Reproductive outcomes in male childhood cancer survivors: a linked cancer-birth registry analysis

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]

Carolyn Drews-Botsch, PhD [g]

Beth A. Mueller, DrPH [a, b]

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

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

[c] Department of Oncological Sciences, 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

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

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ABSTRACT

OBJECTIVE: Compare the risk of reproductive and infant outcomes between male childhood cancer survivors and a population-based comparison group.

DESIGN: Retrospective cohort study.

SETTING: 4 U.S. regions.

PARTICIPANTS: Cancer registries identified males <20 years old diagnosed with cancer 1973-2000. Linked birth certificates identified first subsequent live offspring (n=470). Comparison subjects were identified from remaining birth certificates, frequency-matched on year and age at fatherhood, and race/ethnicity (n=4150).

MAIN EXPOSURE: Cancer diagnosis prior to age 20.

OUTCOME MEASURES: Pregnancy and infant outcomes identified from birth certificates.

RESULTS: Compared with infants born to unaffected males, offspring of cancer survivors had a borderline risk of birth weight <2500 g (RR 1.43, 95% CI 0.99-2.05), with risk associated most strongly with younger age of cancer diagnosis and exposure to any chemotherapy (RR 1.96, 95% CI 1.22-3.17) or radiotherapy (RR 1.95, 95% CI 1.14-3.35). However, they were not at risk of being born prematurely, small for gestational age, having malformations or an altered male:female sex ratio. Overall, female partners of male survivors were not more likely to have maternal complications recorded on birth records versus the comparison group. However, preeclampsia was associated with some cancers, especially central nervous system tumors (RR 3.36, 95% CI 1.63-6.90).

CONCLUSIONS: Most pregnancies resulting in live births among partners of male childhood cancer survivors were not at significantly greater risk of complications versus comparison

subjects. The possibility of a paternal component affected by prior cancer history influencing predisposition towards some adverse perinatal outcomes merits further investigation.

INTRODUCTION

Chemotherapy, radiotherapy, and surgery for cancer treatment may impair future reproductive potential, and concerns about fertility and the health of any progeny are increased among survivors of childhood cancers compared with siblings(1;2). Most prior reports are based on institutional case series with self-reported reproductive outcomes. There have been fewer studies utilizing population-based data, and most were only able to examine a limited number of outcomes: fertility rate, sex ratio, and rates of malformations and cancer among progeny(3-8). In general, these studies suggest that although male survivors are less likely to father children versus comparison subjects or population norms, pregnancies they fathered have few other complications, and adverse outcomes among progeny are not increased.

We identified a population-based sample of male childhood cancer survivors from 4 U.S. regions and linked their records to state birth certificate registries in order to describe the proportion that subsequently fathered live births. We then compared the occurrences of selected pregnancy conditions and infant outcomes between partners of male cancer survivors and those of a population-based comparison group identified from birth records.

METHODS

Subject identification and data linkage

Human subject protection committee approval was received by the appropriate institutions and State Departments of Health prior to the conduct of this study. Methods used to identify subjects and to link data are described in detail in an accompanying paper(9). Briefly, incident cancer cases occurring among males <20 years old, newly diagnosed with cancer (malignant and in-situ) were identified from 4 population-based cancer registries participating in

the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program over the following time intervals: the Cancer Surveillance System of Western Washington in Seattle (1974-95); the Karmanos Cancer Institute of Wayne State University in Detroit, Michigan (1973-2000); the Utah Cancer Registry at the University of Utah (1973-98); and the SEER registry in Atlanta, Georgia (1975-2000). Aside from Utah, these registries are not statewide but only include the named metropolitan region plus surrounding counties (registry details may be found at: http://seer.cancer.gov/registries/index.html). The registries provided data on patients' demographics, tumor characteristics, and initial course of treatment (any chemotherapy, any surgery, any radiotherapy, and non-overlapping combinations). Childhood cancer diagnoses were categorized using the International Classification of Childhood Cancer (ICCC)(10), with categories corresponding to neuroblastoma and related tumors, embryonal renal and hepatic tumors, and retinoblastoma collapsed into a single embryonal tumor category because of small numbers(11). The anatomical primary cancer site also was categorized as to whether it occurred within the pelvis. Cancer relapse information was unavailable.

Birth certificate data from all 4 states were linked to each cancer patient's registry record to identify the live born delivery occurring in closest temporal proximity following the subject's cancer diagnosis date for these available years: Washington 1974-2001, Utah 1973-2001, Michigan 1975-2001, and Georgia 1980-2000. Routine linkage strategies varied by state, with available linkage variables including patient's first and last names, sex, birth dates, birth place (Utah only), race/ethnicity (Georgia only), and social security number (Utah, Michigan, and Georgia). 483 potential subjects were identified from the 4 regions and were linked to the birth records in each state. Records of live born deliveries that occurred prior to a subject's cancer diagnosis were not used in this study.

For comparison, men who fathered infants born during the same year were randomly selected from among the remaining birth records at a comparison:case subject ratio of 4:1 in Michigan, and 10:1 in the other 3 states. These also were frequency matched on the cancer survivor's age at delivery (5-year intervals from <20 to ≥40 years) and race/ethnicity. On examination of the linked file it was determined that some potential cases were ineligible and subsequently excluded: 12 benign lesions and one basal cell skin tumor. In addition, 2 records associated with comparison subjects were of fetal deaths and excluded as the analysis focused on live births only. This resulted in 470 cancer survivors and 4150 comparison subjects used in the final analysis.

Outcomes evaluated

Outcomes occurring to female partners that could be evaluated using birth records included delivery type, maternal anemia, diabetes, and preeclampsia. 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(12)), the presence of any malformation, 5-minute Apgar score <7 (unavailable in Michigan), and infant death <12 months of age (unavailable in Georgia). Other information available for most records included the female partner's prenatal smoking status, 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 certificates and the total number of cases ascertained in each SEER region over the same time period (SEER*Stat database, version 6.1.4, 2005) were used to calculate the proportion of survivors in each region identified with subsequent live births. The distribution of selected parental characteristics, maternal and infant outcomes was described for cancer survivors and comparison subjects. Relative risks (RR) estimated using stratified Mantel-Haenszel methods were used, with results similar to those produced by logistic regression, log-binomial, or Poisson models(13). All RRs were adjusted for state, the frequency-matched variables, and maternal age and parity. Other variables considered for their possible role in the relationships of interest included: infant gender, maternal race/ethnicity, prenatal smoking, marital status, and duration of prenatal care. However, 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 births occurring within 9 months of diagnosis, multiple gestation births, and multiparous partners were excluded showed similar results. Analyses were conducted using STATA (version 9, StataCorp, College Station, TX).

RESULTS

Characteristics of cancer cases and comparison subjects

General diagnostic and treatment characteristics of male cancer survivors (Table 1) were similar across SEER regions, with several exceptions: a greater proportion of cases from Detroit had 11-30 years elapse between diagnosis and subsequent delivery (70% versus 34-39% in other regions); the prevalence of skin cancer ranged from 3% in Detroit to 12% in Utah; and selected cancer treatments varied (chemotherapy only ranged from 8% in Utah to 19% in Seattle; surgery

plus radiotherapy ranged from 5% in Detroit to 18% in Atlanta; and any surgery ranged from 52% in Detroit to 70% in Utah). Overall, the proportion of childhood cancer patients identified from birth records as having fathered a live birth ranged from 4% in Detroit to 11% in Utah, with an overall mean time from cancer diagnosis to fatherhood of 10.2 ± SD 5.8 years.

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 was more likely to be diagnosed in an earlier era (pre-1990, 85% versus 60%) and at an older age (≥10 years, 86% versus 50%), and less likely to have those cancers associated with younger age at diagnosis (leukemia, 11% versus 25%; embryonal tumors, 5% versus 13%).

Paternal race/ethnicity, age, and year of delivery, being frequency matched by design, were similar for cancer survivors and comparison subjects (Table 2). The median age of survivors and comparison subjects at delivery was 25 (range 16-40) and 24 (range 16-47) years, respectively. The two groups also were similar with respect to female partner's age, race/ethnicity, prenatal smoking status, and the proportion with multiple gestation births (3% versus 2%, data not shown). However, greater proportions of survivors had female partners who were recorded as being unmarried, primigravida, and nulliparous.

Overall pregnancy and infant outcomes

Overall, female partners of cancer survivors had similar risks of selected pregnancy-related conditions compared with partners of comparison subjects (Table 3). Among infant outcomes, the male:female offspring sex ratio did not differ significantly between survivors and comparison subjects (1.09 versus 1.04, respectively; RR for having male offspring 1.03, 95% CI 0.93-1.14). Cancer survivors had a borderline risk of fathering infants with low birth weight

<2500 g (RR 1.43, 95% CI 0.99-2.05), but no risk of having infants weighing <1500 g (RR 1.16, 95% CI 0.46-2.93, data not shown). These risk estimates were not affected by adjustment for gestational age and maternal factors such as prenatal smoking, preeclampsia, or diabetes. Offspring of survivors did not have an increased risk of being born <37 weeks gestation. Furthermore, although the proportion of preterm infants <2500 g was slightly greater among cases (55%) than comparison infants (48%), offspring of survivors were not at increased risk of meeting SGA criteria. The RRs for infant malformations and 5-minute Apgar score <7 also were not increased and there were no infant deaths among progeny of cancer survivors.

Outcomes stratified by diagnostic and treatment characteristics

When maternal and infant outcomes were stratified by cancer subtype and pelvic cancer location, no consistent associations were seen for C-section, maternal diabetes or anemia, preterm delivery, and infant malformations. However, partners of males with childhood central nervous system tumors (RR 3.36, 95% CI 1.63-6.90) and leukemia (RR 2.41, 95% CI 1.11-5.22) had an increased risk of preeclampsia (Table 4), even after additional adjustment for maternal diabetes. However, no other consistent associations for preeclampsia were observed among other subgroups.

Significant increased risks of fathering a low birth weight infant were associated with embryonal tumors (RR 3.93, 95% CI 1.68-9.20; Table 4). No secular trends were observed except for an increased risk of low birth weight associated with earlier treatment era (pre-1980) that diminished over subsequent decades. Young age at diagnosis (<5 years) and greatest elapsed time since diagnosis (>10 years) also were associated with birth weight <2500 g. Treatments involving any chemotherapy (RR 1.96, 95% CI 1.22-3.17) or any radiotherapy (RR 1.95, 95% CI

1.14-3.35) were associated with a greater risk of low birth weight, but not exposure to surgery alone. Patients who had primary tumors in the abdomen treated with any radiotherapy also were at risk (RR 3.38, 95% CI 1.49-7.68; data not shown). Risk estimates for combination therapies were more variable, but in general, those containing chemotherapy tended to be greater than those without chemotherapy, with the greatest risk associated with exposure to all three modalities (RR 3.47, 95% CI 1.36-8.85). Borderline associations for SGA infant also were seen following treatment with any radiotherapy (RR 1.58, 95% CI 1.03-2.42) and combination chemotherapy with radiotherapy (RR 2.29, 95% CI 1.13-4.63), but not with other subgroups.

Fathers with pelvic primary tumors had an offspring male:female sex ratio of 1.18, but the likelihood of having male offspring was not increased significantly (RR 1.02, 95% CI 0.84-1.26; data not shown). Infant male:female sex ratios was greatest for those ages 10 to 14 years at diagnosis (1.18), but similar for all other diagnosis age categories (range 1.06-1.07; data not shown). Infant male:female sex ratios following any radiotherapy, any chemotherapy, and surgery only were 1.23, 1.16, and 0.93, respectively, but none of these were significantly different from those of comparison subjects, even after multivariable adjustment or restriction to those with pelvic tumors.

DISCUSSION

Few studies(14;15) have examined associations between paternal cancer history and subsequent pregnancy complications among female partners and outcomes among offspring outside of malformations or cancer. In this study of a relatively contemporary cohort of male childhood cancer survivors, partners and progeny of cancer survivors were not at increased risk

of most complications examined. However, we did observe an increased risk of low birth weight and preeclampsia associated with some treatment characteristics.

Based on self-reported outcomes of more than 1500 live births, the North American Childhood Cancer Survivor Study reported a 3-fold increased risk of low birth weight progeny among male childhood survivors treated with nonalkylating chemotherapy compared with siblings(14). Risk estimates associated with pelvic radiation and alkylating chemotherapy (RR 1.5-1.6) were not significantly increased, but were similar in magnitude to ours. Gestational age was not examined in this study. A registry-based study examining several hundred Norwegian male cancer survivors diagnosed between 15 to 35 years of age did not report an increased risk of low birth weight progeny(15). However, given that our estimates were greatest for males diagnosed <15 years of age, differences in the study populations and their exposures may account for this discrepancy. Nevertheless, in neither study was there a consistent risk of progeny being delivered preterm.

Both maternal and paternal contributions to birth weight have been reported in the general population. Parents who were themselves low birth weight infants tend to give birth to low birth weight infants independent of environmental factors(16;17). Although we did not know parental birth weights, there is no reason to suspect that male cancer survivors or their partners would more likely have been low birth weight infants themselves. Aside from hepatoblastoma (there were no cases in this study), low birth weight has not been associated consistently with an increased risk of childhood cancers(18). Additional maternal demographic and environmental factors associated with low birth weight include nulliparity, very young or older maternal age, prior low birth weight infant, lower socioeconomic status, and substance use including tobacco exposure(19). We attempted to adjust for many of these factors, but it is possible residual

confounding exists as childhood cancer survivors, particularly central nervous system tumor patients, are more likely to be unmarried(20) and unemployed(21), though less likely to smoke(22). Nevertheless, it is interesting that risk was increased after exposure to chemotherapy and radiotherapy, but not to surgery alone. Compared with maternal associations, any paternal influence on infant birth weight is more likely to be genetic rather than environmental(17;23). There is evidence that the imprinting of fetal genes can affect fetal growth and adult health(24), although there is no evidence that prior cancer therapy in the father affects imprinting of germ line cells, particularly as epigenetic therapies would not have been widely used during the study period.

It is unclear why preeclampsia was associated with central nervous system tumors, and to a lesser degree, leukemias. Although we examined maternal factors that can be associated with preeclampsia in our analysis such as age, nulliparity, and diabetes, it is possible these findings could still reflect residual confounding, or be due to chance. Prior studies generally have not examined preeclampsia among partners of male cancer survivors. One study of male hematopoietic cell transplant survivors found that 6% of partners (n=4) experienced preeclampsia(25), similar to the prevalence in our study but also within estimated population rates(26). A paternal contribution to preeclampsia has been reported in the general population, suggesting that paternally-derived fetal genes are involved in pathogenesis(27;28). The mechanism by which paternal genes affect preeclampsia is unclear, although a role for paternally imprinted alleles also has been hypothesized(27). However, as with low birth weight, it is unclear if cancer therapy affects germ line imprinting. Although loss of imprinting is an increasingly recognized phenomena among pediatric and adult cancers, these changes typically

are restricted to tumor cells with the exception of certain rare cancer predisposition syndromes(29).

Previous studies have investigated possible mutagenic effects of cancer therapy on germ cells as manifested by an altered male:female progeny sex ratio, malformations, and miscarriages or stillbirths. In our study, the male:female progeny sex ratio was slightly greater among survivors (1.09) compared with comparison subjects (1.04), and greatest among those with pelvic tumors and those exposed to any chemotherapy or radiotherapy (range 1.16-1.23). In comparison, over the past 50 years the U.S. ratio has been around 1.05(30). Although our estimates did not reach statistical significance, this pattern supports the hypothesis that mutagenic therapies could result in an increased male:female progeny ratio among treated fathers due to dominant lethal X-chromosome mutations. However, male:female sex ratios have not been increased in other studies of male childhood cancer survivors(6;8;31) and even significantly decreased in one(14).

Most studies, including ours, have not reported increased risks of malformations (reviewed in Ref(32)), although our use of birth registry data may under-ascertain more subtle defects not diagnosed at birth. One birth registry study did report a 50% increased risk of malformations among progeny of adolescent and young adult male cancer survivors compared with the general population(15). An increased risk of miscarriage or stillbirths among partners of male cancer survivors(14) also suggests the possibility that mutagenic exposures may affect viability of future offspring.

Our study has several limitations. Although SEER audits have shown that case ascertainment exceeds 95% and that tumor characteristics(33) and broad treatment categories (e.g. chemotherapy, radiotherapy, and surgery) are accurately recorded(34), our data were

limited to initial cancer treatment. Information about treatment for relapse was not available and therefore our estimates for treatment categories contain some misclassification. The effects of this are difficult to predict as chemotherapy, radiotherapy, and surgery are all used for salvage treatments, but patients likely received more multi-modal therapy than shown.

Although >99% of births in the US are captured on birth records(35), birth records have some limitations. Generally, paternal characteristics are not as thoroughly recorded as maternal characteristics, particularly if parents are unmarried(35). As male cancer survivors were less likely to be currently married than comparison subjects, this may in part explain why the percentage of cancer survivors identified as fathers (6.7%) was lower than in other studies, although birth registries do attempt to record paternal information even if the couple is unmarried. Migration to other states would also decrease our cancer-birth registry linkages. However, at least for recent years, U.S. Census surveys report <3% of people who move, move out-of-state, and concern regarding health is rarely cited as the primary reason for moving(36). Furthermore, migration would have affected our outcomes only if cases who moved out-of-state differed from those who remained, information we did not have access to. Finally, as the median age of survivors in this cohort was only 25 years, many survivors also are just entering reproductive age.

Nevertheless, for successful linkages, birth record characteristics such as gravidity/parity, delivery method, infant gender, birth weight, and gestational age are recorded accurately with sensitivity/specificity typically >95% when compared with medical records(37). However, although the specificity of maternal comorbidities such as diabetes, preeclampsia, anemia, and tobacco exposure is typically high, sensitivity can be much more variable(37;38). Overall, there is no reason to suspect that partners of male cancer survivors would have birth record data

recorded differently than others; birth records should not be susceptible to response or recall biases.

Misattributed paternity may also be present within our population. Although one may hypothesize that use of donor sperm may be more prevalent among cancer survivors, there is little information about its prevalence and we did not have any data on use of assisted reproductive techniques. Furthermore, the direction of any bias arising from misattributed paternity is difficult to predict. Among the general population, non-paternity rates have varied greatly across populations and have been associated with different demographic factors in various studies(39).

Lastly, differences may exist between this cohort and the overall population of male childhood cancer cases. Despite follow-up of up to 28 years, our study, like many other studies of childhood illnesses that attempt to examine outcomes in adulthood, our subjects include more individuals who were diagnosed in earlier time periods and who were older at diagnosis. Cancers with increased reproductive morbidity and mortality also would be less represented in any survivor cohort. Nevertheless, for male survivors identified as fathers in state birth records, the vast majority of associated pregnancies resulting in live births were not at significantly greater risk of complications versus comparison subjects. However, our finding of increased low birth weight and preeclampsia associated with some diagnostic groups raise the possibility that prior cancer therapy may affect male germ cells with effects on female partners and progeny of male survivors.

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Table 1. Diagnostic characteristics of male childhood cancer survivors with subsequent live offspring identified.

Characteristic	**N (%) (n=470)**
Cancer registry, U.S. State	
Atlanta, Georgia	91 (19.4)
Detroit, Michigan	103 (21.9)
Seattle, Washington	122 (26.0)
Utah	154 (32.8)
Year of diagnosis	
1973-1979	170 (36.2)
1980-1989	229 (48.7)
1990-2000	71 (15.1)
Age at diagnosis, years	
<5	35 (7.5)
5-9	29 (6.2)
10-14	72 (15.3)
15-19	334 (71.1)
Elapsed years until delivery	
<2	23 (4.9)
2-5	92 (19.6)
6-10	151 (32.1)
11-30	204 (43.4)

Table 1. Diagnostic characteristics of male childhood cancer survivors with subsequent live offspring identified (cont).

Cancer type[1]	
Leukemia	51 (10.9)
Lymphoma	118 (25.1)
Central nervous system	47 (10.0)
Embryonal[2]	25 (5.3)
Malignant bone	33 (7.0)
Soft tissue sarcoma	42 (8.9)
Germ cell/gonadal	61 (13.0)
Thyroid carcinoma	22 (4.7)
Non-basal/squamous cell skin	36 (7.7)
Other carcinoma	27 (5.7)
Other tumors	8 (1.7)
Pelvic primary cancer site	85 (18.1)

[1] Based on the International Classification of Childhood Cancers (Ref 10).
[2] Consists of neuroblastoma and related tumors (n=10), embryonal renal (n=13) and hepatic (n=0) tumors, and retinoblastoma (n=2).

Table 1. Diagnostic characteristics of male childhood cancer survivors with subsequent live offspring identified (cont).

Cancer treatment	
Chemotherapy only	66 (14.0)
Surgery only	137 (29.2)
Radiotherapy only	42 (8.9)
Chemotherapy+surgery	62 (13.2)
Chemotherapy+radiotherapy	50 (10.6)
Surgery+radiotherapy	55 (11.7)
Chemotherapy+surgery+radiotherapy	38 (8.1)
Other / unknown treatment	20 (4.3)
Any chemotherapy	216 (46.0)
Any surgery	292 (62.1)
Any radiotherapy	185 (39.4)

Table 2. Prenatal characteristics of male survivors and their partners at time of first subsequent offspring versus a comparison group.[1]

Characteristic	Cohort, N (%)	
	Cancer survivors (n=470)	**Comparison group (n=4150)**
Father's race/ethnicity		
White	398 (84.5)	3502 (86.9)
African American	49 (10.8)	448 (11.1)
Asian	2 (0.4)	19 (0.5)
Native American	2 (0.4)	16 (0.4)
Other	4 (0.9)	45 (1.1)
Mother's race/ethnicity		
White	399 (86.7)	3532 (86.6)
African American	50 (10.9)	413 (10.1)
Asian	4 (0.9)	43 (1.1)
Native American	3 (0.7)	34 (0.8)
Other	4 (0.9)	57 (1.4)

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

Table 2. Prenatal characteristics of male survivors and their partners at time of first subsequent offspring versus a comparison group (cont).

Father's age at delivery, years		
<20	36 (7.7)	363 (8.8)
20-24	187 (39.8)	1764 (42.5)
25-29	169 (36.0)	1453 (35.0)
30-34	61 (13.0)	461 (11.1)
35-39	16 (3.4)	94 (2.3)
≥40	1 (0.2)	15 (0.4)
Mother's age at delivery, years		
<20	97 (20.6)	783 (18.9)
20-24	176 (37.4)	1804 (43.5)
25-29	129 (27.4)	1042 (25.1)
30-34	59 (12.6)	412 (9.9)
35-39	8 (1.7)	97 (2.3)
≥40	1 (0.2)	11 (0.27)
Year of delivery		
1973-1979	9 (1.9)	90 (2.2)
1980-1989	109 (23.2)	1046 (25.2)
1990-1999	326 (69.4)	2801 (67.5)
2000-2001	26 (5.5)	213 (5.1)

Table 2. Prenatal characteristics of male survivors and their partners at time of first subsequent offspring versus a comparison group (cont).

Unmarried at time of delivery, mother[2]	92 (25.1)	739 (20.0)
Prenatal smoker, mother[3]	64 (16.8)	480 (14.5)
No. prior pregnancies, mother		
0	293 (64.0)	1692 (41.6)
1	96 (21.0)	1239 (30.5)
≥2	69 (15.1)	1135 (27.9)
No. prior births, mother		
0	347 (75.8)	2004 (49.3)
1	78 (17.0)	1291 (31.7)
≥2	33 (7.2)	772 (19.0)
Month prenatal care began, mother		
1st trimester	385 (84.3)	3294 (81.8)
2nd trimester	51 (11.2)	601 (14.9)
3rd trimester or no care	21 (4.6)	133 (3.3)

[2] Data unavailable in Michigan.
[3] Not available for all years.

Table 3. Perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group.[1]

Outcome	Cohort, N (%)		Relative Risk (95% CI)[2]
	Cancer survivors (n=470)	Comparison group (n=4150)	
Maternal conditions			
Any history of C-section	84 (18.5)	721 (18.0)	0.91 (0.73-1.14)
Primary C-section[3]	65 (19.2)	374 (19.4)	0.91 (0.71-1.17)
Diabetes[4]	9 (2.2)	71 (2.0)	1.17 (0.55-2.51)
Preeclampsia/eclampsia[4]	27 (6.5)	160 (4.4)	1.19 (0.76-1.88)
Anemia[4]	3 (0.8)	79 (2.3)	0.46 (0.13-1.55)
Infant outcomes			
Female gender	225 (47.9)	2033 (49.0)	referent
Male gender	245 (52.1)	2117 (51.0)	1.03 (0.93-1.14)
Birth weight, grams			
<2500	41 (8.7)	282 (6.8)	1.43 (0.99-2.05)
2500-3999	380 (80.9)	3465 (83.6)	referent
≥4000	49 (10.4)	397 (9.6)	1.08 (0.79-1.49)

[1] Numbers may not add up to totals because of missing data.
[2] Adjusted for state, infant birth year, paternal and maternal age, paternal race/ethnicity, and maternal parity.
[3] Among 345 male cancer survivors and 1979 comparison men whose partners did not have prior deliveries.
[4] Not available for all years.

Table 3. Perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group (cont).

Gestational age, weeks			
<37	42 (9.1)	366 (9.0)	0.99 (0.70-1.41)
37-41	381 (82.5)	3383 (83.5)	referent
≥42	39 (8.4)	305 (7.5)	1.18 (0.85-1.64)
Small for gestational age	43 (9.4)	414 (10.3)	0.91 (0.64-1.29)
Malformation[4]	9 (2.0)	86 (2.1)	0.83 (0.41-1.69)
5-minute Apgar <7[5]	4 (1.1)	57 (1.6)	0.81 (0.29-2.29)
Infant death[6]	0	20 (0.6)	-

[5] Not available for all years and unavailable in Michigan.
[6] Not available for all years and unavailable in Georgia.

Table 4. Selected perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group, stratified by diagnostic characteristics.

Characteristic	Relative Risk (95% CI)[1]			
	Maternal preeclampsia	**Birth weight <2500 g**	**Gestation <37 weeks**	**Small for gestational age**
Cancer type				
Leukemia	2.41 (1.11-5.22)	1.63 (0.58-4.62)	0.44 (0.10-2.03)	0.81 (0.25-2.59)
Lymphoma	0.26 (0.04-1.70)	1.68 (0.85-3.30)	0.59 (0.22-1.54)	1.41 (0.81-2.46)
Central nervous system	3.36 (1.63-6.90)	1.18 (0.36-3.85)	1.31 (0.55-3.12)	1.02 (0.44-2.41)
Embryonal	0.46 (0.04-4.84)	3.93 (1.68-9.20)	2.17 (0.78-6.02)	1.51 (0.46-4.99)
Bone	2.54 (0.38-16.80)	0.76 (0.10-5.63)	0.42 (0.07-2.56)	0.61 (0.12-3.16)
Soft tissue sarcoma	1.19 (0.22-6.39)	0.69 (0.19-2.44)	0.36 (0.07-1.83)	1.15 (0.38-3.52)
Germ cell/gonadal	0.71 (0.14-3.67)	1.72 (0.75-3.96)	1.61 (0.80-3.26)	0.48 (0.15-1.53)

[1] Adjusted for state, infant birth year, paternal age and race/ethnicity, and maternal age and parity.

Table 4. Selected perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group, stratified by diagnostic characteristics (cont).

Thyroid	1.91	-	-	0.83
	(0.33-10.86)			(0.10-6.98)
Non-basal/squamous	1.08	1.33	2.39	0.56
cell skin	(0.25-4.74)	(0.45-3.95)	(1.19-4.80)	(0.14-2.23)
Other carcinoma	-	1.03	-	0.57
		(0.18-5.93)		(0.11-3.07)
Other tumors	-	1.61	3.95	-
		(0.04-65.73)	(0.37-41.65)	
Pelvic primary cancer site	0.43	1.65	1.61	0.51
	(0.09-2.06)	(0.84-3.26)	(0.92-2.80)	(0.19-1.37)
Diagnosis year				
1973-1979	1.03	1.79	1.06	1.18
	(0.48-2.21)	(1.02-3.13)	(0.57-2.00)	(0.71-1.94)
1980-1989	1.60	1.42	1.10	0.86
	(0.91-2.83)	(0.87-2.30)	(0.69-1.75)	(0.52-1.44)
1990-2000	0.63	0.91	0.66	0.62
	(0.16-2.45)	(0.32-2.63)	(0.28-1.53)	(0.24-1.64)

Table 4. Selected perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group, stratified by diagnostic characteristics (cont).

Age at diagnosis				
<5 years	1.81	2.78	0.86	1.59
	(0.69-4.74)	(1.21-6.38)	(0.21-3.50)	(0.62-4.10)
5-9 years	1.02	2.27	0.55	2.13
	(0.29-3.62)	(0.73-7.09)	(0.11-2.71)	(0.97-4.71)
10-14 years	1.32	2.06	0.76	1.04
	(0.49-3.54)	(0.88-4.80)	(0.23-2.49)	(0.46-2.32)
15-19 years	1.10	1.13	1.08	0.72
	(0.60-2.02)	(0.71-1.79)	(0.74-1.59)	(0.45-1.14)
Time since diagnosis				
<2 years	-	1.20	0.89	1.49
		(0.31-4.58)	(0.22-3.62)	(0.50-4.43)
2-5 years	1.48	0.76	0.74	0.48
	(0.56-3.93)	(0.25-2.29)	(0.31-1.74)	(0.18-1.26)
6-10 years	0.85	1.05	0.84	0.83
	(0.35-2.10)	(0.57-1.93)	(0.47-1.51)	(0.47-1.46)
>10 years	1.44	2.28	1.23	1.27
	(0.80-2.57)	(1.36-3.82)	(0.71-2.15)	(0.76-2.13)

Table 4. Selected perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group, stratified by diagnostic characteristics (cont).

Cancer treatment				
Chemotherapy, only	2.41 (1.03-5.63)	1.55 (0.58-4.11)	0.85 (0.31-2.33)	0.38 (0.07-2.01)
Surgery, only	1.40 (0.60-3.25)	0.83 (0.42-1.66)	1.27 (0.74-2.18)	0.44 (0.19-1.02)
Radiotherapy, only	-	1.91 (0.62-5.89)	0.83 (0.22-3.11)	1.21 (0.43-3.44)
Chemotherapy +surgery	0.70 (0.14-3.64)	1.91 (0.87-4.22)	1.46 (0.76-2.81)	0.81 (0.34-1.94)
Chemotherapy +radiotherapy	1.19 (0.31-4.64)	1.78 (0.68-4.62)	0.23 (0.02-2.66)	2.29 (1.13-4.63)
Surgery +radiotherapy	2.08 (0.95-4.57)	1.35 (0.42-4.30)	0.75 (0.23-2.42)	1.09 (0.46-2.59)
Chemotherapy +surgery +radiotherapy	0.32 0.03-3.38)	3.47 (1.36-8.85)	1.36 (0.46-4.04)	1.96 (0.88-4.36)
Other / unknown	0.93 (0.14-6.18)	1.47 (0.22-9.79)	-	0.69 (0.11-4.44)

Table 4. Selected perinatal outcomes associated with first subsequent offspring among male survivors versus a comparison group, stratified by diagnostic characteristics (cont).

Any chemotherapy	1.16	1.96	1.03	1.23
	(0.60-2.24)	(1.22-3.17)	(0.63-1.70)	(0.78-1.93)
Any surgery	1.19	1.32	1.21	0.79
	(0.67-2.10)	(0.84-2.06)	(0.82-1.78)	(0.51-1.23)
Any radiotherapy	0.97	1.95	0.77	1.58
	(0.49-1.95)	(1.14-3.35)	(0.39-1.50)	(1.03-2.42)