Original Article

Pregnancy After Cancer: Does Timing of Conception Affect Infant Health?

Kathleen P. Hartnett, PhD[1]; Ann C. Mertens, PhD[1,2,3]; Michael R. Kramer, PhD[1]; Timothy L. Lash, DSc[1,3]; Jessica B. Spencer, MD[4]; Kevin C. Ward, PhD[1,3,5]; and Penelope P. Howards, PhD[1,3]

BACKGROUND: The objective of this retrospective cohort study was to determine whether women who conceive soon after treatment for cancer have higher risks of adverse pregnancy outcomes. **METHODS:** Vital records data were linked to cancer registry diagnosis and treatment information in 3 US states. Women who conceived their first pregnancy after diagnosis between ages 20 and 45 years with any invasive cancer or ductal carcinoma in situ were eligible. Log-binomial models were used to compare risks in cancer survivors who conceived in each interval to the risks in matched comparison births to women without cancer. **RESULTS:** Women who conceived ≤1 year after starting chemotherapy for any cancer had higher risks of preterm birth than comparison women (chemotherapy alone: relative risk [RR], 1.9; 95% confidence interval [CI], 1.3-2.7; chemotherapy with radiation: RR, 2.4; 95% CI, 1.6-3.6); women who conceived ≥1 year after starting chemotherapy without radiation or ≥2 years after chemotherapy with radiation did not. In analyses imputing the treatment end date for breast cancer survivors, those who conceived ≥1 year after finishing chemotherapy with or without radiation had no higher risks than women without cancer. The risk of preterm birth in cervical cancer survivors largely persisted but was somewhat lower in pregnancies conceived after the first year (for pregnancies conceived ≤1 year after diagnosis: RR, 3.5; 95% CI, 2.2-5.4; for pregnancies conceived >1 year after diagnosis: RR, 2.4; 95% CI, 1.6-3.5). **CONCLUSIONS:** In women who received chemotherapy, the higher risk of preterm birth was limited to those survivors who had short intervals between treatment and conception. ***Cancer* 2018;124:4401-4407.** © *2018 American Cancer Society.*

KEYWORDS: breast neoplasms, drug therapy, epidemiology, pregnancy, survivorship.

INTRODUCTION

Women who want to have children after a cancer diagnosis face difficult decisions about pregnancy timing. Organizations including the American Cancer Society, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network offer advice on how long women should wait after treatment before attempting to conceive but caution that more evidence is needed.[1-3] Although conceiving after a cancer diagnosis does not appear to increase the risk of cancer recurrence,[4,5] it is unknown whether short intervals between treatment and conception increase the risks of poor pregnancy outcomes.

Many organizations suggest that women postpone pregnancy for 6 to 12 months after finishing chemotherapy, so that they have time to recover and do not conceive with an oocyte that was maturing during treatment. Because chemotherapy kills rapidly dividing cells, it might damage the oocytes being recruited for ovulation, resulting in higher risks of miscarriage and birth defects in pregnancies conceived soon after treatment. This advice is rooted in the hypothesis that oocytes are most vulnerable to damage by chemotherapeutic agents during the period of rapid development before ovulation, but has not been well tested in human studies.[2,3] Other side effects of chemotherapy, including immunosuppression, might increase the risk of having an infant born preterm or small for gestational age (SGA). Some studies have observed an increased risk of preterm birth and/or growth restriction in infants born to cancer survivors,[6,7] but it is not clear whether these risks depend on the time since treatment.

Cervical cancer survivors are at high risk of early delivery.[8] Although some studies have reported higher risks of preterm birth and miscarriage in women who have shorter intervals between cervical surgeries and conception,[9] others have not.[10,11]

Corresponding author: Kathleen P. Hartnett, PhD, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322; kchap01@emory.edu

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; [2]Department of Pediatrics, Aflac Cancer Center, Emory University School of Medicine, Atlanta, Georgia; [3]Cancer Prevention and Control Research Program, Winship Cancer Institute of Emory University, Atlanta, Georgia; [4]Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia; [5]Georgia Center for Cancer Statistics, Georgia Cancer Registry, Atlanta, Georgia.

We are grateful for the work of the Georgia Cancer Registry, the Georgia Department of Public Health, the North Carolina Central Cancer Registry, the North Carolina Center for Health Statistics, the Tennessee Cancer Registry, and the Tennessee Office of Vital Records.

See related editorial on pages 4290-1, this issue.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.31732, **Received:** February 4, 2018; **Revised:** April 25, 2018; **Accepted:** April 30, 2018, **Published online** November 7, 2018 in Wiley Online Library (wileyonlinelibrary.com)

Pregnancy timing after cancer also may be important to thyroid cancer survivors, who require lifelong thyroid hormone replacement. Because hypothyroidism increases the risk of adverse pregnancy outcomes, including miscarriage and preterm birth,[12] the American Thyroid Association recommends that women postpone conception for 6 to 12 months after starting hormone replacement therapy.[13] The objective of the current study was to determine whether the risks of adverse pregnancy outcomes differ by time since diagnosis and treatment for different cancer types.

MATERIALS AND METHODS

Study Populations

Two different populations were used for this study. To assess whether pregnancy timing after cancer is associated with adverse pregnancy outcomes, we used diagnosis and treatment start dates from state cancer registries linked to birth data from vital records in 3 US states, with a comparison group selected from birth records. To impute treatment end dates for breast cancer survivors, we used information from cancer survivors who participated in the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study.

Population for Main Analysis: Cancer Registry Data Linked to Vital Records in 3 States

Cancer registry diagnosis and treatment data from August 23, 1994 to August 22, 2012 in Georgia; from August 23, 1999 to August 22, 2013 in North Carolina; and from January 1, 2004 to August 22, 2013 in Tennessee were linked to vital records. Births to women aged 20 to 45 who were diagnosed with any reportable invasive cancer[14] or ductal carcinoma in situ were eligible. We identified the first birth at >20 weeks gestation that was conceived after a cancer diagnosis reported in vital records from January 1, 1994 to December 31, 2012 in Georgia; from January 1, 2000 to December 31, 2013 in North Carolina; and from May 20, 2004 to December 31, 2013 in Tennessee. Women who were diagnosed during pregnancy were excluded.

Births were eligible for the comparison group if they did not link to a cancer diagnosis in the same state as the birth. Within each state, a random sample of births to women without a record of cancer diagnosis were matched 25:1 to births to cancer survivors using 4 variables from vital records: the mother's exact age at delivery (single-year categories), race and ethnicity (7 categories: Hispanic ethnicity of any race, non-Hispanic white, African American, Asian, Pacific Islander, Native American, and multiracial any ethnicity), parity (0, 1, 2, and ≥3), and maternal education (college graduate: yes or no).

We identified 4922 eligible births to cancer survivors before excluding multiple births (n = 162), deliveries of <20 or >44 weeks gestation (n = 6), improbable combinations of gestational age and birth weight (n = 6), births for which records indicated the delivery was not the mother's first after diagnosis (n = 166), stillbirths (n = 30), and records that were missing values for matching variables (n = 349) and cancer treatment (n = 237). Comparison births also were limited to live, singleton births between 20 and 44 weeks gestation to mothers who were ages 20 to 45 years at delivery.

Study Population for Imputation of Treatment End Dates: The FUCHSIA Women's Study

For a subset of breast cancer survivors who participated in the FUCHSIA Women's Study, treatment type, start date, and end date were abstracted from medical records (n = 283). Participants in the study were diagnosed at ages 20 to 35 years during 1990 through 2009 in metropolitan Atlanta or during 1999 through 2009 in the rest of Georgia. The study was limited to women who were ages 22 to 45 years at recruitment and survived for at least 2 years.

Cancer Treatment and Timing

Treatment type and start date were based on data corresponding to the first course of cancer-directed therapy, as captured by the cancer registry. To calculate the date of pregnancy conception, the clinical estimate of gestational age was subtracted from the infant's birth date.

Because the main treatments of interest for thyroid and cervical cancer were surgeries around the time of diagnosis, the exposure for these cancers was categorized as the time between diagnosis and conception. For women who received chemotherapy and/or radiation, the exposure for the main analysis was categorized as the time from treatment start date in the registry to conception. For women who received both chemotherapy and radiation, treatment start was defined as the day that the patient initiated chemotherapy or radiation, whichever came first. For the subset of survivors who participated in the FUCHSIA Women's Study, treatment type and start date from medical records were used if they differed from the registry, although concordance between medical records and registry data was high.

In a secondary analysis limited to breast cancer survivors, we used the time since treatment completion. Because the date of treatment completion is not captured in cancer registries, we imputed this date for patients with breast cancer by assigning each woman the median treatment duration length (105 days for either

adjuvant or neoadjuvant chemotherapy without radiation, 188 days for adjuvant chemotherapy with radiation, and 258 days for neoadjuvant chemotherapy with radiation) using data abstracted from medical records in the FUCHSIA Women's Study. This allowed an estimation of pregnancy risk by the time since treatment completion in breast cancer survivors.

Outcomes

Outcomes from birth certificate data were preterm birth (<37 weeks gestation), low birth weight (<2500 g), low birth weight at term (<2500 g at ≥37 weeks gestation), SGA (<10% of birth weight for gestational age and sex based on a national distribution),[15] and Cesarean section.

Statistical Analyses

The risks of adverse pregnancy outcomes were estimated for each time interval after cancer. Log-binomial models were used to estimate risk ratios (RRs) comparing the risk of adverse outcomes in pregnancies conceived during each time interval after cancer with the risk in matched comparison women without a history of cancer. Analyses were conducted using the statistical software package SAS (version 9.4; SAS Institute, Inc, Cary, NC). The study was approved by the North Carolina State Center for Health Statistics and the North Carolina Central Cancer Registry and by institutional review boards at Emory University, the Tennessee Department of Health, and the Georgia Department of Public Health.

RESULTS

Cancer survivors in the linked registry study were likely to be married (80%), have a 4-year college degree (44%), and be in their 30s at the time of the first birth after cancer diagnosis (61% were between ages 30 and 39 years). Pregnancy timing after cancer was strongly associated with age at diagnosis. Among births to women who were age ≥40 years at diagnosis, 55% were conceived within 1 year, compared with 21% among women who were ages 20 to 24 years at diagnosis (Table 1). Pregnancy timing also differed by cancer type. Patients with cervical cancer were the most likely to conceive soon after diagnosis, with 32% of births to women with cervical cancer in this study conceived within 1 year.

Among survivors of any cancer who received chemotherapy but not radiation, the risks of preterm birth and low birth weight were highest in pregnancies conceived within 1 year of starting treatment (Table 2). The preterm birth risk in these pregnancies was twice as high as that in the comparison group, with an RR of 1.9 (95% confidence interval [CI], 1.3-2.7) for chemotherapy without radiation and 2.4 (95% CI, 1.6-3.6) for chemotherapy with radiation. The risks in patients who had breast cancer who received chemotherapy with and without radiation mirrored the risks for all survivors, with the highest risks of preterm birth and low birth weight observed in pregnancies that were conceived within 1 year of starting treatment (Table 2). In contrast, survivors who conceived at least 1 year after starting chemotherapy without radiation and greater than 2 years after chemotherapy with radiation did not have higher risks of having a preterm infant, low-birth-weight infant, or an infant born SGA than women without a history of cancer. This was true in both analyses that included all survivors and in those limited to breast cancer survivors. The results did not change when we controlled for method of delivery (Cesarean section vs vaginal birth).

In analyses with imputed treatment end dates, infants born to breast cancer survivors who conceived within 1 year of completing chemotherapy with or without radiation had higher risks of preterm birth and low birth weight (preterm birth for chemotherapy without radiation: RR, 2.4; 95% CI, 1.5-3.9; for chemotherapy with radiation: RR, 2.0; 95% CI-1.2, 3.1) than comparison women (Supporting Table 1). Infants born to breast cancer survivors who conceived at least 1 year after the estimated treatment end date had no higher risk than comparison women without a history of cancer.

We observed a slightly higher RR for preterm birth in cervical cancer survivors who conceived within 1 year of diagnosis (RR, 3.5; 95% CI, 2.2-5.4) than for preterm birth in cervical cancer survivors who conceived after 1 year (RR, 2.4; 95% CI, 1.6-3.5); however, because the CIs for these RRs were wide and overlapping, this may have been a chance finding. Similarly, patients with cervical cancer had higher risks of Cesarean section, which was more common in preterm deliveries, than matched women in the comparison group. For Cesarean section, the RR was 1.7 (95% CI, 1.3-2.3) among cervical cancer survivors who conceived within 1 year and 1.4 (95% CI, 1.1-1.7) among those who conceived after 1 year (Supporting Table 2).

Thyroid cancer survivors did not have higher risks of any adverse outcome, regardless of when they conceived. The risk of having an infant born SGA was highest in women who had the longest intervals between treatment start and conception (Table 2). The SGA risk was twice as high in births to chemotherapy recipients who waited at least 5 years to conceive compared with the risk among women without cancer.

TABLE 1. Characteristics of the First Eligible, Live, Singleton Birth to Women Aged 20 to 45 Years Conceived After Cancer Diagnosis, by Time Between Diagnosis and Conception

			Time Between Diagnosis and Conception							
	All Cancers		≤1 Year		>1-2 Years		>2-5 Years		>5 Years	
Characteristic	No.	Column %[a]	No.	Row %[b]	No.	Row %	No.	Row %	No.	Row %
Cancer type										
Breast	754	18	168	22	212	28	273	36	101	13
Cervical	131	3	42	32	33	25	41	31	15	11
Hodgkin lymphoma	293	7	55	19	67	23	114	39	57	19
Melanoma	981	23	282	29	252	26	321	33	126	13
Thyroid	970	23	263	27	244	25	352	36	111	11
Other	1074	26	291	27	270	25	376	35	137	13
Age at diagnosis, y										
20-24	910	22	192	21	188	21	332	36	198	22
25-29	1412	34	337	24	359	25	511	36	205	15
30-34	1283	31	336	26	365	28	457	36	125	10
35-39	532	13	200	38	146	27	167	31	19	4
40-45	66	2	36	55	20	30	10	15	0	—
Maternal age at birth, y										
20-24	251	6	128	51	76	30	47	19	0	—
25-29	1084	26	305	28	299	28	390	36	90	8
30-34	1480	35	359	24	396	27	525	35	200	14
35-39	1089	26	237	22	257	24	408	37	187	17
40-45	299	7	72	24	50	17	107	36	70	23
Maternal race and ethnicity										
White, non-Hispanic	3074	73	782	25	786	26	1101	36	405	13
African American, non-Hispanic	810	19	234	29	212	26	262	32	102	13
Other non-Hispanic	191	5	53	28	52	27	64	34	22	12
Hispanic, any race	128	3	32	25	28	22	50	39	18	14
Maternal education										
<High school	259	6	89	34	68	26	75	29	27	10
High school or GED	801	19	207	26	239	30	270	34	85	11
Some college or associate degree	1278	30	348	27	298	23	462	36	170	13
≥4 Years of college	1865	44	457	25	473	25	670	36	265	14
Mother married										
Yes	3380	80	860	25	878	26	1206	36	436	13
No	819	20	241	29	199	24	270	33	109	13
Missing	4	0	0	—	1	—	1	—	2	—

[a]Percentages across maternal characteristics are shown.
[b]Percentages across years between diagnosis and conception are shown.

Low birth weight at term was a rare outcome in infants born to cancer survivors. Among term infants born to survivors of any cancer who received chemotherapy, the risk of low birth weight was 5% (7 of 148 infants; 95% CI, 2%-10%) among infants conceived within 1 year of maternal treatment initiation, 2% (12 of 525 infants; 95% CI, 1%-4%) among infants conceived from >1 to 5 years after maternal treatment, and 6% (8 of 134 infants; 95% CI, 3%-11%) among infants conceived >5 years after maternal treatment versus 3% among matched women without a history of cancer.

We excluded stillbirths from primary analyses because of small numbers and concerns that missing data in fetal death records could cause us to underestimate stillbirths in cancer survivors due to missed links between fetal death records and cancer registry diagnosis data. However, we did not observe an increased risk of stillbirth in cancer survivors. Among eligible pregnancies after any cancer diagnosis that reached 20 weeks, 0.7% (30 of 4582 pregnancies) ended in stillbirth, which was the same as the risk (also 0.7%) in all unmatched, eligible pregnancies to women without a cancer diagnosis. Of the 9 cancer survivors who received chemotherapy and whose first pregnancy after treatment ended in stillbirth, 3 conceived within 1 year of starting treatment.

DISCUSSION

In this study, the elevated risks of preterm birth and low birth weight in infants born to cancer survivors were limited to pregnancies conceived soon after treatment.

TABLE 2. Risk and Risk Ratios for Pregnancy Outcomes by the Time Between Treatment Start and Conception of the First Live Birth After Cancer Compared With the Risk in Matched Women Without Cancer

		Preterm Birth			Low Birth Weight			Small for Gestational Age		
Time Between Treatment Start and Conception, y	No. of Live Births	No.	Risk %, (95% CI)	RR (95% CI)	No.	Risk %, (95% CI)	RR (95% CI)	No.	Risk %, (95% CI)	RR (95% CI)
All cancers: Chemotherapy without radiation										
≤1	121	26	21 (15-30)	1.9 (1.3-2.7)	22	18 (12-26)	2.0 (1.4-3.0)	15	12 (7-20)	1.1 (0.7-1.7)
>1-2	163	20	12 (8-18)	1.1 (0.7-1.7)	18	11 (7-17)	1.4 (0.9-2.2)	21	13 (8-19)	1.1 (0.8-1.7)
>2-5	179	17	9 (6-15)	0.9 (0.6-1.4)	17	9 (6-15)	1.3 (0.8-2.1)	21	12 (7-17)	1.2 (0.8-1.9)
>5	68	5	7 (2-16)	0.6 (0.3-1.4)	8	12 (5-22)	1.4 (0.7-2.7)	16	24 (14-35)	2.0 (1.3-3.1)
All cancers: Chemotherapy and radiation										
≤1	72	19	26 (17-38)	2.4 (1.6-3.6)	16	22 (13-34)	2.7 (1.7-4.2)	12	17 (9-27)	1.5 (0.9-2.5)
>1-2	95	14	15 (8-23)	1.5 (0.9-2.4)	9	9 (4-17)	1.4 (0.7-2.6)	10	11 (5-19)	1.2 (0.6-2.1)
>2-5	158	19	12 (7-18)	1.2 (0.8-1.8)	15	9 (5-15)	1.4 (0.8-2.3)	15	9 (5-15)	1.0 (0.6-1.6)
>5	76	5	7 (2-15)	0.6 (0.2-1.3)	5	7 (2-15)	0.6 (0.3-1.5)	13	17 (9-27)	1.4 (0.9-2.4)
Breast cancer: Chemotherapy without radiation										
≤1	37	11	30 (16-47)	2.4 (1.4-4.0)	10	27 (14-44)	3.3 (1.9-5.8)	7	19 (8-35)	1.7 (0.9-3.4)
>1-2	60	6	10 (4-21)	0.9 (0.4-2.0)	5	8 (3-18)	1.3 (0.6-3.1)	5	8 (3-18)	0.8 (0.3-1.8)
>2	77	7	9 (4-18)	0.8 (0.4-1.7)	9	12 (5-21)	1.3 (0.7-2.5)	14	18 (10-29)	1.7 (1.0-2.7)
Breast cancer: Chemotherapy and radiation										
≤1	36	11	31 (16-48)	2.9 (1.7-5.0)	10	28 (14-45)	3.4 (1.9-6.0)	8	22 (10-39)	1.7 (0.9-3.2)
>1-2	59	12	20 (11-33)	2.1 (1.2-3.6)	8	14 (6-25)	1.9 (1.0-3.7)	8	14 (6-25)	1.2 (0.6-2.4)
>2	113	12	11 (6-18)	1.0 (0.6-1.7)	11	10 (5-17)	1.2 (0.7-2.1)	15	13 (8-21)	1.3 (0.8-2.1)
Cervical cancer[a]										
≤1	42	15	36 (22-52)	3.5 (2.2-5.4)	13	31 (18-47)	3.5 (2.1-5.7)	5	12 (4-26)	1.2 (0.5-2.7)
>1	89	22	25 (16-35)	2.4 (1.6-3.5)	15	17 (10-26)	2.6 (1.6-4.2)	5	6 (2-13)	0.6 (0.3-1.4)
Thyroid cancer[a]										
≤1	263	21	8 (5-12)	0.8 (0.6-1.3)	21	8 (5-12)	1.2 (0.8-1.9)	25	10 (6-14)	1.0 (0.7-1.4)
>1-2	244	28	11 (8-16)	1.3 (0.9-1.8)	17	7 (4-11)	1.1 (0.7-1.7)	24	10 (6-14)	1.1 (0.7-1.5)
>2-5	352	37	11 (8-14)	1.1 (0.8-1.6)	14	4 (2-7)	0.6 (0.4-1.1)	19	5 (3-8)	0.6 (0.4-0.9)
>5	111	15	14 (8-21)	1.4 (0.9-2.3)	12	11 (6-18)	1.5 (0.9-2.6)	14	13 (7-20)	1.2 (0.7-2.0)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a]For cervical and thyroid cancers, the timing categories reflect the time from diagnosis to conception rather than the time from treatment start to conception.

Infants born to women who conceived more than 1 year after starting chemotherapy without radiation and more than 2 years after chemotherapy and radiation did not have any higher risks for preterm delivery than women without a cancer history. In breast cancer survivors with imputed treatment end dates, the higher risks of adverse outcomes were only among women who conceived less than 1 year after finishing treatment. Patients with breast cancer who waited least 1 year after treatment before getting pregnant did not have higher risks than matched women without cancer. We observed higher risks of infants born SGA after chemotherapy, with or without radiation, among women who conceived more than 5 years after starting treatment. Patients with thyroid cancer did not have higher risks for preterm birth, or an infant born with low birth weight, or an infant born SGA at any time after diagnosis.

Some have hypothesized that conceiving too soon after cervical cancer could increase the risk of preterm birth because of inflammation from incomplete wound healing. However, it is also possible that the slightly higher risk we observed among women who conceived quickly was caused by other underlying differences between the patients who conceive quickly and those who wait, such as the type of cervical procedure or the risk of recurrence.

The mechanism by which chemotherapy might cause a temporary increase in preterm births may be through transient effects, such as immunosuppression[16,17] associated with preterm birth.[18,19] Studies have indicated that immunosuppression in patients with breast cancer persists months or years after chemotherapy, with CD4-positive counts at one-half of pretreatment levels 12 to 14 months after treatment,[20,21] and weaker vaccine responses in breast cancer survivors with a mean of 2.6 years since chemotherapy.[22] Other possible mechanisms by which chemotherapy could cause adverse outcomes include chronic anemia, cardiovascular effects, physical stress, or insufficient weight gain in pregnancy. However, the mechanism by which long intervals between cancer treatment and delivery could result in growth restriction is unclear. It is possible that adverse pregnancy outcomes

in women who have long intervals between cancer and conception are not caused by the wait time itself but by underlying differences, such as poorer cancer prognosis or underlying reproductive conditions, which cause both infertility and adverse pregnancy outcomes.

This study has limitations. If the oocytes that were maturing during treatment are most susceptible to damage from chemotherapeutic agents, women who conceive soon after treatment could have a higher risk of birth defects and miscarriage, which we could not assess. A second limitation is that, although the effects of chemotherapy likely depend on regimen and dose, these data are not available in cancer registry data. A third limitation is that cancer registries report only the first course of cancer treatment, which excludes treatment for relapse or treatment initiated after the first treatment failed. Consequently, we underreport the time to conception among women who conceived after a second course of treatment. To assess the extent of treatment misclassification, we compared registry data with medical records for the subset of breast cancer survivors who also participated in the FUCHSIA Women's Study. In that population, the sensitivity for treatment with chemotherapy at any time before conception was 91%, with 99% specificity, and radiation before pregnancy had 82% sensitivity and perfect specificity. Only 1 of 91 women for whom we had treatment start dates from both medical records and the registry was classified into the wrong category of time since treatment based on the registry date, indicating that the magnitude of misclassification is likely small.

Our current study has important strengths, including its population-based cohort design and large sample size. This allowed us to match precisely on important potential confounders, including the mother's exact age at delivery. Studies have indicated that the accuracy of vital records is excellent for birth weight and our matching variables[23-26] and generally is good for clinical estimates of gestational age.

The best pregnancy timing after cancer is a complex and individual question that depends on factors beyond the scope of this study, including whether the woman needs long-term hormone treatment. Some clinicians advise women not to conceive within 2 years of diagnosis, when the risk of relapse is highest, to reduce the risk of needing more cancer treatment during pregnancy. Others may not have time to wait, because treatments like alkylating chemotherapy can accelerate ovarian aging.[27] Women diagnosed at older ages have to decide whether the risks of declining fertility with time outweigh the potential risks of a short interval between treatment and conception. In this population, survivors who postponed conception for 1 year after starting chemotherapy without radiation, 2 years after starting chemotherapy with radiation, and 1 year after cervical cancer diagnosis had the lowest risks of preterm birth. Although additional studies are needed to confirm our results, this evidence can help guide clinicians in counseling women who are diagnosed with cancer during their reproductive years.

FUNDING SUPPORT

This study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant 1R01HD066059); a Reproductive, Perinatal, and Pediatric training grant (T32HD052460); and the Achievement Rewards for College Scientists (ARCS) Foundation.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Kathleen P. Hartnett: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, and writing–original draft. **Michael R. Kramer:** Conceptualization, methodology, and writing–review and editing. **Timothy L. Lash:** Conceptualization, methodology, and writing–review and editing. **Ann C. Mertens:** Conceptualization, methodology, and writing–review and editing. **Jessica B. Spencer:** Conceptualization, methodology, and writing–review and editing. **Kevin C. Ward:** Data curation, methodology, software, resources, and writing–review and editing. **Penelope P. Howards:** Conceptualization, funding acquisition, methodology, supervision, and writing–review and editing.

REFERENCES

1. Cancer.Net, American Society of Clinical Oncology. Having a Baby After Cancer: Pregnancy. Alexandria, VA: American Society of Clinical Oncology; 2018. Available at: https://www.cancer.net/survivorship/life-after-cancer/having-baby-after-cancer-pregnancy. Accessed January 8, 2018.
2. American Cancer Society. How Cancer Treatments Can Affect Fertility in Women: Chemo and Pregnancy. Atlanta, GA: American Cancer Society; 2018. Available at: https://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/sexualsideeffectsinwomen/fertilityandwomenwithcancer/fertility-and-women-with-cancer-how-cancer-treatments-affect-fertility. Accessed January 8, 2018.
3. National Comprehensive Cancer Network. Pregnancy After Cancer. Fort Washington, PA: National Comprehensive Cancer Network; 2018. Available at: https://www.nccn.org/patients/resources/life_after_cancer/pregnancy.aspx. Accessed January 8, 2018.
4. Azim HA Jr, Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer*. 2011;47:74-83.
5. Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv*. 2010;65:786-793.
6. Madanat-Harjuoja LM, Malila N, Lahteenmaki PM, Boice JD Jr, Gissler M, Dyba T. Preterm delivery among female survivors of childhood, adolescent and young adulthood cancer. *Int J Cancer*. 2010;127:1669-1679.
7. Stensheim H, Klungsoyr K, Skjaerven R, Grotmol T, Fossa SD. Birth outcomes among offspring of adult cancer survivors: a population-based study. *Int J Cancer*. 2013;133:2696-2705.

8. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. *Fertil Steril*. 2016;106:1195-1211, e1195.
9. Himes KP, Simhan HN. Time from cervical conization to pregnancy and preterm birth. *Obstet Gynecol*. 2007;109:314-319.
10. Ortoft G, Henriksen T, Hansen E, Petersen L. After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy. *BJOG*. 2010;117:258-267.
11. Heinonen A, Gissler M, Riska A, Paavonen J, Tapper AM, Jakobsson M. Loop electrosurgical excision procedure and the risk for preterm delivery. *Obstet Gynecol*. 2013;121:1063-1068.
12. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21:1081-1125.
13. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules, Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167-1214.
14. Adamo M, Dickie L, Rhul J. SEER Program Coding and Staging Manual 2015. Bethesda, MD: National Cancer Institute; 2015.
15. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference [serial online]. *BMC Pediatr*. 2003;3:6.
16. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer*. 2004;40:2293-2306.
17. Mackall CL. T-cell immunodeficiency following cytotoxic antineoplastic therapy: a review. *Stem Cells*. 2000;18:10-18.
18. Romero R, Espinoza J, Goncalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. *Semin Reprod Med*. 2007;25:21-39.
19. Allen LH. Anemia and iron deficiency: effects on pregnancy outcome. *Am J Clin Nutr*. 2000;71:1280S-1284S.
20. Hakim FT, Cepeda R, Kaimei S, et al. Constraints on CD4 recovery postchemotherapy in adults: thymic insufficiency and apoptotic decline of expanded peripheral CD4 cells. *Blood*. 1997;90:3789-3798.
21. Verma R, Foster RE, Horgan K, et al. Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer [serial online]. *Breast Cancer Res*. 2016;18:10.
22. Wiser I, Orr N, Kaufman B, et al. Immunosuppressive treatments reduce long-term immunity to smallpox among patients with breast cancer. *J Infect Dis*. 2010;201:1527-1534.
23. Dobie SA, Baldwin LM, Rosenblatt RA, Fordyce MA, Andrilla CH, Hart LG. How well do birth certificates describe the pregnancies they report? The Washington State experience with low-risk pregnancies. *Matern Child Health J*. 1998;2:145-154.
24. Vinikoor LC, Messer LC, Laraia BA, Kaufman JS. Reliability of variables on the North Carolina birth certificate: a comparison with directly queried values from a cohort study. *Paediatr Perinat Epidemiol*. 2010;24:102-112.
25. DiGiuseppe DL, Aron DC, Ranbom L, Harper DL, Rosenthal GE. Reliability of birth certificate data: a multi-hospital comparison to medical records information. *Matern Child Health J*. 2002;6:169-179.
26. Northam S, Knapp TR. The reliability and validity of birth certificates. *J Obstet Gynecol Neonatal Nurs*. 2006;35:3-12.
27. Anderson RA, Themmen AP, Al-Qahtani A, Groome NP, Cameron DA. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum Reprod*. 2006;21:2583-2592.