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Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis

Beth A. Mueller, DrPH[a,b], **Eric J. Chow, MD, MPH**[a], **Aruna Kamineni, MS**[a,b], **Janet R. Daling, PhD**[a,b], **Alison Fraser, MSPH**[c], **Charles L. Wiggins, PhD**[d], **Geraldine P. Mineau, PhD**[c], **Merlin R. Hamre, MD**[e], **Richard K. Severson, PhD**[f], and **Carolyn Drews-Botsch, PhD**[g]

[a] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[b] Department of Epidemiology, University of Washington, Seattle, WA

[c] Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

[d] New Mexico Tumor Registry, Epidemiology and Cancer Control Program, University of New Mexico, Albuquerque, NM

[e] Children's Hospital at Providence, Anchorage, AK

[f] Departments of Family Medicine and Public Health Sciences, Population Studies and Prevention Program, Karmanos Cancer Institute, Wayne State University, Detroit, MI

[g] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

Abstract

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

Design: Retrospective cohort study.

Setting: 4 U.S. regions.

Participants: Cancer registries identified girls <20 years, diagnosed with cancer 1973-2000. Linked birth records identified first live births after diagnosis (n=1898). Comparison subjects were selected from birth records (n=14278). Cervical/genital tract cancer cases were analyzed separately.

Main Exposure: Cancer diagnosis <20 years.

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

Results: Childhood cancer survivors' infants were more likely to be preterm (relative risk [RR] 1.54, 95% CI 1.30-1.83) and weigh <2500 g (RR 1.31, 95% CI 1.10-1.57). For cervical/genital cancer patients' offspring, estimates were 1.33 (95% CI 1.13, 1.56), and 1.29 (95% CI 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 (RR 3.05, 95% CI 1.16-7.98) and childhood cancer survivors with initial treatment of chemotherapy only (RR 2.45, 95% CI 1.16-5.17).

Conclusions: Infants of female childhood and adolescent cancer patients were not at increased risk of malformations or death. Increased occurrence of preterm delivery and low birth weight suggest

Corresponding author: Eric J. Chow, MD, MPH, Fred Hutchinson Cancer Research Center, PO Box 19024, Mailstop M4-C308, Seattle, WA, 98109-1024 Phone: 206-667-7724, FAX: 206-667-5948, Email: ericchow@u.washington.edu.

close monitoring is warranted. Increased diabetes and anemia among sub-groups have not been reported, suggesting areas for study.

Keywords

cancer survivors; pregnancy outcome; low birth weight; premature birth; congenital abnormalities

INTRODUCTION

Cancer therapies may affect future reproductive potential. One concern of female childhood and adolescent cancer survivors 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 to provide additional information to reports from large follow-up studies. Using data from 4 U.S. regions, we conducted an exploratory, population-based study to compare the occurrence of infant outcomes among offspring and selected pregnancy conditions among female cancer survivors, and 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 Departments of Health prior to study conduct. Data from 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, Michigan; the Utah Cancer Registry at the University of Utah; and the SEER registry in Atlanta, Georgia. These registries perform active surveillance and follow-up of incident cancer cases in each region, which aside from Utah, 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 <20 years old, newly diagnosed with cancer were identified from each registry for the following periods: Seattle, Washington 1974-95; Utah 1973-98; Detroit, Michigan 1973-2000; and Atlanta, Georgia 1975-2000. Data available included demographic information (birth date, diagnosis age, race/ethnicity), tumor characteristics (diagnosis date, primary site, histologic type per the International Classification of Diseases for Oncology [version 2], SEER summary stage), and initial course of treatment (chemotherapy, surgery, radiation, and combinations). Childhood cancer diagnoses were categorized using the International Classification of Childhood Cancer (ICCC)[2]. 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[3]. The anatomical primary cancer site also was categorized as to whether it occurred within the abdomen, and further sub-categorized as occurring within the pelvis. Initial course of treatment was examined as a yes/no variable for each modality (e.g., any chemotherapy, any surgery, etc.), and also by non-overlapping 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 delivery after the subject's cancer diagnosis for these available years: Washington 1974-2001, Utah 1973-2001, Michigan 1975-2001, and Georgia 1980-2000. Live born deliveries that occurred prior to a subject's cancer diagnosis were not included in this analysis. Linkage strategies varied by state and included probabilistic and deterministic strategies

utilized for routine data linkages within each health department or agency[4-5]. Variables available for linkage included patient's maiden and married names, birth dates, sex, birth place (Utah only), race/ethnicity (Georgia only) and social security number (Utah, Michigan, and Georgia). Comparison subjects were randomly selected from remaining birth records at a comparison:case ratio of 10:1 in Washington, Utah, and Georgia, and a ratio of 4:1 in Michigan. Women were frequency matched on delivery year and age (<20, 20-24, 25-29, 30-34, ≥35 years), and race/ethnicity (white, African American, Asian, Native American, other; as recorded by cancer registries and birth records).

On examination of the merged file we determined that some potential cases were ineligible and subsequently excluded: 74 benign/possibly benign lesions, 1 squamous and 1 basal cell skin lesion, and 2 with only deliveries identified prior to their cancer diagnosis. Three fetal death records were identified among cases and 22 among controls. These also were excluded as the analyses focused on live births only. This resulted in 1898 cancer survivors and 14,278 comparison women. Analyses were conducted separately for the 1006 cases with genital tract carcinomas (SEER topography codes 51.0-58.9, 96% being in-situ cervical lesions diagnosed at 15-19 years) and the remaining childhood cancer survivors (n=892).

Outcomes evaluated

Infant outcomes included birth weight (<2500, 2500-3999, ≥4000 g), gestational age (<37, 37-41, ≥42 weeks), small for gestational age (SGA; defined as <10% birth weight for gestational age and gender based on a representative national sample[6]), presence of any malformation, 5-minute Apgar score <7 (yes/no; unavailable in Michigan), and infant death <12 months of age (unavailable in Georgia). Maternal outcomes that could be evaluated using birth records included delivery type (C-section or vaginal) and anemia. Because birth records in all states did not distinguish gestational and established diabetes, or preeclampsia and eclampsia, these were collapsed into any diabetes (yes/no) and any preeclampsia (yes/no). Other information available included maternal prenatal smoking (yes/no), marital status, number of prior pregnancies and births, and when prenatal care was initiated. 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 over the same time period (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 for comparison subjects and girls with childhood cancer and cervical/genital carcinoma separately. Because many outcomes were relatively common, odds ratio estimates of the relative risk (RR) from logistic regression were determined to overestimate the RR, and stratified analyses using Mantel-Haenszel methods were used, with results similar to those produced by log-binomial or Poisson models[7]. All RRs were adjusted for state, frequency-matched variables (delivery year, maternal age, 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 gender. Except where noted, adjustment by these variables did not meaningfully alter the RR estimates, and only those variables whose inclusion resulted in such change were retained in the analyses. Sensitivity analyses where deliveries occurring within 9 months of diagnosis, multiple gestation births, and multiparous mothers were excluded showed similar results. Sub-analyses were conducted stratifying by cancer type, primary cancer site, year and age of diagnosis, time interval between diagnosis and subsequent delivery, and initial course of cancer treatment. Analyses were conducted using STATA (version 9, StataCorp, College Station, TX).

RESULTS

Characteristics of cancer cases and comparison subjects

The proportion of childhood cancer patients identified with live births ranged from 13-17% across the 4 regions, with an overall mean time from diagnosis to delivery of 8.5 ± SD 5.8 years (Table 1). Among cervical/genital carcinoma cases, the proportions with subsequent live deliveries identified ranged from 28-55%, and the overall mean time from diagnosis to delivery was 4.0 ± SD 3.4 years.

This difference in elapsed time between cancer diagnosis and subsequent live birth between the two cohorts reflected the younger age at diagnosis of childhood cancer survivors (median 16 years [range 0-19]) compared with cervical/genital carcinoma cases (median 18 years [range 14-19]). However, the majority (84%) of childhood cancer survivors were ≥10 years old at diagnosis (Table 2). The most common childhood cancer diagnoses were lymphoma (23%), thyroid carcinoma (13%), central nervous system tumors and leukemias (10% each), and skin tumors (9%). As 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 cervical/genital cohort, 98% were in-situ lesions and 96% involved the cervix. The distribution of childhood cancer types across regions generally was similar (data not shown), except Atlanta had fewer thyroid carcinomas (7%) compared with the other 3 regions (15%), and Utah and Atlanta had more skin tumors (13%) compared with Seattle and Detroit (6%). The distribution of any chemotherapy, surgery, and radiotherapy exposures was similar across regions.

Compared with all childhood cancer cases ascertained by SEER in the 4 regions during the study period (per SEER*Stat), the subset of cases linked in this study were more likely to be diagnosed in an earlier era (pre-1990, 82% versus 61%) and at an older age (≥10 years, 84% versus 53%). Similarly, the distribution of cancer diagnoses more likely included cancers associated with older age at diagnosis (lymphoma, 23% versus 14%; non-genital tract carcinomas, 30% versus 13%). The genital tract cases linked in this study were similar to the overall genital tract cohort ascertained by SEER with respect to diagnosis age and diagnosis year distributions.

Age and year of delivery, and race/ethnicity were similar across cohorts except for a slightly greater proportion of African Americans (26%) among the cervical/genital tract cases compared to the childhood cancer (18%) and comparison group (20%; Table 3). Cervical/genital tract cases were more likely to have smoked prenatally (37%) than comparison subjects (19%) and childhood cancer survivors (12%). A greater proportion of cervical/genital tract cases were unmarried at delivery (49%), compared to childhood cancer survivors and comparison women (33-34%). Childhood cancer survivors were less likely to have had a prior pregnancy or birth compared with cervical/genital tract carcinoma patients 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 cases had a borderline increased risk of C-section delivery relative to comparison women (RR 1.15, 95% CI 0.99-1.33 overall; RR 1.14, 95% CI 0.97-1.33 among those without prior deliveries). C-section deliveries were not more common among cervical/genital carcinoma cases. The male:female ratio among infants born to the two cancer cohorts and 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 at <37 weeks gestation or weighing <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 deliveries of at least 37 weeks gestation, the RR remained significantly increased for childhood cancer cases (RR 1.56, 95% CI 1.12-2.16), but not for cervical/genital cases (RR 1.27, 95% CI 0.90-1.79, data not shown). These estimates were unchanged if adjusted for maternal anemia, diabetes, and preeclampsia. Neither cohort was more likely than comparison subjects to have infants with birth weights <1500 g, malformations, or who died at <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 cases were twice as likely to have a C-section delivery, relative to comparison women (Table 5). However, C-section was not significantly more common among women who had childhood cancers primarily located in the abdomen or 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 only chemotherapy (RR 2.45, 95% CI 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 women who received combination chemotherapy, surgery, and radiotherapy (RR 2.57, 95% CI 0.99-6.68; data not shown).

Having an infant delivered <37 weeks or weighing <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 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 age at diagnosis and elapsed time since diagnosis categories. After adjusting for gestational length, modest increased risks of birth weight <2500 g were observed for women with a history of leukemia, central nervous system, and germ cell/related tumors, as well as those with primary abdominal and pelvic tumors. Increased risk of low birth weight also was seen following chemotherapy or any radiotherapy exposure. No significantly increased RRs for SGA, malformations, 5 minute Apgar score <7, or infant death were observed across diagnostic and treatment categories (data not shown).

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

DISCUSSION

In this population-based study, 15% of female childhood cancer survivors and 43% of cervical/genital carcinoma cases identified within the registry in each region had a live birth recorded within the same state during the study period (up to 28 years of follow-up). The childhood cancer survivors we identified with subsequent live births differ 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 carcinoma cases with subsequent deliveries were generally similar to all patients with the same diagnosis in the registries. Out-of-state migration of cases 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 born delivery in Washington during the years 1987-2006 (data not shown). Although this latter linkage included only women aged 21-37 years old at delivery, it suggests that any possible loss-to-follow up because of out migration among childhood cancer cases is similar to 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 due to development of therapies more likely to conserve fertility, and increased assisted fertilization options for survivors.

Approximately 30% of 6494 female childhood cancer survivors in the Childhood Cancer Survivor Study reported they became pregnant after diagnosis[8], 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[9]. Although a majority (76%) of childless individuals with a history of childhood cancer report a desire to parent[1,10], the birth rate of female childhood cancer survivors is significantly lower than that of sibling controls[8]. Nevertheless, there remains limited information about the proportion of childhood cancer survivors who ultimately bear children, and thus the extent to which our linkage may have underestimated the true proportion is unclear.

Overall, our results may be reassuring to female childhood cancer patients who subsequently bear children. Although offspring 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:female sex ratio that might indicate increased germ cell mutagenicity. Our results related to malformations[11-14] and sex ratio[8] are consistent with recent previous reports. Although C-section deliveries were slightly more common among childhood cancer survivors, they were not consistently so. Among cervical/genital carcinoma patients, the majority of whom are treated surgically, we primarily observed an increased risk of preterm delivery. In a prior study, preterm delivery was associated with conization[15], treatment information unavailable to us.

Studies in different countries using various methodology also have reported an increased risk of preterm delivery and low birth weight among female childhood cancer survivors[9,16,17]. An increased risk of low birth weight and prematurity may be partly due to decreased uterine volume as a result of pelvic radiation[17-19]. However, our observation of increased prematurity and/or low birth weight among cancer types typically not treated with pelvic radiation (such as leukemia or brain tumors) and among patients treated with chemotherapy only suggest that other factors may also contribute. Nevertheless, despite increased low birth weight and/or preterm delivery, risk of having SGA offspring has not been observed in our study and in a prior study[17], 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 received chemotherapy, surgery, 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 towards a hypertension-related disorder during pregnancy, especially with reports of increased levels of hypertension among some childhood cancer survivors[20,21]. Our finding of a nearly 5-fold increased occurrence of diabetes among childhood bone cancer survivors is without precedent and should be further explored.

Our study has several limitations. We did not have information about in- 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 <3% annually[22], and migration is unlikely to have affected our comparison of outcomes unless cases who moved out of state differed from those who remained. It is also possible that our comparison group contained women diagnosed with 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 towards 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. SEER registries have demonstrated nearly complete case ascertainment[23], and non-response was not an issue. We also were not restricted to children and adolescents involved in clinical trials, which exclude some individuals identified by registries[24]. However, we did not have detailed information about initial cancer treatment and thus were unable to evaluate radiation field location or specific chemotherapy exposures. It may be possible, however, for prospective studies with detailed treatment information 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 there is likely some misclassification of treatment categories. However, given that any of the modalities 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 >95% sensitivity and specificity compared to medical records for delivery method, gravidity/parity, birth weight and gestational age[25]. However, the recording of maternal conditions such as diabetes may be less sensitive, albeit highly specific[26]. Although birth records are not subject to biases associated with self-report, bias may still occur if differential levels of screening are employed for cancer survivors versus 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, anemia, as well as infant malformations. However, the vast majority of both survivors and comparison women initiated prenatal care prior to the third trimester, and we observed no increased risk of malformations. One could speculate that care providers might be more likely to use C-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.

For children and adolescents with cancer, it is reassuring 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 cases, and of preterm delivery among young cervical/genital carcinoma cases that we and others have observed may indicate relatively less severe potential problems among offspring. However, these outcomes can still impact families greatly, are associated with significantly increased costs[27], and indicate a need for close monitoring of pregnancies among childhood and adolescent cancer survivors.

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Table 1

Female childhood cancer and adolescent cervical/genital cancer cases with subsequent live birth identified.

Region	Seattle	Utah	Detroit	Atlanta	Total
No. childhood cancer cases[1]	1393	1249	2414	1039	6095
No. (%) identified with subsequent live births	183 (13.1)	215 (17.2)	345 (14.3)	149 (14.3)	892 (14.6)
Mean years ± SD from diagnosis to delivery (range)	9.7 ± 5.7 (0-25)	8.0 ± 5.5 (0-24)	8.4 ± 5.9 (0-27)	7.6 ± 5.6 (0-22)	8.5 ± 5.8 (0-27)
No. cervical/genital carcinoma cases[2]	746	176	766	305	1994
No. (%) identified with subsequent live births	210 (28.2)	89 (50.6)	397 (51.6)[3]	167 (54.8)[4]	863 (43.3)
Mean years ± SD from diagnosis to delivery (range)	4.5 ± 3.4 (0-18)	2.4 ± 1.9 (0-8)	3.9 ± 3.3 (0-17)	4.4 ± 4.0 (0-19)	4.0 ± 3.4 (0-19)

[1] In-situ and malignant lesions except female genital tract carcinomas per SEER*Stat, version 6.1.4.

[2] In-situ and malignant lesions reported through 1995 per SEER*Stat. Beginning in 1996, SEER no longer routinely reported cervical in-situ lesions.

[3] Not including 142 cases diagnosed 1996-2000 included in subsequent tables.

[4] Not including 1 case diagnosed in 1997 included in subsequent tables.

Table 2

Diagnostic characteristics of female childhood cancer and adolescent cervical/genital cancer cases with subsequent live birth.

Characteristic	Cohort, N (%)	
	Childhood cancer (n=892)	Cervical/genital (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, years		
<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[1]		
Leukemia	87 (9.8)	-
Lymphoma	202 (22.7)	-
Central nervous system	89 (10.0)	-
Embryonal[2]	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 (7.9)	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)
Surgery, only	328 (36.8)	789 (78.4)
Radiotherapy, only	87 (9.8)	-
Chemotherapy+Surgery	83 (9.3)	-
Chemotherapy+Radiotherapy	86 (9.6)	1 (0.1)
Surgery+Radiotherapy	111 (12.4)	2 (0.2)
Chemotherapy+Surgery+Radiotherapy	48 (5.4)	-

Characteristic	Cohort, N (%)	
	Childhood cancer (n=892)	Cervical/genital (n=1006)
Other / unknown	37 (4.2)	212 (21.1)
Any chemotherapy	329 (36.9)	3 (0.3)
Any surgery	570 (63.9)	791 (78.6)
Any radiotherapy	332 (37.2)	3 (0.3)

[1]Based on International Classification of Childhood Cancers, 1996 (Ref 2), and includes in-situ lesions: 989 genital tract carcinomas, 4 non-genital tract carcinomas, and 7 skin lesions.

[2]Neuroblastoma and related tumors, embryonal renal and hepatic tumors, and retinoblastoma.

Table 3

Prenatal characteristics of female childhood and adolescent cancer cases at time of first subsequent birth versus a comparison group.[1]

Characteristic	Cohort, N (%)		
	Childhood cancer (n=892)	Cervical/ genital (n=1006)	Comparison (n=14278)
Race/ethnicity			
White	702 (80.0)	711 (71.8)	10729 (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, years			
<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)	38 (3.5)	450 (3.2)
1980-1989	271 (30.4)	296 (26.9)	4418 (30.9)
1990-1999	522 (58.5)	650 (59.0)	8368 (58.6)
2000-2001	71 (8.0)	117 (10.6)	1042 (7.3)
Prenatal smoking[2]	72 (11.6)	280 (36.9)	1994 (19.4)
Unmarried at time of delivery[3]	178 (32.5)	228 (48.9)	3615 (34.1)
No. 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. 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)
Time prenatal care began			
1st trimester	721 (82.9)	771 (79.2)	10472 (75.4)
2nd trimester	118 (13.6)	148 (15.2)	2631 (19.0)
3rd trimester or no care	31 (3.6)	55 (5.7)	783 (5.6)

[1] Numbers may not add up to totals because of missing data.

[2] Not available all years.

[3] Unavailable in Michigan.

Table 4

Pregnancy outcomes associated with first subsequent birth among childhood cancer and adolescent cervical/genital cancer cases versus a comparison group.[1]

Outcome	Cohort, N (%)			Relative Risk (95% CI)[2]	
	Childhood cancer (n=892)	Cervical/ genital cancer (n=1006)	Comparison (n=14278)	Childhood cancer	Cervical/ genital cancer
Maternal conditions					
Any C-section[3]	163 (21.5)	154 (17.2)	2212 (17.1)	1.15 (0.99-1.33)	0.97 (0.83-1.13)
Primary C-section[4]	145 (21.8)	110 (20.8)	1216 (18.5)	1.14 (0.97-1.33)	1.11 (0.92-1.32)
Diabetes[3]	11 (1.6)	13 (1.5)	174 (1.4)	1.02 (0.53-1.95)	0.86 (0.49-1.53)
Preeclampsia[3]	37 (5.4)	34 (3.9)	452 (3.7)	1.01 (0.73-1.42)	0.99 (0.70-1.41)
Anemia[3]	18 (2.7)	12 (1.4)	269 (2.3)	1.30 (0.81-2.08)	0.65 (0.36-1.17)
Infant outcomes					
Female gender	444 (49.8)	507 (50.4)	7058 (49.4)	referent	referent
Male gender	448 (50.2)	499 (49.6)	7220 (50.6)	1.00 (0.93-1.07)	0.97 (0.90-1.03)
Gestational age (weeks)					
<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 (76.2)	11088 (79.9	referent	referent
≥42	68 (7.8)	89 (9.1)	1371 (9.9)	0.86 (0.68-1.08)	0.91 (0.74-1.11)
Birth weight (grams)[5]					
<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)	11917 (83.6)	referent	referent
≥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[6]	96 (11.1)	149 (15.3)	1549 (11.3)	0.87 (0.67-1.12)	1.09 (0.90-1.33)
Malformation[3]	10 (1.3)	14 (1.6)	220 (1.7)	0.92 (0.48-1.75)	1.16 (0.66-2.04)
5-min Apgar <7[7]	13 (2.4)	15 (3.3)	172 (1.7)	1.30 (0.72-2.35)	2.01 (1.15-3.50)
Infant death[8]	7 (1.0)	6 (0.7)	93 (0.9)	1.08 (0.47-2.48)	0.83 (0.36-1.89)

[1] Numbers may not add up to totals because of missing data.

[2] Adjusted for state, maternal age, year of delivery, race/ethnicity, and parity.

[3] Not available all years.

[4] Among 679 childhood cancer cohort members, 539 genital tract cases, and 6804 comparison women without prior deliveries.

[5] Also adjusted by gestational length (<32, 32-36, 37-41, ≥42 weeks).

[6] Also adjusted for maternal prenatal smoking.

[7] Not available all years, unavailable in Michigan.

[8] Not available all years, unavailable in Georgia.

Table 5

Selected pregnancy outcomes associated with first subsequent birth among childhood cancer survivors (n=892) and a comparison group, stratified by diagnostic characteristics.

Characteristic	Relative Risk (95% CI)[1]				
	Primary C-section	Maternal Diabetes	Maternal Anemia	Gestation <37 weeks	Birth weight <2500 g[2]
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)	0 -	0 -	1.78 (1.07-2.96)	0.88 (0.36-2.12)
Germ cell, gonadal, trophoblastic	1.36 (0.81-2.29)	0 -	0 -	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)	0 -	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)	0 -	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					

Characteristic	Relative Risk (95% CI)[1]				
	Primary C-section	Maternal Diabetes	Maternal Anemia	Gestation <37 weeks	Birth weight <2500 g[2]
1973-79	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)
1980-89	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					
<5 years	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 years	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 years	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 years	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					
<2 years	1.23 (0.68-2.20)	0 -	2.16 (0.56-8.35)	2.58 (1.72-3.87)	1.38 (0.97-1.97)
2-5 years	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 years	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 years	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)
Surgery 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)

Characteristic	Relative Risk (95% CI)[1]				
	Primary C-section	**Maternal Diabetes**	**Maternal Anemia**	**Gestation <37 weeks**	**Birth weight <2500 g[2]**
Chemotherapy +surgery	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)
Surgery +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 +surgery +radiotherapy	0.90 (0.44-1.87)	0 -	0 -	2.14 (1.27-3.63)	1.19 (0.53-2.69)
Other / unknown	0.52 (0.14-1.93)	0 -	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 surgery	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)

[1] Adjusted for state, maternal age, year of delivery, race/ethnicity, and parity.

[2] Also adjusted for gestational length (<32, 32-36, 37-41, ≥42 weeks).