among 892 Childhood Cancer Survivors and a Comparison Group, Stratified by Diagnostic Characteristics

Characteristic	RR (95% CI) ^a				
	Primary Cesarean Section	Maternal Diabetes	Maternal Anemia	Gestation <37 wk	Birth Weight <2500 g ^b
Cancer type					
Leukemia	0.97 (0.59-1.60)	1.47 (0.37-5.83)	2.14 (0.82-5.60)	2.55 (1.78-3.64)	1.47 (1.04-2.10)
Lymphoma	1.04 (0.75-1.43)	0.41 (0.06-2.95)	1.00 (0.34-2.97)	1.78 (1.27-2.49)	1.01 (0.69-1.48)
Central nervous system	0.85 (0.48-1.49)	1.22 (0.16-9.44)	3.05 (1.16-7.98)	1.59 (0.94-2.69)	1.88 (1.23-2.89)
Embryonal	0.65 (0.28-1.47)	1.96 (0.28-13.78)	1.55 (0.36-6.68)	1.06 (0.50-2.24)	0.92 (0.29-2.90)
Bone	2.02 (1.38-2.95)	4.92 (1.60-15.13)	0.92 (0.14-6.08)	2.18 (1.23-3.86)	1.01 (0.60-1.68)
Soft-tissue sarcoma	1.44 (0.89-2.33)	1.78 (1.07-2.96)	0.88 (0.36-2.12)
Germ cell, gonadal, trophoblastic	1.36 (0.81-2.29)	1.42 (0.77-2.63)	2.52 (1.59-3.98)
Thyroid carcinoma	1.11 (0.72-1.73)	0.82 (0.12-5.63)	0.71 (0.10-4.93)	0.54 (0.23-1.24)	1.04 (0.52-2.07)
Non-basal/squamous cell skin	1.39 (0.90-2.15)	...	1.22 (0.17-8.59)	1.49 (0.78-2.83)	0.90 (0.35-2.34)
Other carcinoma	1.47 (0.85-2.55)	2.82 (0.37-21.83)	1.13 (0.17-7.68)	1.17 (0.64-2.15)	1.43 (0.72-2.81)
Other	0.31 (0.05-1.76)	...	2.77 (0.41-18.67)	1.07 (0.38-2.96)	2.79 (1.17-6.68)
Primary cancer site					
Abdomen	1.19 (0.85-1.66)	0.64 (0.09-4.67)	0.98 (0.33-2.92)	1.48 (1.05-2.09)	1.72 (1.22-2.43)
Pelvis only	1.28 (0.86-1.93)	0.97 (0.13-7.05)	0.94 (0.25-3.59)	1.37 (0.87-2.13)	1.93 (1.30-2.86)
Diagnosis year					
1973-1979	1.03 (0.77-1.40)	2.03 (0.81-5.09)	1.80 (0.75-4.30)	1.38 (1.00-1.90)	1.37 (0.98-1.92)
1980-1989	1.13 (0.91-1.40)	0.82 (0.31-2.21)	0.99 (0.47-2.08)	1.52 (1.19-1.93)	1.30 (1.01-1.68)
1990-2000	1.30 (0.97-1.76)	0.39 (0.05-2.88)	1.45 (0.65-3.19)	1.85 (1.33-2.56)	1.21 (0.86-1.70)
Age at diagnosis, y					
<5	0.83 (0.46-1.52)	0.99 (0.14-7.01)	2.03 (0.78-5.25)	1.56 (0.88-2.78)	1.59 (0.93-2.69)
5-9	1.22 (0.78-1.92)	3.16 (1.00-10.01)	1.32 (0.31-5.65)	2.00 (1.28-3.10)	1.31 (0.78-2.21)
10-14	1.27 (0.96-1.67)	1.26 (0.40-4.00)	0.31 (0.04-2.18)	1.61 (1.16-2.24)	1.35 (0.98-1.86)
15-19	1.12 (0.91-1.38)	0.55 (0.18-1.70)	1.53 (0.85-2.73)	1.45 (1.15-1.82)	1.26 (0.99-1.60)
Time since diagnosis, y					
<2	1.23 (0.68-2.20)	...	2.16 (0.56-8.35)	2.58 (1.72-3.87)	1.38 (0.97-1.97)
2-5	1.03 (0.75-1.43)	0.48 (0.07-3.39)	1.59 (0.73-3.45)	1.43 (1.07-1.91)	1.17 (0.84-1.63)
6-10	1.39 (1.08-1.79)	0.79 (0.20-3.17)	0.70 (0.23-2.14)	1.49 (1.08-2.05)	1.22 (0.84-1.76)
>10	1.03 (0.81-1.32)	1.52 (0.72-3.21)	1.42 (0.67-2.99)	1.44 (1.05-1.99)	1.55 (1.14-2.11)
Cancer treatment					
Chemotherapy only	1.22 (0.83-1.80)	1.25 (0.31-4.99)	2.45 (1.16-5.17)	1.99 (1.38-2.86)	1.56 (1.10-2.22)
Surgical treatment only	1.25 (0.99-1.58)	0.80 (0.25-2.56)	0.91 (0.34-2.44)	1.35 (1.01-1.82)	0.97 (0.68-1.38)
Radiotherapy only	1.06 (0.66-1.70)	1.34 (0.18-9.84)	0.80 (0.12-5.45)	1.06 (0.56-2.00)	1.34 (0.62-2.90)
Chemotherapy + surgical treatment	1.34 (0.86-2.09)	2.54 (0.67-9.65)	1.23 (0.32-4.64)	1.63 (0.99-2.68)	1.40 (0.91-2.14)
Chemotherapy + radiotherapy	1.04 (0.64-1.68)	0.89 (0.13-6.12)	0.59 (0.08-4.14)	2.22 (1.45-3.40)	1.40 (0.98-2.00)
Surgical treatment + radiotherapy	1.02 (0.64-1.61)	0.95 (0.13-7.10)	1.98 (0.65-6.07)	1.04 (0.55-1.97)	1.50 (0.75-2.99)
Chemotherapy + surgical treatment + radiotherapy	0.90 (0.44-1.87)	2.14 (1.27-3.63)	1.19 (0.53-2.69)
Other/unknown	0.52 (0.14-1.93)	...	2.64 (0.28-25.08)	1.32 (0.59-2.97)	2.26 (1.21-4.24)
Any chemotherapy	1.15 (0.91-1.47)	1.26 (0.53-3.04)	1.39 (0.73-2.63)	1.98 (1.58-2.48)	1.43 (1.16-1.78)
Any surgical treatment	1.18 (0.98-1.43)	0.98 (0.42-2.28)	1.10 (0.57-2.12)	1.42 (1.13-1.77)	1.14 (0.89-1.46)
Any radiotherapy	1.02 (0.79-1.33)	0.90 (0.29-2.81)	0.97 (0.40-2.32)	1.57 (1.19-2.06)	1.38 (1.03-1.85)

Abbreviations: CI, confidence interval; RR, relative risk; ellipses, not applicable.

^aAdjusted for region, maternal age, year of delivery, race/ethnicity, and parity.

^bAlso adjusted for gestational age (<32, 32-36, 37-41, and ≥42 weeks).

a history of childhood cancer (76%) report a desire to parent,^{1,11} the birth rate among female childhood cancer survivors is significantly lower than that among their sibling controls.⁹ Nevertheless, there remains limited information about the proportion of childhood cancer survivors who ultimately give birth, and thus the extent to which our linkage may have underestimated the true proportion is unclear.

Overall, our results may be reassuring to female survivors of childhood cancer who subsequently bear children. Although their infants may be more likely to be preterm or of low birth weight, we observed no increased risk of SGA, malformations, or infant death and no altered male to female sex ratio that might indicate in-

creased germ cell mutagenicity. Our results related to malformations¹²⁻¹⁵ and sex ratio⁹ are consistent with those of recent previous reports. Although cesarean section deliveries were slightly more common among childhood cancer survivors, they were not consistently so. Among genital tract carcinoma survivors, most of whom were treated surgically, we primarily observed an increased risk of preterm delivery. In a previous study, preterm delivery was associated with conization.¹⁶ However, this type of treatment information was unavailable to us.

Studies in different countries also have reported an increased risk of preterm delivery and low birth weight among female survivors of childhood cancer.^{10,17,18} An increased risk of low birth weight and prematurity may be

due in part to decreased uterine volume as a result of pelvic radiation.¹⁸⁻²⁰ However, our observation of increased prematurity and/or low birth weight among survivors of cancer types typically not treated with pelvic radiation (such as leukemia or brain tumors) and among patients treated with chemotherapy only suggests that other factors may also contribute. Nevertheless, despite increased low birth weight and/or preterm delivery, the risk of having SGA offspring has not been observed in our study or in a previous study,¹⁸ suggesting that the observed decreases in birth weight are not severe enough to meet SGA criteria.

To our knowledge, preeclampsia has not been evaluated before among childhood cancer survivors. It is reassuring that the only increased risk we observed was a borderline finding among those who had received chemotherapy, surgical treatment, and radiation for their initial treatment. Although this may be a chance finding, it is plausible that respiratory/circulatory compromise secondary to cancer treatment may predispose toward a hypertension-related disorder during pregnancy, especially with reports of increased levels of hypertension among some childhood cancer survivors.^{21,22} Our finding of a nearly 5-fold increased occurrence of diabetes among childhood bone cancer survivors is without precedent and should be explored further.

Our study has several limitations. We did not have information about in-state or out-of-state migration of subjects. However, the proportion of individuals 1 year or older who move out of state, at least in recent years, is less than 3% annually,²³ and migration is unlikely to have affected our comparison of outcomes unless survivors who moved out of state differed from those who remained. It is also possible that our comparison group contained women diagnosed as having childhood cancer in other states who then migrated into a study region. The misclassification of cancer cases among the comparison group (if a history of cancer indeed increases the risk of an adverse pregnancy outcome) would have biased our results toward the null.

Our study also was limited because we lacked information about fetal loss or childbearing intent, and thus our findings are relevant to women who were able to have live births and to the first birth recorded after diagnosis. One advantage of our study, however, is its population-based nature. The SEER registries have demonstrated nearly complete case ascertainment,²⁴ and nonresponse was not an issue. We also were not restricted to children and adolescents involved in clinical trials, which exclude some individuals identified by registries.²⁵ However, we did not have detailed information about initial cancer treatment and thus were unable to evaluate radiation field location or specific chemotherapy exposures. Nevertheless, prospective studies with detailed treatment information might be able to obtain comprehensive data about pregnancy, delivery, and infant outcomes as case cohorts mature and enter their reproductive years. This would allow closer examination of the maternal and pregnancy characteristics we evaluated. We also did not have information about treatments used for cancer relapse, and therefore some misclassification of treatment categories is likely. However, given that any of the mo-

dalities evaluated are used for recurrent disease, it is difficult to predict the direction of bias introduced by such misclassification.

Birth records have been shown to be fairly accurate, with more than 95% sensitivity and specificity compared with medical records for delivery method, gravidity/parity, birth weight, and gestational age.²⁶ However, the recording of maternal conditions such as diabetes may be less sensitive, albeit highly specific.²⁷ Although birth records are not subject to biases associated with self-report, bias may still occur if differential levels of screening are used for cancer survivors vs comparison subjects. Differential monitoring of women with a cancer history could have resulted in the increased identification of some prenatal conditions such as preeclampsia, gestational diabetes, and anemia, as well as infant malformations. However, most of the cancer survivors and comparison women initiated prenatal care before the third trimester, and we observed no increased risk of malformations. One could speculate that health care providers might be more likely to use cesarean section deliveries for women with cancer histories as a precaution, resulting in the modest borderline increased RRs observed. Bias secondary to differential monitoring would not have influenced gestational age or birth weight measurements.

Children and adolescents with cancer can be reassured that we did not find an increased risk of malformations or infant death among their first subsequent offspring. The increased occurrence of low birth weight and preterm delivery among childhood cancer survivors and of preterm delivery among young genital tract carcinoma survivors that we and others^{10,16-18} have observed may indicate relatively less severe potential problems among offspring. However, these outcomes can still greatly affect families, are associated with significantly increased costs,²⁸ and indicate a need for close monitoring of pregnancies among childhood and adolescent cancer survivors.

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