Birth Outcomes Among Adolescent and Young Adult Cancer Survivors

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IMPORTANCE Cancer diagnosis and treatment may adversely affect reproductive outcomes among female cancer survivors.

OBJECTIVE To compare the birth outcomes of adolescent and young adult cancer survivors (AYA [diagnosed at ages 15-39 years]) with those of women without a cancer diagnosis.

DESIGN, SETTING, AND PARTICIPANTS The North Carolina Central Cancer Registry (CCR) was used to identify female AYA cancer survivors diagnosed from January 2000 to December 2013; CCR records were linked to statewide birth certificate files from January 2000 to December 2014 to identify postdiagnosis live births to AYA survivors (n = 2598). A comparison cohort of births to women without a recorded cancer diagnosis was randomly selected from birth certificate files (n = 12 990) with frequency matching on maternal age and year of delivery.

MAIN OUTCOMES AND MEASURES Prevalence of preterm birth, low birth weight, small-for-gestational-age births, cesarean delivery, and low Apgar score.

RESULTS Overall, 2598 births to AYA cancer survivors (mean [SD] maternal age, 31 [5] years) were included. Births to AYA cancer survivors had a significantly increased prevalence of preterm birth (prevalence ratio [PR], 1.52; 95% CI, 1.34-1.71), low birth weight (PR, 1.59; 95% CI, 1.38-1.83), and cesarean delivery (PR, 1.08; 95% CI, 1.01-1.14) relative to the comparison cohort of 1299. The higher prevalence of these outcomes was most concentrated among births to women diagnosed during pregnancy. Other factors associated with preterm birth and low birth weight included treatment with chemotherapy and a diagnosis of breast cancer, non-Hodgkin lymphoma, or gynecologic cancers. The prevalence of small-for-gestational-age births and low Apgar score (<7) did not differ significantly between groups.

CONCLUSIONS AND RELEVANCE Live births to AYA cancer survivors may have an increased risk of preterm birth and low birth weight, suggesting that additional surveillance of pregnancies in this population is warranted. Our findings may inform the reproductive counseling of female AYA cancer survivors.

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In the United States, adolescent and young adult (AYA) cancers are defined as those diagnosed between 15 and 39 years of age.[1] Though nonuniform across cancer sites, 5-year relative survival rates of over 80% have been estimated for the AYA cancer population in the United States.[2,3] With continued improvements in early diagnosis and treatment,[3] a growing number of AYA patients with cancer will become long-term survivors, prompting concerns about the late effects of malignancy and treatment in this population.

For the more than 45 000 US women diagnosed with AYA cancers each year,[4] such concerns may include future fertility and reproductive outcomes. Though recent studies[5,6] suggest that 60% of female AYA cancer survivors want the possibility of having children, there is currently limited information available regarding the potential risk of adverse birth outcomes in this population. Studies of births to childhood cancer survivors (diagnosed at ages 0-14 years) in the United States suggest an increased risk of outcomes such as preterm birth and low birth weight relative to the general population.[7,8] Yet little research has focused specifically on birth outcomes among AYA cancer survivors, who were diagnosed and treated during childbearing years and thus may have a risk profile distinct from that of survivors diagnosed during childhood. Studies from Australia[9] and Europe[10-13] have documented an increase in adverse birth outcomes among survivors diagnosed with cancer during reproductive years. However, given potential differences in the racial and ethnic makeup of these countries, as well as in the prevalence of other risk factors, it is unclear whether AYA cancer survivors in the United States have similarly elevated risks. Furthermore, few studies have examined whether various treatment modalities, such as radiation therapy and chemotherapy, are associated with adverse birth outcomes among births to AYA cancer survivors.[9]

In the current study, we used a data linkage between the North Carolina Central Cancer Registry and state birth certificate files to compare selected birth outcomes of female AYA cancer survivors to those of women without a history of cancer. We also evaluated risks of adverse birth outcomes according to factors such as cancer site group, treatment type, and the interval between diagnosis and birth.

Key Points

Question Are adverse birth outcomes more prevalent among births to adolescent and young adult (AYA, diagnosed at ages 15-39 years) cancer survivors than among births to women without a recorded cancer diagnosis?

Findings This case-control cohort study used a data linkage between the North Carolina Central Cancer Registry and statewide birth certificate files to identify births to AYA cancer survivors, and a comparison cohort of births to women without a recorded cancer diagnosis randomly selected from birth certificate files. The results suggest an excess risk of preterm birth and low birth weight among births to AYA cancer survivors.

Meaning These findings may inform the preconception and prenatal counseling of AYA cancer survivors and suggest the need for additional surveillance of pregnancies in this population.

Methods

Data Sources

To identify AYA cancer survivors, we used data from the North Carolina Central Cancer Registry (CCR). As required by state law, all cancer cases and benign brain and/or central nervous system tumors diagnosed in North Carolina are reported to the CCR by health care providers. We identified all women diagnosed with an incident cancer at ages 15 to 39 years from January 2000 to December 2013. Information recorded in the CCR includes cancer site, stage, date of diagnosis, and primary treatments (surgery, radiation, chemotherapy). We defined cancer site groupings for commonly diagnosed AYA cancers (breast, melanoma/skin carcinoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and gynecologic) using AYA-specific recodes of *International Classification of Diseases for Oncology* (*ICD-O-3*) definitions, available from the National Institutes of Health Surveillance, Epidemiology, and End Results Program (eTable 1 in the Supplement).[14]

Live births occurring in North Carolina from January 2000 to December 2014 were identified using statewide vital records. Data abstracted from birth certificates included birth weight, gestational age, infant sex, mode of delivery, plural birth, and Apgar score (a measure of the physiologic condition of the newborn).[15] Gestational age recorded on birth certificates may be determined from the mother's self-reported last menstrual period, from ultrasound findings, or other perinatal factors.[16] Maternal characteristics, including race/ethnicity, parity, smoking during pregnancy, education, and marital status, were also abstracted from birth certificates.

To identify births to AYA cancer survivors, data from the CCR and birth certificate files were linked using a probabilistic linkage strategy in Link Plus.[17] Variables used in the linkage included maternal name, date of birth, and social security number. Estimates of reliability for variables used in the linkage, ranging from 0% (totally unreliable) to 100% (completely reliable), were 98%, 96%, 97%, 96%, and 96% for social security number, date of birth, last name, first name, and middle name, respectively.

This study was approved by the institutional review board of the University of North Carolina and by the North Carolina State Center for Health Statistics; patient written informed consent was not required for the analysis of existing, deidentified records.

Selection of Study Population

From the CCR, we identified 21 716 women with a cancer diagnosis between ages 15 and 39 years from January 2000 to December 2013. By linking with state birth certificate files, we found that 8529 of these women had a total of 14 132 live births from January 2000 to December 2014. We excluded births to women with nonmalignant diagnoses and to women whose recorded diagnosis was not their first or only cancer (n = 1857 births). We excluded births that occurred before diagnosis (n = 8622) and those missing infant date of birth (n = 53). To

focus our analyses on births closest to the mother's cancer diagnosis and treatment, we included only the first postdiagnosis birth to each cancer survivor that occurred from January 2000 to December 2014, excluding second or later births that also occurred during this time period (n = 924). We further excluded multiple births (n = 72) and those with fewer than 20 weeks gestation or a birthweight less than 500 g (n = 6). Thus, final analyses included 2598 births to AYA cancer survivors.

In North Carolina from January 2000 to December 2014, a total of 1 846 939 births occurred to 1 369 916 women without a recorded cancer diagnosis. After excluding second or later births to the same mother during this time period (n = 477 023), birth records missing infant date of birth (n = 12 360), multiple births (n = 23 355) and births with fewer than 20 weeks gestation or a birth weight less than 500 g (n = 3504), we were left with 1 330 697 eligible births. Among these, we randomly sampled 5 comparison births for every included birth to an AYA cancer survivor. Births were frequency matched on year of delivery and maternal age. The resulting comparison cohort included 12 990 births to women without a recorded cancer diagnosis.

Outcomes

Outcomes included preterm birth, low birth weight (LBW), small-for-gestational-age (SGA) birth, a 5-minute Apgar score less than 7, and cesarean delivery. Low birth weight was defined as less than 2500 g. We evaluated preterm birth before 37 weeks gestation and before 34 weeks gestation, to distinguish early preterm and late preterm. National standards for US births, published by Oken et al,[18] were used to determine SGA, defined as birth weight below the 10th percentile of infants of the same sex and gestational age.

Statistical Analyses

Poisson regression models with robust error variance[19] were used to estimate prevalence ratios (PR) for all birth outcomes, comparing births to AYA cancer survivors with the comparison cohort. All regression models were adjusted for variables considered a priori as potential confounders: year of birth (2000-2003, 2004-2006, 2007-2009, 2011-2012, 2013-2014), maternal age (<24, 25-29, 30-34, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, other), maternal education (high school or less, some college, Bachelor's degree or higher), previous live births (0, 1, 2, ≥3), marital status (married, not married), and maternal smoking during pregnancy (any, none). Because maternal education and smoking during pregnancy were missing for all births in 2010, due to a change in the format of the North Carolina birth certificate that occurred that year, these births were necessarily excluded from multivariable models for all outcomes. Cesarean deliveries were also missing for 2010 births.

We conducted further analyses stratified by cancer site group, treatment (radiation and/or chemotherapy), time between diagnosis and birth, and age at diagnosis. In analyses stratified by time between diagnosis and birth, we assumed that a mother's cancer diagnosis occurred during pregnancy if the infant's gestational age was longer than the interval between the mother's diagnosis and the infant's date of birth. We also evaluated risks associated with chemotherapy and/or radiation within cancer site groups.

Within the AYA survivor group, we then evaluated risks associated with chemotherapy and/or radiation compared with those who received surgery only. Births to gynecologic cancer survivors were excluded from these analyses owing to potential associations between gynecologic surgery and adverse birth outcomes.[20]

To address whether preterm birth was related to medical intervention, rather than spontaneous labor, we performed sensitivity analyses excluding all cesarean deliveries (844 births to AYA cancer survivors; 3907 births to comparison cohort). We then excluded both cesarean deliveries and induced labor (1323 births to AYA cancer survivors; 5903 births to comparison cohort). All analyses were conducted using SAS 9.4 (SAS Institute).

Results

Characteristics of births to AYA cancer survivors and the comparison cohort are shown in **Table 1**. The mean (SD) maternal age was 31.1 (5.3) years. A greater proportion of AYA cancer survivors were non-Hispanic white (n = 2013 of 2598 [78%]) compared with the comparison cohort (n = 7683 of 12 990 [59%]). The proportion of births that were preterm (overall preterm, <37 weeks; early preterm, <34 weeks), low birth weight, or cesarean delivery was higher among births to AYA cancer survivors.

Among the 2598 AYA cancer survivors with an included birth, common diagnoses included melanoma/skin carcinoma (n = 536 [21%]), thyroid cancer (n = 484 [19%]), and breast cancer (n = 367 [14%]), Hodgkin lymphoma (n = 179 [7%]), gynecologic cancers (n = 129 [5%]), and non-Hodgkin lymphoma (n = 110 [4%]) (**Table 2**). Other diagnoses frequently included melanoma in situ (n = 258 [10%]), soft tissue sarcomas (n = 69 [3%]), central nervous system neoplasms (n = 66 [3%]), and carcinomas of the gastrointestinal tract (n = 61 [2%]). The mean (SD) age at diagnosis was 28.1 (5.5) years, and the mean (SD) time between diagnosis and birth was 3.1 (2.5) years. The majority were diagnosed with localized disease (n = 1454 [56%]) and underwent surgery (n = 2201 [85%]). Approximately one-fourth of included AYA cancer survivors received radiation (n = 595 [23%]) or chemotherapy (n = 646 [25%]).

Overall, preterm birth (PR, 1.52; 95% CI, 1.34-1.71), early preterm birth (PR, 2.03; 95% CI, 1.62-2.55), and LBW (PR, 1.59; 95% CI, 1.38-1.83) were increased among births to AYA cancer survivors relative to the comparison cohort (**Table 3**). A small but statistically significant increase in cesarean deliveries was also identified among survivors. The prevalence of SGA and low Apgar score did not differ between groups.

In analyses stratified by cancer site group, the prevalence of preterm birth was elevated among births to women diagnosed with breast cancer (PR, 1.98; 95% CI, 1.56-2.51), Hodgkin lymphoma (PR, 1.59; 95% CI, 1.06-2.37), non-Hodgkin lymphoma (PR, 2.11; 95% CI, 1.42-3.13), and gynecologic cancer (PR, 2.58; 95% CI, 1.83-3.63), relative to the comparison cohort. The prevalence of LBW was increased among births to survivors of breast cancer (PR, 1.59; 95% CI, 1.18-2.15), non-Hodgkin lymphoma (PR, 2.41; 95% CI, 1.58-3.67), and gynecologic cancer (PR, 2.74; 95% CI, 1.86-4.05).

Preterm birth (PR, 2.97; 95% CI, 2.47-3.58), LBW (PR, 2.82; 95% CI, 2.25-3.53), cesarean delivery (PR, 1.21; 95% CI, 1.06-1.38), and low Apgar score (PR, 1.90; 95% CI, 1.04-3.46) were more common among births to AYA cancer survivors diagnosed during pregnancy than among comparison births. The prevalence of preterm birth (PR, 1.23; 95% CI, 1.07-1.43) and LBW (PR, 1.36; 95% CI, 1.16-1.59) remained significantly elevated among births to women diagnosed with cancer before the start of pregnancy.

Overall, births to women treated with chemotherapy without radiation, were more likely to be preterm (PR, 2.11; 95% CI, 1.68-2.66) and LBW (PR, 2.36; 95% CI, 1.84-3.03) than births to the comparison cohort. Cesarean deliveries were also increased among women treated with chemotherapy without radiation (PR, 1.16; 95% CI, 1.01-1.32). None of the adverse birth outcomes evaluated were significantly increased among births to women treated with radiation who did not also receive chemotherapy.

When associations with treatment were evaluated separately within each cancer site group, LBW (PR, 1.78; 95% CI, 1.09-2.92) and preterm birth (PR, 1.81; 95% CI, 1.18-2.79) were more common among births to breast cancer survivors who were treated with chemotherapy without radiation (eTable 2 in the Supplement). Relative to the comparison cohort, elevations in preterm birth (PR, 6.03; 95% CI, 3.13-11.63) and LBW (PR, 4.56; 95% CI, 1.88-11.06) were observed among births to Hodgkin lymphoma survivors treated with radiation (without chemotherapy). Among births to non-Hodgkin lymphoma survivors, preterm birth (PR, 2.68; 95% CI, 1.67-4.30) and LBW (PR, 3.31; 95% CI, 2.06-5.31) were increased among those treated with chemotherapy without radiation Among births to gynecologic cancer survivors, treatment with surgery only was associated with an increased prevalence of preterm birth (PR, 3.20; 95% CI, 2.11-4.87), LBW (PR, 3.33; 95% CI, 2.04-5.46), and cesarean delivery (PR, 1.57; 95% CI, 1.22-2.01) and with a marginal increase in low Apgar score (PR, 2.83; 95% CI, 0.91-8.78).

Among births to cancer survivors, those to women treated with chemotherapy (without radiation) had an increased prevalence of preterm birth (PR, 2.12; 95% CI, 1.56-2.86) and LBW (PR, 2.13; 95% CI, 1.51-3.00), and a marginally increased prevalence of SGA compared with births to women treated with surgery only (PR, 1.43; 95% CI, 1.00-2.04 (eTable 3 in the Supplement).

In sensitivity analyses excluding cesarean deliveries alone, or cesarean deliveries and induced labors, increases in the prevalence of preterm birth (PR, 1.73; 95% CI, 1.47-2.04 and PR, 1.50; 95% CI, 1.23-1.82, respectively) and LBW (PR, 1.67; 95% CI, 1.37-2.02 and PR, 1.44; 95% CI, 1.13-1.84, respectively) were still observed among births to cancer survivors relative to the comparison cohort.

Table 1. Pregnancy Characteristics of AYA Cancer Survivors and the Comparison Cohort of Women Without Cancer

Characteristic	No. (%)[a]	
	AYA Cancer Survivors (n = 2598)	Women Without Cancer (n = 12 990)
Year of birth		
2000-2003	276 (11)	1380 (11)
2004-2006	477 (18)	2385 (18)
2007-2009	657 (25)	3285 (25)
2010-2012	680 (26)	3400 (26)
2013-2014	508 (20)	2540 (20)
Maternal age		
Mean (SD), y	31.1 (5.3)	31.1 (5.3)
<24	322 (12)	1610 (12)
25-29	630 (24)	3150 (24)
30-34	914 (35)	4570 (35)
>35	732 (28)	3660 (28)
Mother's race/ethnicity		
Non-Hispanic white	2013 (78)	7683 (59)
Non-Hispanic black	387 (15)	2455 (19)
Other	195 (8)	2845 (22)
Mother's marital status		
Married	2024 (78)	9549 (74)
Not married	573 (22)	3436 (26)
Mother's education		
High school or less	588 (25)	3960 (33)
Some college	640 (27)	3189 (27)
Bachelor's degree or higher	1140 (48)	4679 (40)
Maternal smoking during pregnancy		
None	2179 (92)	10927 (92)
Any	184 (8)	912 (8)
Previous live births		
0	1259 (48)	5916 (46)
1	777 (30)	3652 (28)
2	350 (13)	2015 (16)
>3	211 (8)	1402 (11)
Preterm birth, wk		
<37	327 (13)	1119 (9)
<34	107 (4)	302 (2)
Low birth weight	259 (10)	887 (7)
SGA	242 (9)	1356 (10)
Cesarean delivery	844 (36)	3907 (33)
Apgar <7	55 (2)	238 (2)

Abbreviations: AYA, adolescent and young adult cancer survivors; SGA, small for gestational age.

[a] Numbers may not sum to total due to missing values.

Discussion

In this population-based study, we found an increased prevalence of preterm birth and LBW among births to female survivors of AYA cancer compared with the general population. A slight increase in cesarean deliveries was also observed among births to survivors of AYA cancers. The higher prevalence of these outcomes was most pronounced among births to mothers diagnosed with cancer during pregnancy, with a more modest increase among those with a longer interval between diagnosis and birth. Elevations in preterm birth persisted when cesarean deliveries and/or induced labor were excluded, suggesting an increase in spontaneous preterm deliveries among AYA cancer survivors. Overall, the prevalence of other adverse birth outcomes, including SGA and low Apgar score, did not differ significantly between births of survivors and those of the comparison cohort.

Table 2. Characteristics and Birth Outcomes Among 2598 Births Among AYA Cancer Survivors With a Postdiagnosis Birth

Patient Characteristic, No. (%)	All (n = 2598)	Breast (n = 367)	Hodgkin Lymphoma (n = 179)	Melanoma/Skin Carcinoma (n = 536)	Non-Hodgkin Lymphoma (n = 110)	Thyroid (n = 484)	Gynecologic (n = 129)	Other (n = 793)
Age at diagnosis								
Mean (SD), y	28 (6)	32 (4)	25 (5)	28 (5)	28 (6)	28 (5)	27 (6)	28 (6)
15-19	203 (8)	2 (1)	34 (19)	20 (4)	14 (13)	33 (7)	14 (11)	86 (11)
20-24	496 (19)	20 (5)	67 (37)	115 (21)	21 (19)	100 (21)	18 (22)	145 (18)
25-29	762 (29)	80 (22)	40 (22)	191 (36)	24 (22)	170 (35)	39 (30)	218 (27)
30-34	812 (31)	171 (47)	29 (16)	164 (31)	34 (31)	134 (28)	36 (28)	244 (31)
35-39	325 (13)	94 (26)	9 (5)	46 (9)	17 (15)	47 (10)	12 (9)	100 (13)
Time between diagnosis and birth, y								
Mean (SD), y	3 (2)	3 (2)	4 (3)	3 (3)	3 (2)	3 (2)	3 (2)	3 (2)
During pregnancy[a]	431 (17)	91 (25)	16 (9)	98 (18)	17 (15)	56 (12)	26 (20)	127 (16)
<2	687 (26)	67 (18)	43 (24)	158 (29)	25 (23)	140 (29)	27 (21)	227 (29)
2 to <3	455 (18)	66 (18)	26 (15)	84 (16)	22 (20)	102 (21)	25 (19)	130 (16)
3 to <5	559 (22)	76 (21)	48 (27)	112 (21)	26 (24)	96 (20)	29 (22)	172 (22)
≥5	466 (18)	67 (18)	46 (26)	84 (16)	20 (18)	90 (19)	22 (17)	137 (17)
Summary stage								
In situ	387 (15)	52 (14)	0	0	0	0	0	335 (42)
Localized	1454 (56)	177 (48)	34 (19)	496 (93)	46 (42)	330 (68)	96 (74)	275 (35)
Regional	469 (18)	122 (33)	94 (53)	22 (4)	22 (20)	137 (28)	15 (12)	57 (7)
Distant	188 (7)	11 (3)	42 (23)	3 (1)	34 (31)	7 (1)	11 (9)	80 (10)
Unstaged	100 (4)	5 (1)	9 (5)	15 (3)	8 (7)	10 (2)	7 (5)	46 (6)
Surgery	2201 (85)	344 (94)	56 (32)	505 (94)	27 (25)	461 (98)	109 (85)	699 (88)
Radiation	595 (23)	150 (41)	79 (44)	3 (1)	28 (25)	256 (53)	6 (5)	73 (9)
Chemotherapy	646 (25)	245 (68)	164 (92)	2 (1)	72 (70)	0	45 (36)	118 (15)
Adverse birth outcomes, %								
Preterm birth, wk								
<37	327 (13)	68 (19)	26 (15)	44 (8)	22 (20)	36 (7)	30 (23)	101 (13)
<34	107 (4)	15 (4)	4 (2)	12 (2)	11 (10)	8 (2)	14 (11)	43 (5)
Low birth weight	259 (10)	47 (13)	18 (10)	27 (5)	21 (19)	32 (7)	26 (20)	88 (11)
SGA	242 (9)	41 (11)	21 (12)	29 (5)	13 (12)	41 (8)	12 (9)	85 (11)
Cesarean delivery	844 (36)	148 (43)	54 (33)	164 (34)	43 (42)	134 (31)	57 (49)	244 (33)
Apgar <7	55 (2)	6 (2)	3 (2)	9 (2)	5 (5)	8 (2)	5 (4)	19 (2)

Abbreviations: AYA, adolescent and young adult cancer survivors; SGA, small for gestational age.

[a] Calculated from date of delivery and gestational age as pregnancies that started before the diagnosis date.

Our findings regarding preterm birth and LBW are in line with those of recent studies based outside the United States.[9-12] In a study of births to AYA cancer survivors diagnosed in Western Australia between 1982 and 2007, Haggar et al[9] reported comparable increases in preterm birth (relative risk [RR], 1.68; 95% CI, 1.23-2.12) and LBW (RR, 1.51; 95% CI, 1.23-2.12) compared with women without a previous cancer diagnosis.[9] As in the current study, the first completed postdiagnosis pregnancy was included, regardless of the interval between diagnosis and birth. Other non-US studies with similar inclusion criteria have observed a similarly elevated prevalence of these outcomes among female cancer survivors diagnosed during reproductive years.[10,12] In our study, the large sample size allowed us to stratify by the length of time between a woman's cancer diagnosis and her first postdiagnosis birth. Our results suggest that the increased prevalence of preterm birth and LBW may be most concentrated among births to AYA cancer survivors diagnosed during pregnancy, some of whom may deliver early to begin treatment. However, modest though significant elevations in preterm birth and LBW remained among births to women diagnosed before pregnancy, indicating that the elevated prevalence of these outcomes may not be limited to births to women diagnosed during pregnancy.

Long-term effects of cancer treatment are a possible explanation for these findings. In all cancer site groups combined, both preterm birth and LBW were more common among births to women treated with chemotherapy. This may be partly explained by cardiovascular or pulmonary impairments due to chemotherapy, which may impact blood volume regulation and adversely affect pregnancy outcomes.[21,22] Treatment with radiation, in the absence of chemotherapy, did not appear to be strongly associated with these outcomes. Our findings contrast with those of Haggar et al,[9] in which the strongest associations with preterm birth and LBW among AYA

Table 3. Adverse Birth Outcomes Overall and According to AYA Characteristics for 2598 Births

Characteristic	Adjusted Prevalence Ratio (95% CI) vs Noncancer Comparison Group (n = 1299)[a,b]					
	Preterm Birth, wk					
	<37	<34	Low Birth Weight	SGA	Cesarean Delivery	Apgar <7
Overall	1.52 (1.34-1.71)	2.03 (1.62-2.55)	1.59 (1.38-1.83)	0.97 (0.85-1.11)	1.08 (1.01-1.14)	1.18 (0.87-1.61)
Site group						
Breast	1.98 (1.56-2.51)	1.56 (0.92-2.63)	1.59 (1.18-2.15)	1.00 (0.73-1.36)	1.17 (1.04-1.33)	0.90 (0.40-2.02)
Hodgkin lymphoma	1.59 (1.06-2.37)	1.27 (0.48-3.37)	1.44 (0.89-2.33)	1.08 (0.71-1.64)	1.08 (0.88-1.34)	0.92 (0.30-2.79)
Non-Hodgkin lymphoma	2.11 (1.42-3.13)	3.42 (1.88-6.21)	2.41 (1.58-3.67)	1.09 (0.66-1.81)	1.18 (0.94-1.49)	2.07 (0.89-4.86)
Melanoma/skin carcinoma	1.12 (0.82-1.52)	1.67 (0.93-3.01)	0.99 (0.67-1.47)	0.65 (0.44-0.95)	1.04 (0.91-1.17)	0.88 (0.41-1.87)
Thyroid	0.97 (0.69-1.36)	0.92 (0.44-1.94)	1.23 (0.86-1.75)	0.94 (0.69-1.29)	0.97 (0.85-1.12)	1.10 (0.55-2.21)
Gynecologic	2.58 (1.83-3.63)	4.29 (2.43-7.58)	2.74 (1.86-4.05)	0.67 (0.36-1.26)	1.48 (1.21-1.79)	2.34 (0.99-5.56)
Time between diagnosis and birth						
Diagnosed during pregnancy	2.97 (2.47-3.58)	3.44 (2.34-5.05)	2.82 (2.25-3.53)	1.05 (0.77-1.42)	1.21 (1.06-1.38)	1.90 (1.04-3.46)
Diagnosed before pregnancy, y	1.23 (1.07-1.43)	1.77 (1.37-2.30)	1.36 (1.16-1.59)	0.96 (0.83-1.11)	1.05 (0.98-1.12)	1.06 (0.76-1.50)
<2	1.35 (1.07-1.70)	2.19 (1.48-3.25)	1.47 (1.13-1.91)	0.86 (0.65-1.12)	1.02 (0.91-1.15)	0.99 (0.53-1.84)
2 to <3	1.32 (1.00-1.74)	1.49 (0.86-2.59)	1.40 (1.02-1.92)	0.88 (0.64-1.20)	1.01 (0.88-1.15)	1.13 (0.56-2.26)
3 to<5	0.98 (0.73-1.32)	1.48 (0.90-2.46)	1.20 (0.88-1.63)	0.89 (0.67-1.18)	1.11 (0.99-1.24)	0.83 (0.41-1.66)
>5	1.27 (0.95-1.69)	1.80 (1.11-2.90)	1.34 (0.98-1.83)	1.23 (0.96-1.58)	1.07 (0.94-1.21)	1.31 (0.75-2.30)
Treatment						
Surgery only	1.21 (1.01-1.45)	1.84 (1.33-2.55)	1.29 (1.05-1.59)	0.85 (0.70-1.04)	1.04 (0.96-1.13)	1.07 (0.70-1.64)
Radiation, no chemotherapy	1.21 (0.85-1.72)	0.52 (0.17-1.62)	1.34 (0.91-1.98)	0.92 (0.64-1.34)	1.08 (0.92-1.26)	1.52 (0.76-3.06)
Chemotherapy, no radiation	2.11 (1.68-2.66)	2.93 (1.97-4.36)	2.36 (1.84-3.03)	1.14 (0.85-1.52)	1.16 (1.01-1.32)	1.20 (0.62-2.30)
Chemotherapy and radiation	2.28 (1.77-2.93)	2.90 (1.83-4.60)	2.01 (1.48-2.72)	1.17 (0.86-1.60)	1.15 (0.98-1.35)	0.43 (0.11-1.72)
Age at diagnosis, y						
15-19	1.65 (1.14-2.40)	1.49 (0.66-3.36)	1.26 (0.77-2.05)	1.01 (0.70-1.46)	1.27 (1.03-1.56)	0.74 (0.24-2.33)
20-24	1.26 (0.93-1.70)	2.36 (1.44-3.88)	1.61 (1.18-2.19)	0.81 (0.59-1.10)	0.94 (0.80-1.10)	1.03 (0.83-2.02)
25-29	1.67 (1.35-2.06)	2.57 (1.75-3.76)	1.75 (1.38-2.23)	0.97 (0.76-1.24)	1.12 (1.01-1.24)	1.17 (0.67-2.03)
30-34	1.42 (1.15-1.74)	1.74 (1.18-2.56)	1.46 (1.16-1.85)	0.99 (0.78-1.25)	1.07 (0.97-1.17)	1.38 (0.84-2.27)
35-39	1.64 (1.25-2.15)	1.85 (1.13-3.04)	1.72 (1.28-2.33)	1.15 (0.83-1.60)	1.09 (0.95-1.25)	1.29 (0.60-2.76)

Abbreviation: SGA, small for gestational age.

[a] Excludes 2010 births (missing variables for cesarean delivery, mother's education, and smoking).

[b] Adjusted for year of birth, maternal age, race/ethnicity, mother's education, previous live births, marital status, and maternal smoking during pregnancy.

survivors were observed for treatment with radiation alone. This may be attributable to differences in site group makeup between study populations, as our results also suggest potential differences in treatment effects according to cancer site. In our sample, treatment with chemotherapy was most strongly associated with preterm birth and LBW among births to women diagnosed with breast cancer or non-Hodgkin lymphoma. Surgical treatment among gynecologic cancer survivors appeared to be associated with an increase in both preterm birth and LBW, as did treatment with radiation among survivors of Hodgkin lymphoma. However, these findings were based on small numbers of outcomes, and further investigation is warranted to assess treatment effects within site groups.

Although LBW was increased among AYA survivors, we observed little difference in the prevalence of SGA relative to the comparison cohort. This is consistent with findings of prior studies among childhood and AYA cancer survivors.[7,8,11,13] Births to AYA survivors that met the criteria for LBW (<2500 g) were generally not small enough to fall below the 10th percentile for their gestational age, suggesting that the increase in LBW may be largely driven by shorter gestation relative to the comparison cohort.

Limitations

Strengths of this study include the large sample of births to AYA cancer survivors and the availability of individual treatment information. Some limitations should also be considered. Information regarding childbearing intent and the number and timing of attempts of parenthood was not available for this study. Additionally, misclassification may occur in administrative data sources such as birth certificates and cancer registries. For example, gestational age recorded on birth certificates is usually estimated from the mother's self-reported last menstrual period, and may therefore be subject to some inaccuracy. However, validation studies have demonstrated high reliability for birth outcome variables on US birth certificates,[23-27] including those in North Carolina.[23,25] Furthermore, we lacked information on women who moved out of the state during the study period. North Carolina census data for 2000 through 2010, only 7% of women overall moved out of state.[28] Thus, even if outcomes differed among women who moved out of North Carolina, we expect the influence on our estimates would be small. Furthermore, the number of outcomes was small within some subgroups; thus, we had limited statistical power to detect significant differences in some stratified analyses.

Conclusions

Overall, our results suggest an increased risk of preterm birth and LBW among births to AYA cancer survivors. Treatment with chemotherapy may be associated with increases in these outcomes. Our findings may inform the preconception and prenatal counseling of AYA cancer survivors and suggest the need for additional surveillance of pregnancies in this population.

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Acquisition, analysis, or interpretation of data: Anderson, Engel, Wood, Nichols.
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