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A Population-Based Study of Pregnancy Outcomes in Female Cancer Survivors

By

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Doctor of Philosophy

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A Population-Based Study of Pregnancy Outcomes in Female Cancer Survivors

By

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M.P.H., Emory University, 2011
B.A., Emory University, 2000

Advisor: Penelope P. Howards, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
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Abstract

A Population-Based Study of Pregnancy Outcomes in Female Cancer Survivors
By Kathleen Chapman Hartnett

Although some cancer treatments reduce fertility, it is unclear whether they increase the risk of adverse pregnancy outcomes. The aims of this study were to examine whether cancer survivors have higher risks of preterm birth, fetal growth restriction, low birth weight, and pregnancy complications than women without a history of cancer, and whether these risks differ by cancer type, treatment, or timing of conception. Data from cancer registries was linked to pregnancy outcomes from birth certificates in three U.S. states. Analyses were limited to the first, live singleton birth conceived after diagnosis. Births to comparison women without a previous cancer diagnosis in the registry were matched on age at delivery, parity, race/ethnicity, and education. Infants born after cervical cancer had sharply higher risks of preterm birth than comparison women, with a 36% risk of delivery before 37 weeks in pregnancies conceived ≤1 year after diagnosis and 25% for >1 year. The risks of preterm birth were slightly higher among infants born to survivors of invasive breast cancer, but only in women who conceived ≤1 year after starting chemotherapy alone (RR=2.4, 95% CI: 1.4, 4.0) or ≤2 years after chemotherapy with radiation. We observed a higher risk of infants born small for gestational age in survivors of brain cancer and extranodal non-Hodgkin lymphoma. Thyroid cancer survivors had higher risks of gestational diabetes (RR=1.8, 95% CI: 1.2, 2.6) and possibly gestational hypertension, but not other adverse outcomes. We did not see an increased risk of adverse outcomes in pregnancies conceived after ductal carcinoma in situ, melanoma, nodal non-Hodgkin lymphoma, or Hodgkin lymphoma. This research supports the recommendation that women delay pregnancy for a year after starting chemotherapy for breast cancer and slightly longer if they receive both chemotherapy and radiation. Cervical cancer patients might also have better outcomes if they delay pregnancy, and thyroid cancer survivors may need closer monitoring gestational diabetes and hypertension. Given that chemotherapy might increase the risk of preterm birth through mechanisms including immunosuppression and anemia, future studies should focus on biomarkers that may better pinpoint when patients have recovered from treatment and can safely conceive.

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This study would not have been possible without the dedication of Kevin Ward, who helped me bring together vital records and cancer data, developed a linkage strategy, and consulted with his counterparts in other states to standardize methods. I am also thankful for Lyn Almon, who patiently answered all of my questions, doggedly worked through several iterations of the linking process, and generously gave her time to help collaborators in other states. I would also like to thank Rana Bayakly and Gordon Freyman at the Georgia Department of Public Health; Gary Leung, Soundarya Radhakrishnan, and Chandrika Rao at the North Carolina Central Cancer Registry; Matt Avery and Eleanor Howell at the North Carolina Center for Health Statistics; Martin Whiteside and Jake Richards at the Tennessee Cancer Registry; and Benjamin Crumpler at the Tennessee Office of Vital Statistics for their work on the data linkage.

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1. MOTIVATION AND AIMS

An estimated 356,000 women in the United States are survivors of cancers diagnosed between ages 20 and 39, a number that is projected to rise dramatically over the next decade due to advances in treatment.[1] Women who face a cancer diagnosis during their reproductive years say that after survival, the ability to have children is their most important concern.[2,3] However, the risk of adverse pregnancy outcomes after cancer treatment and the factors associated with poor birth outcomes in survivors are not fully understood. Many cancer patients are receiving recommendations from medical providers about how long to wait after treatment before attempting to conceive. Therefore, the goal of this study is to determine whether cancer treatment before pregnancy affects the risk of adverse pregnancy outcomes, and whether longer intervals between diagnosis or treatment are associated with lower risks of these outcomes. To address this gap in the literature, we linked live birth, fetal death, and infant death certificates to cancer diagnosis and treatment data from registries in Georgia, North Carolina, and Tennessee. For a subset of women who participated in a population-based study of reproductive outcomes in Georgia survivors, we have cancer diagnosis and treatment data abstracted from medical records. These data serve as a validation sub-study for the cancer treatment analyses, allowing us to quantitatively assess the potential for bias caused by under-ascertainment of treatment data in the registry.

Our specific aims are the following:

Aim 1: To assess whether different cancer types are associated with an increased risk of adverse pregnancy outcomes. Primary analyses will focus on the cancers that are most commonly diagnosed in reproductive-aged women: invasive breast cancer and ductal carcinoma in situ, cervical cancer, Hodgkin lymphoma, nodal and extranodal non-Hodgkin lymphoma, melanoma and thyroid cancer.

Aim 2: To assess whether different cancer treatments are associated with an increased risk of adverse pregnancy outcomes. Chemotherapy and radiation, identified based on first course of treatment recorded in the cancer registries, are the primary treatments of interest. As part of this aim, we will perform bias analyses to adjust for misclassified treatment information in the cancer registries using data from our validation sub-study, which has treatment data abstracted from medical records.

Aim 3: To determine whether the risks of adverse pregnancy outcomes differ by time since diagnosis or treatment and characterize pregnancy timing advice received by cancer patients. We will compare women's risks of adverse pregnancy outcomes by categorized time between diagnosis or treatment and conception, stratified by cancer and treatment type. For the subset of Georgia survivors who participated in a study evaluating reproductive health after cancer, we will describe women's responses to a telephone interview question asking how long they were told to wait before attempting to conceive.

Results from the proposed study will address critical gaps in knowledge on pregnancy outcomes after treatments for different cancers. These results will provide important evidence-based information for oncologists counseling cancer survivors who want to have children after cancer and for obstetricians who manage the care of pregnant survivors.

2. BACKGROUND

Advances in cancer treatment have led to a dramatic increase in the number of cancer survivors in the U.S. and worldwide. In 2012, 15% of all U.S. births were to women 35 or older, and there were almost as many births to 30 to 34 year-olds (26%) as 25 to 29 year-olds (28%).[5]

Many young women say that the potential loss of fertility due to cancer treatment is almost as painful as the diagnosis itself.[3,6] In one survey, 76% of women who were childless at

diagnosis said they wanted to have a child after cancer, and 60% said they would still want a child even if they died prematurely.[6] Women who cannot have children after treatment consistently report worse mental health than those who are able to give birth,[7,8] and female cancer patients say that they need more information from their doctors about childbearing after treatment.[9-11] In a recent survey of 249 U.S. oncologists, 86% would be willing to sacrifice less than a 5% reduction in disease-free survival if the treatment had better fertility outcomes, and 36% thought their patients would be willing to exchange more than a 5% reduction in survival for better fertility.[12]

Although the stress and uncertainty of cancer makes some women less likely to want children, some survivors say that a cancer diagnosis heightened the value that they place on family ties and parenthood.[2] In qualitative studies, many survivors say that pregnancy helped them to focus on a future after cancer.[2,13]

2.1 Possible effects of cancer treatment

Many treatments for cancer have been shown to reduce fertility, and also have the potential to result in adverse pregnancy outcomes. Alkylating agents for chemotherapy have been associated with temporary amenorrhea, and in some women, the onset of premature menopause,[14,15] with the extent of the injury to the ovaries depending on the agent, dose, length of treatment and age at treatment.[16] Many chemotherapy regimens also cause anemia[17] and immunosuppression,[18] both of which are associated with adverse pregnancy outcomes.[19,20] Some research has shown that radiation, especially to the pelvic region, may decrease vascularization of the uterus, resulting in reduced blood supply.[14,15] Fertility-sparing surgeries for cervical cancer such as conization and trachelectomy shorten the cervix, which can increase the risk of preterm birth due to both cervical insufficiency and infection.[21,22]

2.2 Studies in childhood cancer survivors

Studies in cohorts of childhood cancer survivors have found higher risks of adverse pregnancy outcomes after some diagnoses and treatments. In a population-based study of births to survivors of childhood and adolescent cancers, Mueller et al. found an increased risk of preterm birth in survivors of (aOR=1.5, 95% CI 1.3-1.8), compared to women with no cancer diagnosis. The study did not, however, find increased odds of having an infant born small for gestational age or of pregnancy complications such as pre-eclampsia.[23] This study, while large, did not stratify by diagnosis or treatment type.

Studies in cohorts of women diagnosed with cancer as children have consistently shown higher risks of adverse pregnancy outcomes after pelvic radiation. Studies have found higher risks of spontaneous abortion, neonatal death, preterm birth, fetal malposition, low birth weight, and infants born small for gestational age in pregnancies conceived after radiation to the pelvic field.[15,24] In the U.S. Childhood Cancer Survivor Study, half of the 46 childhood cancer survivors who received pelvic radiation at the highest doses (>500 Gy) delivered preterm.[25] Researchers using data from the same cohort observed a higher risk of hypertension in those received pelvic radiation for Wilms tumor,[26] and stillbirth and neonatal death among 28 women who received uterine and ovarian irradiation before age 21 with an adjusted odds ratio (aOR) of 9.1, (95% CI 3.4-24.6). The adjusted risk ratio (aRR) comparing survivors whose ovaries were in the radiation field to their female siblings were 1.9 for spontaneous abortion (95% CI 0.8-4.2) and 2.2 for low birth weight (95% CI 1.2-3.7). In a study of 7,300 pregnancies from the British Childhood Cancer Survivor Study, Reulen et al. found that women exposed to abdominal radiation had higher odds of preterm birth (aOR=3.2, 95% CI 2.1-4.7), low birth weight (aOR=1.9, 95% CI 1.1-3.2), and spontaneous abortion (aOR=1.4, 95% CI 1.0-1.9) than women in the general population of England and Wales[27].

However, the possible effects of chemotherapy exposure in childhood are less clear. In the U.S. survivors, Signorello et al.[28] found no association between perinatal death and treatment with alkylating chemotherapy (aOR= 0.9, 95% CI 0.5-1.5). In the British Childhood Cancer Survivor Study, Reulen et al. [27] found weak associations between adverse outcomes and chemotherapy. The aORs for pregnancy after chemotherapy in childhood, compared with the general population, were 1.2 for preterm birth (0.8-1.7), 1.3 for low birth weight (95% CI 0.8-2.2), and 1.2 for spontaneous abortion (95% CI 0.9-1.7). Among the U.S. survivors, Green et al.[29] estimated a higher risk of low birth weight in women who received non-alkylating agent chemotherapy (aRR=2.3, 95% CI 1.4-3.7) than their female siblings.

While the results of these studies provide important evidence about the possible effects of cancer treatment, they may not be generalizable to adults. One key difference is cancer type; young adults are more commonly diagnosed with breast, thyroid, and cervical cancers, which require different treatments. Thyroid and many breast cancer survivors require long-term hormonal treatment, and surgery for early stage cervical cancer may result in premature dilation and softening of the cervix. A second difference is that treatments such as chemotherapy may have transient effects that cause poor pregnancy outcomes only in those who conceive within months or a few years afterward.

2.3 Studies in adult cancer survivors

The largest studies in adult cancer survivors to date have been in Denmark,[30-32] Finland,[33,34] Norway,[35] Scotland,[36] Sweden,[37] and Florida [38], where researchers have linked vital records to cancer registry data (see Table 2.1 for study description and Table 2.2 for results). Of the eight population-based studies that analyzed preterm birth, five[33,35-38] estimated a weak association between previous cancer diagnosis and delivery before 37 weeks of gestation. Most of these studies appear to be underpowered to evaluate stillbirth, neonatal death or birth defects, with wide confidence intervals for these outcomes.

2.4 Pregnancy outcomes by treatment type

Most population-based studies of adult cancer survivors have not evaluated the effects of chemotherapy and radiation, although some estimated risks by cancer type. Unlike the studies in childhood cancer survivors, many of which were conducted in large long-term cohorts, studies among adult cancer survivors have been limited by a lack of medical records. Most compared all women with a history of cancer to women without cancer, which mixes the possible effects of radiation, chemotherapy, and reproductive surgeries. It is possible that certain treatments are driving the slightly increased odds of adverse pregnancy outcomes seen in the population-based studies, while other treatments have no effect on perinatal health. Among the population-based registry studies in Table 2.1, only the Finnish study[33] presented estimated effects stratified by treatment type. Of 21 women who received abdominal radiation in adulthood, three had preterm births, but the sample was too small to draw conclusions (aOR comparing to female siblings= 2.4, 95% CI 0.7–8.9). The study did find an increased odds of preterm birth in 155 women who received chemotherapy but no radiation, with an aOR of 2.4 (95% CI 1.5–4.1). In Denmark, Langagergaard et al.[30] reported similar odds of adverse pregnancy outcomes in Danish breast cancer survivors who received radiation and/or chemotherapy as those who received surgery alone, but did not include the ORs for individual treatment type.

Table 2.1. Overview of registry-linked studies on pregnancy outcomes after adult cancer diagnoses.

First Author Location, Year	Cancer types	N births post-cancer	Years of dx	Age at dx	Exposure	Outcomes
Clark Scotland, 2007	All	917	1980-2005	0-43	cancer diagnosis >10 months before birth	preterm birth, low birth weight, stillbirth, neonatal death, complications of labor and delivery, Apgar score, NICU admission
Dalberg Sweden, 2006	Breast	331	1973-2002	not given	invasive breast cancer during or before pregnancy	gestational age, mortality, birth weight, Apgar score, birth trauma, birth defects
Langagergaard Denmark, 2006	Breast	216	1943-2002, births since 1973	not given	breast cancer diagnosis before pregnancy	preterm birth, low birth weight at term, stillbirth, birth defects
Langagergaard Denmark, 2007	malignant melanoma	620	1943-2002; births since 1973	not given	malignant melanoma diagnosis before pregnancy	preterm birth, low birth weight at term, stillbirth, birth defects
Langagergaard Denmark, 2008	Hodgkin's lymphoma	192	1943-2002; births since 1973	not given	Hodgkin's lymphoma diagnosis before pregnancy	preterm birth, low birth weight at term, stillbirth, birth defects
Madanat-Harjuoja Finland, 2010	All	763	1953-2004	20-34	no radiotherapy, abdominopelvic radiation, cranial radiation, other radiotherapy; chemotherapy with and without surgery	preterm birth, low birth weight, small for gestational age
Madanat-Harjuoja Finland, 2013	All	2,417	1953-2004	20-34	cancer diagnosis >9 months before pregnancy	neonatal mortality, infant mortality, stillbirth, resuscitation, monitoring or NICU admission, birth asphyxia

Table 2.1. *Continued*

First Author Location, Year	Cancer types	N births post-cancer	Years of dx	Age at dx	Exposure (all compared with women with no cancer history)	Outcomes
Mogos Florida, 2013	breast, uterus, ovaries, cervix, fallopian tubes, vagina, vulva	3,212	1998-2007	not given	reproductive cancer diagnosis before or during pregnancy, and up to 30 days postpartum	preterm birth, low birth weight, and small for gestational age
Stensheim Norway, 2013	All	1,828	1967-2004	16-45	cancer diagnosis; sub-analyses that excluded melanoma	preterm birth, low birth weight, perinatal death, spontaneous abortion, pre-eclampsia, Apgar score, Cesarean delivery, birth defects

2.5 Pregnancy outcomes by cancer type

Although few of the studies outside Denmark analyzed risks separately by cancer type, Stensheim et al.[35] found the highest risks of preterm birth after cervical, ovarian, and brain tumors. Evidence from clinic-based studies support a high risk of preterm birth after fertility-sparing surgeries for cervical cancer.[39,40] In a compilation of all published data to date, Mogos et al.[40] found that nearly half of all births after surgery for cervical cancer were preterm. Although the sample size was extremely small, Madanat-Hurjuoja et al. reported a possible association between brain and central nervous system cancers and birth before 34 weeks gestation (OR=2.7, 95% CI: 1.0-6.9). For births before 37 weeks, however, the aOR was 1.3 (95% CI: 0.7-2.6).

2.6 Other limitations of existing research

Another limitation of the adult cancer survivor studies to date is that the population-based studies in small countries have included diagnoses dating back to the 1940s-1970s, when both cancer treatment and management of pregnancy were very different. Although most studies controlled for year of diagnosis or birth, the inclusion of previous generations could still result in different estimates than would be seen in a sample that limits diagnoses to the past 20 years. Interestingly, Dalberg et al.[37] found higher odds of malformations in births to Swedish cancer survivors after 1988, coinciding with an increase in the use of chemotherapy for young adult patients. The OR comparing the risk in births to cancer survivors to comparison births in 1988-2002 was 2.1 (95% CI: 1.2, 3.7), in contrast with an OR of 1.3 (95% CI: 0.7, 2.5) for births in 1973-1987. Control for complications of pregnancy in some adult cancer studies may also have affected the effect estimates. The studies in Finland[33] and Florida[38] controlled for complications of both pregnancy and delivery, which are likely to be the result of the exposure, rather than potential confounders. Because these complications are on the causal pathway between treatment and outcome, including them as covariates the model would likely bias the estimates.

Table 2.2. Results of registry-linked studies on adverse pregnancy outcomes after cancer.

	Comparison	Adj OR (95% CI)	Covariates*
Admitted to the neonatal intensive care unit			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.1 (0.9–1.3)	year of birth and maternal age
Antepartum hemorrhage			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.5 (0.9–2.6)	year of birth and maternal age
Birth defects			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.5 (0.9–2.5)	year of birth and maternal age
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	2.1 (1.2–3.7)	year of birth, maternal age, parity
Langagergaard Denmark, 2006	previous breast cancer vs. no previous breast cancer	0.9 (0.4–1.9)	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2007	previous malignant melanoma vs. no previous malignant melanoma	1.2 (0.8–1.8)	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2008	previous Hodgkin's disease vs. no previous Hodgkin's disease	1.7 (0.9–3.1)	year and month of birth, maternal age, parity, county
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	no births before dx: 0.99 (0.71-1.38) one birth before dx: 1.09 (0.69-1.70)	period of birth, maternal age, parity, maternal education
Birth trauma			
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	0.6 (0.3-1.3)	year of birth, maternal age, parity
C-section			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.2 (1.0–1.4)	year of birth and maternal age
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	1.3 (1.0-1.7)	year of birth, maternal age, parity

Table 2.2. *Continued*

	Comparison	Adj OR (95% CI)	Covariates*
Delivery complications			
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	1.5 (1.2-1.9)	year of birth, maternal age, parity
Early neonatal death (<7 days after birth)			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.4 (0.4–4.5)	year of birth and maternal age at delivery
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	1.8 (0.5-7.4)	year of birth, maternal age, parity
Madanat-Hurjuoja Finland, 2013	previous cancer diagnosis vs. female siblings without cancer	1.6 (0.8-3.3)	decade of birth, maternal age, child sex, birth order, previous history of neonatal death
Infant death (up to one year)			
Madanat-Hurjuoja Finland, 2013	previous cancer diagnosis vs. female siblings without cancer	1.2 (0.7–2.3)	decade of birth, maternal age, child sex, birth order, previous history of neonatal death
Instrumental vaginal delivery			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.2 (1.0–1.5)	year of birth and maternal age
Labor induction			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.0 (0.9–1.2)	year of birth and maternal age
Low Apgar score (<7 at 5 min)			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.5 (0.9–2.5)	year of birth and maternal age
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	1.4 (0.7-3.1)	year of birth, maternal age, parity
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	no births before dx: 0.8 (0.5–1.4) one birth before dx: 0.8 (0.3–1.9)	period of birth, maternal age, parity, maternal education

Table 2.2. *Continued*

	Comparison	Adj OR (95% CI)	Covariates*
Low birthweight			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.0 (0.8–1.4)	year of birth and maternal age
Dalberg, 2006 Sweden	previous invasive breast cancer vs. no previous invasive breast cancer	<1,500 g: 2.9 (1.4-5.8) 1,500-2,449 g: 1.0 (0.6-1.8)	year of birth, maternal age, parity
Madanat-Hurjuoja Finland, 2010	previous cancer dx vs. female siblings without cancer	1.0 (0.6–1.7)	year of birth, maternal age, child sex, maternal smoking, hypertension, placental problems, use of ART, malpresentation, C-section
Mogos, 2013 Florida	previous reproductive cancer dx vs. no previous reproductive cancer dx, stratified by race and ethnicity	white: 1.0 (0.8–1.2) black: 1.8 (1.4–2.4) Hispanic: 1.2 (0.9–1.7)	maternal age, parity, maternal education, marital status, prenatal care, tobacco use, alcohol use, drug abuse, anemia, gestational hypertension, pre-existing hypertension, gestational diabetes, diabetes mellitus, preeclampsia, placenta absorption, placenta previa, placenta accreta, period of birth, maternal age, parity, maternal education, complications
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	no births before dx: 1.3 (1.0–1.6) one birth before dx: 2.3 (1.7–3.2)	period of birth, maternal age, parity, maternal education
Low birth weight at term			
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	no births before dx: 1.1 (0.8–1.6) one birth before dx: 2.0 (1.2–3.6)	period of birth, maternal age, parity, maternal education

Table 2.2. *Continued*

	Comparison	Adj OR (95% CI)	Covariates*
Langagergaard Denmark, 2006	previous breast cancer vs. no previous breast cancer	1.2 (0.4–3.8)	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2007	previous malignant melanoma vs. no previous malignant melanoma	1.1 (0.6–2.0)	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2008	previous Hodgkin lymphoma vs. no previous Hodgkin lymphoma	0.6 (0.2–2.6)	year and month of birth, maternal age, parity, county
Malpresentation			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.1 (0.8–1.5)	year of birth and maternal age
Neonatal death (<28 days after birth, first week included)			
Madanat-Hurjuoja Finland, 2013	previous cancer diagnosis vs. female siblings without cancer	1.5 (0.7-3.5)	decade of birth, maternal age, child sex, birth order, previous history of neonatal death
Perinatal death (stillbirth from 22 weeks or death within 7 days of birth)			
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	no births before dx: 0.9 (0.5–1.8) one birth before dx: 1.9 (1.0–3.8)	period of birth, maternal age, parity, maternal education
Preterm birth			
Clark Scotland, 2007	previous cancer vs. no previous cancer	<37 weeks 1.3 (1.0–1.8) <34 weeks: 1.2 (0.9–2.2)	year of birth and maternal age
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	32-36 weeks: 1.5 (1.0-2.3) <32 weeks: 3.2 (1.7–6.0)	year of birth, maternal age, parity
Langagergaard Denmark, 2006	previous breast cancer vs. no previous breast cancer	<37 weeks: 1.3 (0.7–2.2)	year and month of birth, maternal age, parity, county

Table 2.2. *Continued*

	Comparison	Adj OR (95% CI)	Covariates*
Langagergaard Denmark, 2007	previous malignant melanoma vs. no previous malignant melanoma	<37 weeks: 1.1 (0.8–1.6)	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2008	previous Hodgkin's disease vs. no previous Hodgkin's disease	<37 weeks: 1.1 (0.6–2.0)	year and month of birth, maternal age, parity, county
Madanat-Hurjuoja Finland, 2010	previous cancer dx vs. female siblings without cancer	<37 weeks: 1.4 (1.0–1.9) <34 weeks: 1.5 (0.9–2.7)	year of birth, maternal age, child sex, maternal smoking, hypertension, placental problems, use of ART, malpresentation, C-section
Mogos Florida, 2013	previous reproductive cancer dx vs. no previous reproductive cancer dx, stratified by race and ethnicity	white: 1.2 (1.0–1.4) black: 1.5 (1.1–1.9) Hispanic: 1.3 (0.9–1.7)	maternal age, parity, maternal education, marital status, prenatal care, tobacco use, alcohol use, drug abuse, anemia, gestational hypertension, pre-existing hypertension, gestational diabetes, diabetes mellitus, preeclampsia, placenta absorption, placenta previa, placenta accreta, period of birth, maternal age, parity, maternal education, complications
Stensheim Norway, 2013	previous cancer diagnosis vs. no previous cancer diagnosis	<37 weeks no births before dx: 1.3 (1.1–1.6) one birth before dx: 1.9 (1.4–2.6) <32 weeks no births before dx: 1.3 (0.8-2.2) one birth before dx: 3.0 (1.7-5.4)	period of birth, maternal age, parity, maternal education

Table 2.2. *Continued*

	Comparison	Adj OR (95% CI)	Covariates*
Preterm premature rupture of membranes			
Clark Scotland, 2007	previous cancer vs. no previous cancer	1.4 (1.0–2.0)	year of birth and maternal age
Small for gestational age			
Madanat-Hurjuoja Finland, 2010	previous cancer dx vs. female siblings without cancer	0.9 (0.5-1.4)	year of birth, maternal age, child sex, maternal smoking, hypertension, placental problems, use of ART, malpresentation, C-section
Mogos Florida, 2013	previous reproductive cancer dx vs. no previous reproductive cancer dx, stratified by race and ethnicity	white: 0.9 (0.8–1.1) black: 1.6 (1.2–2.2) Hispanic: 1.0 (0.7–1.4)	maternal age, parity, maternal education, marital status, prenatal care, tobacco use, alcohol use, drug abuse, anemia, gestational hypertension, pre-existing hypertension, gestational diabetes, diabetes mellitus, preeclampsia, placenta absorption, placenta previa, placenta accreta, complications
Stillbirth			
Clark Scotland, 2007	previous cancer vs. no previous cancer	0.9 (0.3–2.1)	year of birth and maternal age
Dalberg Sweden, 2006	previous invasive breast cancer vs. no previous invasive breast cancer	1.2 (0.3-4.7)	year of birth, maternal age, parity
Langagergaard Denmark, 2006	previous breast cancer vs. no previous breast cancer	no stillbirths among 216 breast cancer survivors	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2007	previous malignant melanoma vs. no previous malignant melanoma	no stillbirths among 620 melanoma survivors	year and month of birth, maternal age, parity, county
Langagergaard Denmark, 2008	previous Hodgkin's disease vs. no previous Hodgkin's disease	defined as death >28 weeks gestation: 2.0 (0.3–15.4)	year and month of birth, maternal age, parity, county

2.7 Possible disparities by race in pregnancy outcomes after cancer

Nearly all of the previous studies on pregnancy after cancer have been conducted in mostly white, European populations. But the risks for African-American women may differ. African-American women have higher baseline risks of many adverse pregnancy outcomes, including preterm birth (in 2012, 16% vs. 11% for white women), low birth weight (13% vs. 7% for white women)[5] and stillbirth (1 in 93 births vs. 1 in 203 for white women).[41] At every stage of breast cancer diagnosis, African-American women have lower survival rates than white women. The reasons for the differences are complex, but may be the result of lower access to care, socio-economic status, and/or biological differences in their cancer types.[42]

In a registry-based study in Florida, Mogos et al.[38] reported an interaction between African-American race and birth outcomes in women diagnosed with cancer before or during pregnancy, and up to 30 days postpartum (Table 2.2). Compared with African-American women not diagnosed with cancer, African-American cancer survivors had higher odds of preterm birth, low birth weight, and infants born small for gestational age. In contrast, the aORs comparing white survivors to white women without cancer were null for low birth weight and small for gestational age, with a weaker association for preterm birth (aOR=1.2, 95% CI 1.0-1.4). The confidence intervals for the association of previous cancer and adverse pregnancy outcome for white and African-American women overlapped with each other for preterm birth, but not for low birth weight or small for gestational age. The authors did not separate cancers diagnosed before pregnancy from those during pregnancy and postpartum, so the estimated effects include these different exposures.

2.8 Pregnancy timing after cancer

Until recent years, there was a concern that the hormonal fluctuations of pregnancy and the postpartum period could cause hormonally-sensitive cancers, such as breast and thyroid, to recur. But to date, more than a dozen studies have agreed that pregnancy after cancer treatment

does not shorten disease-free or overall survival, and may actually improve a woman's prognosis. In a 2011 meta-analysis of 14 studies,[43] eight showed a survival advantage among women who were pregnant after cancer, and the other six had a trend favoring pregnancy. Although all studies to date have been small, none have supported a maternal survival advantage for women who postpone pregnancy after cancer. In a review, Valachis et al.[44] cited three older studies that saw no difference in survival time among women who conceived soon after breast cancer diagnosis, compared to those who waited.[45-47] Although studies assessing the safety of pregnancy after thyroid cancer are small, they similarly have found no increased risk of relapse or progression in survivors who have children.[48,49]

However, the question of when to have a child after cancer remains complex, and depends on the woman's risk of recurrence, health and readiness for a child, and her partner's wishes. Below are the current recommendations for patients posted on the web sites of U.S. cancer organizations:

American Society of Clinical Oncology[50]

"In general, becoming pregnant after cancer treatment is considered safe for both the mother and the baby, and pregnancy does not appear to raise the risk of cancer recurring. However, women may still be advised to wait a number of years before trying to become pregnant. The amount of time depends on the type and stage of cancer, the type of treatment the woman received, and the woman's age and preferences.

Some doctors recommend that women not get pregnant within the first six months after finishing chemotherapy because any eggs that may have been damaged by treatment are thought to leave the body within this time period. Other doctors recommend waiting at least two to five years because that is the window of time in which a cancer is most likely to recur and/or the time

needed to receive optimal treatment for some types of cancer, such as hormone-sensitive breast cancer."

American Cancer Society[51]

"It can harm the baby if you get pregnant too soon after chemo: Women are often advised not to get pregnant within the first 6 months after chemo because the medicine may have damaged the eggs that were maturing during treatment. If a damaged egg is fertilized, the embryo could miscarry or develop into a baby with a genetic problem. Studies about this are hard to find. This is something you should talk to your doctor about before trying to become pregnant.

Many studies have found that babies conceive after cancer treatment don't have birth defects or health problems any more often than babies whose parent didn't have cancer. But problems are more likely if a baby is conceived soon after cancer treatment, so it's important to know how long to wait before trying to have a baby."

MD Anderson Cancer Center[52]

"It is important to know that you should prevent pregnancy during chemotherapy or radiation treatment and for at least six months after treatment. Although cancer treatment may lower a man's sperm count or cause a woman's menstrual period to stop, a pregnancy may still be possible. Talk to your doctor or nurse about the best method of birth control for you.

…

By six to 12 months after cancer treatment, the sperm that were exposed to chemotherapy or radiation have all been ejaculated. Eggs that are healthy enough to be ovulated are also more likely to be undamaged. In fact, both the eggs and the stem cells that produce sperm have some ability to repair genetic damage during the first several years after cancer treatment. However, genetic damage is common in human embryos, even when neither parent has had cancer

treatment. A third of very early pregnancies miscarry because the embryo had genetic damage, often without a woman's ever realizing she was pregnant."

National Comprehensive Cancer Network[53]

"Although there are no official guidelines determining the length of time to wait after cancer treatment before attempting pregnancy, clinical nurse specialist Joanne Frankel Kelvin, RN, MSN, AOCN, of Memorial Sloan Kettering Cancer Center in New York, who established a program called Cancer and Fertility, says it is generally recommended to wait at least one year. "There are generally three factors for a woman to consider. These include making sure that (1) eggs that have been exposed to chemotherapy or radiation and may have been damaged are no longer in her body, (2) she is fully recovered from her treatment and its effects, and (3) she has been 'cleared' by her oncologist because an acceptable period of time has passed in which she is not likely to have a recurrence."

Thus, the factors that clinicians consider in counseling cancer patients on pregnancy timing include 1) the risk that a woman will recur during pregnancy, when cancer may be more difficult to diagnose[54-56] and more complicated to treat;[57-59] 2) whether the woman is receiving long-term hormonal treatment such as Tamoxifen that is contraindicated during pregnancy;[60] 3) whether the woman is at high risk of not being able to conceive if she postpones pregnancy, because many cancer patients are diagnosed after age 35, when fertility and fecundity are in rapid decline,[61] and some cancer treatments can accelerate ovarian aging;[62-65] and 4) whether waiting to conceive may affect her risk of an adverse pregnancy outcome.

2.9 Biological hypotheses underlying the current pregnancy timing recommendations

Some recommendations to postpone pregnancy are rooted in the biological hypothesis that oocytes are most subject to damage from certain chemotherapeutic agents during the six-

month period of rapid growth prior to ovulation. There is some evidence from in vivo[66] and in vitro[67] studies that follicles in the growth stage prior to ovulation may be targets of chemotherapy, which kills rapidly-dividing cells. In a study of rats, Meirow et al.[63] found that rats had higher proportions of failed pregnancies if mated one week after injection with the chemotherapy agent cyclophosphamide, whereas by two weeks after injection, the risks were similar to controls. The malformation rates were highest in rats mated within four weeks of cyclophosphamide injection but declined to the same proportions as controls by 12 weeks after treatment.

If ovarian follicles are most sensitive to chemotherapy during this period of rapid growth and somatic cell division, there could be a biologic basis to postpone conception until the damaged oocytes have been ovulated. For this reason, some studies[14] have recommended that breast cancer patients wait 6 months after completing chemotherapy, endocrine therapy, or targeted therapy before attempting to conceive. However, this hypothesis that developing oocytes, but not primordial follicles, are damaged by chemotherapy has not been evaluated in epidemiologic studies. None have specifically examined whether women who conceive within 6 months of chemotherapy treatment are at higher risk for adverse pregnancy outcomes such as spontaneous abortion, chromosomal abnormalities, or birth defects.

2.10 Previous studies analyzing pregnancy outcomes by time since diagnosis

In the registry-linked study from Norway, Stensheim et al. [35] concluded that most aORs comparing adverse pregnancy outcomes in women who delivered within two years of diagnosis with outcomes in women who did not have cancer were similar to aORs comparing all cancer survivors to women without cancer. However, the authors only presented data for the one outcome that was dissimilar: a slightly higher point estimate for the odds of perinatal death in births to women who had exactly one birth before cancer and then delivered again within two years of diagnosis, compared with women of the same parity but no cancer (Table 2.3). However, due to the wide confidence interval, this aOR of 3.1 (95% CI 1.2-8.5) in women who conceived

quickly does not appear meaningfully different than the aOR of 1.9 (95% CI: 1.0-3.8) comparing the odds of perinatal death in all survivors with women of the same parity but no cancer.

In a similar study using registry-linked data from Finland, Madanat-Hurjuoja et al. evaluated whether the risks of preterm birth (<37 and <34 weeks) and low birth weight were higher in women who delivered 10 or more years after any cancer diagnosis [33]. There did appear to be higher odds of preterm birth <37 weeks and possibly low birth weight among women who delivered 10 years or more after diagnosis than in women who delivered within 10 years, controlling for maternal age and other risk factors (Table 2.3). However, this higher risk may be due to underlying differences such as reproductive problems or residual confounding by age in the small number of women who conceive long after diagnosis. Many of the conditions that cause infertility, including endometriosis, polycystic ovary syndrome (PCOS) and large fibroids have also been associated with adverse pregnancy outcomes, including preterm birth.[68-70]

2.11 Pregnancy timing after cervical cancer

The loop electrosurgical excision procedure (LEEP) is performed after an abnormal Pap smear to remove abnormal cervical tissue. Only some of the women who have undergone a LEEP procedure are cancer survivors; others have small, pre-cancerous lesions that have not invaded the surrounding tissue.

Studies on whether the timing of pregnancy after these procedures might affect perinatal outcomes have yielded mixed results.[71-73] In a multicenter cohort study of 596 U.S. women who underwent LEEP procedures between 1996 and 2006, Conner et al. found a higher risk of spontaneous abortion in women who conceived within 12 months. Compared with a LEEP-to-pregnancy interval of at least 12 months, a time interval of less than 12 months was associated with an increased risk of spontaneous abortion (17.9% compared with 4.6%; OR=5.6; 95% CI:2.5-12.7) and possibly preterm birth (Table 2.3). Women who conceived within 12 months of the procedure were slightly younger (mean age 26.6 ± 5.4 sd vs. 28.3 ± 5.0 sd) and thinner (mean

BMI=29.5 ± 6.2 vs. 31.7 ± 6.7) than women with an interval of 12 months, but the two groups did not differ on parity, race, smoking, or previous history of preterm birth.

Himes et al. examined pregnancy outcomes after conization using either LEEP or the large loop excision of the transformation zone (LLETZ) procedure.[73] The study included 111 women who were treated and subsequently delivered in the University of Pittsburgh hospital system. Among the five women who had preterm births, the mean time from conization to conception was 2.5 months, compared to 10.5 months for the 111 women who had term births.

Heinonen et al. briefly mentioned timing of pregnancy in a study of 20,011 women who underwent LEEP procedures in Finland.[72] The study, which linked the national hospital register to vital records, found higher odds of preterm birth (<37 weeks) in 5,114 women who had a LEEP procedure before a singleton pregnancy than in women without a previous LEEP procedure (aOR=1.7, 95% CI=1.5–1.9). The authors reported that time interval since LEEP was not associated with outcome (OR=0.98, 95% CI 0.96-1.00), but did not describe the comparison or referent, how time interval was classified, or whether other variables were included in this model. In this study, 7.2 percent of pregnancies after LEEP resulted in preterm birth, higher than the Finnish general population but lower than in the general U.S population.

2.12 Pregnancy timing after thyroid cancer

Most women with thyroid cancer undergo a complete thyroidectomy and thus require lifelong supplementation with thyroid replacement hormones. Optimal levels of thyroid hormone are critical during pregnancy, and studies have found hypothyroidism during pregnancy to be associated with spontaneous abortion, preterm birth, placental abruption, and pre-eclampsia.[74-76] Thus, clinicians typically advise thyroid cancer patients to wait 6-12 months before conceiving so that they have time to establish the optimal dose of levothyroxine before women become pregnant.[77] In a small study cited to support the American Thyroid Association recommendation

to wait 6-12 months before conceiving,[78] 4 out of 10 thyroid cancer patients treated with radioactive iodine in the year before conception had spontaneous abortions.[79]

2.13 Relevance and implications of the current study

Thus, there is not enough evidence about the individual effects of chemotherapy, radiation and certain surgeries on pregnancy after cancer diagnosed in adulthood, or the optimal timing of pregnancy after diagnosis. Studies have not found higher risks of cancer recurrence in women who get pregnant soon after cancer, but there is limited evidence on whether the timing of conception affects pregnancy outcomes. This large population-based study of pregnancy after adult cancer diagnosis is one of the only studies to include a large number of African-American women, who have a higher risk of aggressive breast cancers and a higher baseline risk of adverse pregnancy outcomes after cancer. It is also the first to include validation data from medical records for a subset of women, allowing us to assess whether under-ascertainment of treatment in cancer registries could bias the study. The results will provide evidence on whether women treated for cancer during their reproductive years need closer monitoring during pregnancy and will inform recommendations on pregnancy timing for survivors who want to have children after cancer.

Table 2.3. Results from three studies assessing whether timing of pregnancy after cancer diagnosis or a procedure to remove abnormal cervical tissue are associated with adverse pregnancy outcomes.

First Author, Year Location, N births	**Adjusted Odds Ratio (95% CI)**	
Stensheim, 2013 Norway, N=632 first births after cancer diagnosis to women with exactly one birth before cancer diagnosis	**Diagnosis to delivery <2 year vs. births to women with same parity and no cancer**	**All first births after cancer vs. births to women with same parity and no cancer**
perinatal death	3.1 (1.2–8.5)	1.9 (1.0–3.8)
preterm birth (<37 weeks)	No difference found; data not shown	1.9 (1.4–2.6)
very preterm birth (<32 weeks)		3.0 (1.7-5.4)
low birth weight (<2,500 g)		2.3 (1.7–3.2)
low birth weight at term		2.0 (1.2–3.6)
low Apgar score (<7 at 5 min)		1.1 (0.8–1.8)
major congenital anomalies		0.8 (0.3–1.9)
Cesarean delivery		1.8 (1.4–2.2)
pre-eclampsia		1.6 (1.0–2.4)
Covariates: maternal age, period of birth, maternal education		
N=1,196 first births after cancer diagnosis to women with no births before cancer diagnosis	**Diagnosis to delivery <2 years vs. no cancer**	**All first births after cancer vs. no cancer**
perinatal death	No difference found; data not shown	0.9 (0.5–1.8)
preterm birth (<37 weeks)		1.3 (1.1–1.6)
very preterm birth (<32 weeks)		1.3 (0.8-2.2)
low birth weight (<2,500 g)		1.3 (1.0–1.6)
low birth weight at term		1.2 (0.8–1.7)
low Apgar score (<7 at 5 min)		0.8 (0.5–1.4)
major congenital anomalies		1.0 (0.7–1.4)
Cesarean delivery		1.0 (0.9–1.2)
pre-eclampsia		1.0 (0.8–1.3)
Covariates: maternal age, period of birth, maternal education		
	All cancers	
Madanat-Hurjuoja, 2010 Finland, N=763	**Diagnosis to delivery <10 years vs. no cancer**	**Diagnosis to delivery ≥10 years vs. no cancer**
preterm delivery (<37 weeks)	1.3 (0.9–1.7)	2.7 (1.3–5.6)
preterm delivery (<34 weeks)	1.6 (0.9–2.9)	0.7 (0.1–5.6)
low birth weight	0.9 (0.5–1.6)	2.1 (0.7–6.1)
Covariates: maternal age, delivery year, child sex, maternal smoking, hypertension, placental problems, use of ART, malpresentation and Cesarean delivery		

Table 2.3. *Continued*

Conner, 2013 United States, N=596	**Interval from loop electrosurgical excision procedure (LEEP) for cervical dysplasia to conception <12 months vs. >=12 months**
spontaneous abortion <20 weeks gestation	5.6 (2.5-12.7)
spontaneous abortion <12 weeks gestation	7.3 (3.1-17.1)
preterm birth (<37 weeks gestation)	1.5 (0.7-3.1)
preterm birth (<34 weeks gestation)	1.8 (0.7-4.5)
Covariate: maternal age	

3. AIM 1: THE RISK OF PRETERM BIRTH AND FETAL GROWTH RESTRICTION IN PREGNANCY AFTER CANCER

3.1 Manuscript information

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Key words: cancer survivor, pregnancy, birth outcome

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Abbreviations: RR: risk ratio, CI: confidence interval, OR: odds ratio, DCIS: ductal carcinoma in situ, NHL: non-Hodgkin lymphoma, LBW: low birth weight, VLBW: very low birth weight, SGA: small for gestational age, NICU: neonatal intensive care unit

Additional Supporting Information may be found in the online version of this article.

Article Category: Cancer Epidemiology

Novelty and Impact: In the first pregnancy conceived after diagnosis, cervical cancer survivors had a preterm birth risk three times higher than women without a cancer history. Breast cancer survivors had a slightly higher risk of preterm birth than comparison women. Survivors of extranodal NHL and brain cancer had higher risks of infants born small for gestational age. We observed an increased risk of gestational diabetes in thyroid cancer survivors, although this outcome is underreported in vital records.

3.2 Abstract

It is unclear whether cancer and its treatments increase the risk of adverse pregnancy outcomes. Our aim was to examine whether cancer survivors have higher risks of preterm birth and fetal growth restriction than women without cancer, and whether risks differ by cancer type and race. Diagnosis data from cancer registries was linked to pregnancy outcomes from birth certificates in three U.S. states. Analyses were limited to the first, live singleton birth conceived after diagnosis. Births to women without a previous cancer diagnosis in the registry were matched to cancer survivors on age at delivery, parity, race/ethnicity, and education. Log-binomial regression was used to estimate risk ratios. Cervical cancer survivors had higher risks of preterm birth (Risk Ratio=2.8, 95% Confidence Interval 2.1, 3.7), as did survivors of invasive breast cancer (RR=1.3, 95% CI 1.1, 1.7) and leukemia (RR=2.0, 95% CI 1.2-3.3). We observed a higher risk of small for gestational age (SGA) infants (<10% of weight for age based on a national distribution) in survivors of brain cancer (RR=1.7, 95% CI 1.1-2.8) and extranodal non-Hodgkin lymphoma (RR=2.4, 95% CI 1.6, 3.7). Thyroid cancer survivors had higher estimated risks of gestational diabetes (RR=1.8, 95% CI 1.2, 2.6) and possibly gestational hypertension. We did not see an increased risk of infants born preterm, low birth weight, or SGA in pregnancies conceived after ductal carcinoma in situ, thyroid cancer, melanoma, Hodgkin lymphoma, or nodal non-Hodgkin lymphoma. While our results are reassuring for survivors of many cancers, some will need closer monitoring during pregnancy.

3.3 Introduction

Advances in cancer treatment and screening have led to a dramatic increase in the number of cancer survivors.[4] At the same time, maternal age at first birth has steadily increased, meaning that a growing number of women have not achieved their desired family size at the time of cancer diagnosis.[5] Women diagnosed with cancer during their reproductive years say that, after survival, pregnancy is their most important concern, with an estimated 56-70% of patients aged 40 or younger wanting children after cancer.[3,65,80] Although there is growing evidence from fertility studies that some cancer treatments can damage the female reproductive system, less is known about pregnancy outcomes in the many women who are able to conceive after cancer.

Preterm birth is a leading cause of neonatal mortality worldwide, and infants born early are at higher risk of lifelong effects including cerebral palsy, developmental disabilities, and sensory impairment.[81] In the United States, 10% of live births are preterm (<37 weeks gestation) and 8% are low birth weight (<2,500g). The risks are higher among African-American women, who have a 13% risk of preterm delivery and of low birth weight.[82]

Several population-based studies in Europe have found a higher risk of preterm birth in pregnancies conceived after cancer.[33,35,36] However, few of these studies were powered to stratify by cancer type. Grouping different cancers may obscure risks specific to each diagnosis. Only one population-based study, limited to reproductive cancers, has been able to calculate risks specific to African-American women.[38]

The aim of this study was to determine whether risks of adverse pregnancy outcomes are higher in cancer survivors than women who have not had cancer, and how these risks may vary by cancer type and race.

3.4 Material and Methods

3.4.1 Study population

To identify births to women with a previous cancer history, cancer registry staff in three U.S. states linked cancer diagnosis data to vital records. Cancer registries in the states of Georgia, North Carolina, and Tennessee all used the same linking protocol, which was developed by the Georgia Cancer Registry and incorporated both deterministic and probabilistic methods (see Supplement). Women diagnosed with any reportable invasive cancer[83] or ductal carcinoma in situ (DCIS) between the ages of 20 and 45 were eligible. The study included cancers diagnosed August 23, 1993 to August 22, 2012 linked to births from 1994 to 2012 in Georgia (cancer diagnoses before 1999 were from metropolitan Atlanta only), cancers diagnosed August 23, 1999 to August 22, 2012 linked to births from 2000-2013 in North Carolina, and cancers diagnosed Jan. 1, 2004 to August 22, 2013 linked to births from May 20, 2004-2013 in Tennessee.

We identified the first pregnancy reaching 20 weeks that was conceived after a cancer diagnosis in each state. Although stillbirths were included to determine the first pregnancy after cancer, these deliveries were excluded from analysis because a high proportion of stillbirths had missing values for matching variables. Women diagnosed during pregnancy were excluded.

Live births from the same period were eligible for the comparison group if there was no record of cancer diagnosis in the state's registry during the years covered by the study. Comparison women were matched to cancer survivors within the same state on four primary confounders recorded on the birth certificate: 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 women of any ethnicity), parity (0, 1, 2, and ≥3), maternal education (college graduate yes or no). For the three most common cancers (invasive breast, melanoma, and thyroid) a random sample of comparison births were matched 5:1 to cancer survivor births. For cancer diagnoses with smaller sample sizes

(brain, cervical, DCIS, Hodgkin lymphoma, leukemia and both nodal and extranodal NHL), comparison women were matched 25:1 to decrease random error. For both cancer survivors and comparison women, we limited our analyses to singleton births between 20 and 44 weeks completed gestation, to mothers who were between the ages of 20 and 45 at the time of delivery.

3.4.2 Cancer Type

Cancer type was classified by primary site and histology, using site recode values from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

3.4.3 Outcomes

The primary analyses assessed whether cancer survivors were at higher risk of adverse outcomes recorded in vital records: preterm birth (<37 weeks gestation), very preterm birth (<32 weeks gestation), low birth weight (<2,500g), very low birth weight (<1,500g), low birth weight at term (<2,500g at ≥37 weeks gestation), and small for gestational age (SGA), defined as <10% of birth weight for gestational age and sex based on a national distribution.[84] A small number of infants with implausible combinations of birth weight and gestational age, based on the values used by Alexander et al.,[85] were excluded. Secondary outcomes included whether the mother had gestational hypertension, gestational diabetes, Cesarean section, and whether the infant had an Apgar score <7 at 5 minutes or was admitted to the neonatal intensive care unit.

3.4.4 Covariates

To identify potential confounders of the association between cancer diagnosis and adverse pregnancy outcomes, we used both the literature and bivariate associations in our data to inform a causal diagram. Based on the diagram, the variables available in vital records that we considered as potential confounders, in addition to the matching factors, included the mother's self-reported smoking during pregnancy and marital status. These variables were not included in

the final models, because after we matched on maternal age, race/ethnicity, parity, and education, adding these covariates to the model did not change our estimates of effect. Two measures of household income— women's eligibility for public health insurance through Medicaid and for food assistance from the Women, Infants, and Children (WIC) program— were available for all years in Tennessee, 2008-2012 in Georgia, and 2011-12 in North Carolina. Because these variables were only available for a subset of women, we conducted a sensitivity analysis to assess whether adding these measures of household income substantially changed the results. We also conducted a sensitivity analysis adding pre-pregnancy BMI to the model for breast cancer and preterm birth for cancer survivors in Tennessee.

3.4.5 Statistical methods

The study population was described using frequencies, proportions, and risks. Log-binomial models were used to estimate risk ratios. Separate models were fit for each cancer diagnosis and outcome, so that the risk ratio compares women with a specific cancer to women without a previous cancer diagnosis.

In stratified analyses, risk ratios and risk differences for breast, reproductive cancers, and thyroid cancers were calculated separately for white women and African-American women. Reproductive cancers were grouped in stratified analyses because there was insufficient sample size to estimate measures of effect for individual reproductive cancers. To assess whether the effects of cancer diagnosis differ by race, we estimated the interaction contrast (IC) using linear binomial regression. Interaction contrasts represent the risk difference for the estimated effect of cancer diagnosis among white women, subtracted from the risk difference among African-American women.

In all analyses, risk ratios are reported for pregnancy outcomes with $n \geq 10$ cancer survivors. Analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

3.5 Results

Among the 4,203 eligible women with a live birth conceived after cancer, the most common cancer types were melanoma (23%), thyroid cancer (23%), breast cancer (18%), Hodgkin lymphoma (7%), and cervical cancer (3%) (Appendix Table 3.A1). Women who gave birth after a cancer diagnosis were older, more educated, more likely to be married, and more likely to be having their first child than women without cancer who were eligible to be sampled for our matched comparison group (Table 3.1).

The characteristics of mothers at the first birth after a diagnosis differed by cancer type. Breast cancer survivors were older at the time of delivery than melanoma and cervical cancer survivors. In these three U.S. states, 35% of all breast cancer survivors, and 25% of both cervical and Hodgkin lymphoma survivors were African-American.

Infants born to survivors of certain cancers were at higher risk of low birth weight, due to being born preterm or small for gestational age (SGA). Births to women with a history of invasive breast cancer were more likely to be preterm (RR for delivery before 37 weeks=1.3, 95% CI: 1.1, 1.7) and very preterm (RR for delivery before 32 weeks=1.7, 95% CI: 1.0, 2.8) than those to matched comparison women (Table 3.2). Infants born to survivors of invasive breast cancer also had higher risks of other outcomes associated with prematurity (Tables 3.2 and 3.3), including low birth weight (RR for <2,500g=1.6, 95% CI: 1.3, 2.0), very low birth weight (RR for <1,500g=2.1, 95% CI: 1.3, 3.6), and 5-minute Apgar score below 7 (RR=1.8, 95% CI: 1.1, 2.9). The RR for NICU admission among infants born to breast cancer survivors was 1.5 (95% CI: 0.9, 2.6).

There was a high risk of preterm birth in cervical cancer survivors (Table 3.2), with 28% of live births delivered before 37 weeks (RR=2.8, 95% CI: 2.1, 3.7), and 10% delivered before 32 weeks (RR=5.4, 95% CI: 3.1, 9.6). Infants born to cervical cancer survivors also had higher risks of low birth weight (RR=2.8, 95% CI: 2.0, 4.0) and very low birth weight (RR=4.3, 95% CI: 2.3,

8.2) than infants born to matched comparison women, and were more likely to be delivered by C-section (RR=1.5, 95% CI: 1.3, 1.8).

Infants born to leukemia survivors were more likely to be preterm (RR=2.0, 95% CI: 1.2, 3.3). The RR comparing the risk of SGA births in leukemia patients to matched women was 1.4 (95% CI: 0.8, 2.6). There was a higher risk of SGA in infants born to brain cancer survivors than matched comparison women (RR=1.7, 95% CI: 1.1, 2.8), but only 1 infant out of 104 born to brain cancer survivors was small enough to be classified low birth weight at term (Table 3.2). Survivors of extranodal non-Hodgkin lymphoma had higher risks of infants born both SGA (RR=2.4, 95% CI: 1.6, 3.7) and low birth weight (RR=2.0, 95% CI: 1.1, 3.5).

Thyroid cancer survivors were more likely to be diagnosed with gestational diabetes than matched comparison women (RR=1.8, 95% CI: 1.2, 2.6). For gestational hypertension, the RR was 1.5 (95% CI: 0.9, 2.3). Thyroid cancer survivors did not have higher risks of other pregnancy complications or adverse outcomes (Tables 3.2 and 3.3). No other cancer type was associated with higher risks of gestational diabetes or hypertension.

Although risks of delivering by C-section were slightly higher for survivors of most cancers (Table 3.3), women diagnosed with DCIS, Hodgkin lymphoma, nodal non-Hodgkin lymphoma, and melanoma did not have a higher estimated risk of any other adverse outcome for their first live births after diagnosis than matched comparison women (Tables 3.2 and 3.3).

African-American cancer survivors were at higher overall risks for adverse pregnancy outcomes than white cancer survivors (Table 3.4). The disparity was starkest for thyroid cancer, where African-American survivors had a 17% risk (95% CI: 11%, 24%) of low birth weight in the first pregnancy conceived after diagnosis, compared with 5% (95% CI: 4%, 7%) in white survivors. But because African-American women also have much higher baseline risks of adverse outcomes, the excess risk attributable to breast and thyroid cancer was not meaningfully different for African-American women than white women. For all three pregnancy outcomes, the risk differences comparing white breast cancer survivors to white women without cancer were nearly

the same as the risk differences comparing African-American breast cancer survivors to African-American women without cancer (Interaction Contrast=0.02, 95% CI -0.04, 0.08 for preterm birth; 0.03, 95% CI -0.03, 0.09 for low birth weight, and 0.04, 95% CI -0.02, 0.09 for SGA). Interaction contrasts comparing risk differences in white and black women after thyroid cancer were similarly null. However, white women did have a higher risk of low birth weight after reproductive cancer than white women without cancer (14% after cancer vs. 5% in comparison women), while African-American women did not have an increase in risk associated with cancer (14% vs. 13%) (Table 3.4).

The results did not change substantially when we: 1) added BMI to the model for preterm birth in breast cancer survivors from Tennessee, 2) controlled for household income as measured by eligibility for public insurance through the Medicaid program, 3) controlled for household income as measured by eligibility for nutrition assistance through the WIC program, or 4) excluded women diagnosed with a more than one cancer before conception of the pregnancy.

3.6 Discussion

This large, multi-state, population-based study allowed us to analyze the risks of adverse pregnancy outcomes specific to the most common cancer types of young adulthood. We observed a high risk of preterm delivery in cervical cancer survivors, whose risks of preterm birth and low birth weight were three times higher than in women without a history of cancer. In infants born to breast cancer survivors, we saw a slightly higher risk of preterm birth than in women without cancer, and a moderately higher risk of low birth weight. Leukemia may be associated with elevated risks of both preterm birth and SGA, and diagnosis with brain cancer and extranodal non-Hodgkin lymphoma were associated with higher risks of having an infant born SGA. Thyroid cancer survivors in our study had higher risks of gestational diabetes and possibly gestational hypertension, but not of other adverse outcomes. Aside from slightly higher risks for delivery by

C-section, we did not see a higher risk of pregnancy complications or adverse outcomes after DCIS, Hodgkin lymphoma, nodal non-Hodgkin lymphoma, or melanoma.

Previous studies have found a slightly elevated risk of some adverse pregnancy outcomes in cancer survivors compared with women who have not had cancer, with odds ratios for preterm birth between 1.3 and 1.5.[33,35,36,38] When comparing all women with any previous cancer diagnosis to matched women without cancer, we see a similar overall association (RR=1.2, 95% CI: 1.1, 1.3). However, this study suggests that the increased risks are limited to certain cancers. Our results are consistent with population-based studies in Denmark that did not observe increased risks in women diagnosed with Hodgkin lymphoma[32] or melanoma.[31] Our estimated RR for preterm birth in breast cancer survivors was 1.3 (95% CI: 1.0, 1.6). A Danish study of births to breast cancer survivors between 1943 and 2002 had a similar result, although with a wider confidence interval reflecting that study's smaller sample size (OR=1.3, 95% CI: 0.7, 2.2). We similarly found higher risks of very preterm birth in survivors of invasive breast cancers (RR=1.7, 95% CI: 1.0, 2.8).

For breast and cervical cancer survivors, the higher number of low birth weight infants appears to be driven by prematurity rather than growth restriction. A study of survivors in Finland, which included cancers diagnosed in both childhood and adulthood, also reported increased odds of low birth weight and preterm birth in all cancer survivors, but no increased odds of infants born small for gestational age.[33] We observed higher risks of small for gestational age infants among survivors of extranodal non-Hodgkin lymphoma and brain cancer, but not in survivors of any other cancers.

To our knowledge, no other studies to date have examined gestational diabetes or hypertension in thyroid cancer survivors. However, several recent studies in women with normal thyroid function have found lower levels of the free thyroxine (T4) in the second and third trimesters of pregnancy associated with higher incidence and prevalence of gestational diabetes,[86-88] and one study found higher risks of gestational hypertension in hypothyroid

pregnancies.[89] Patients who have their thyroid removed after cancer diagnosis require supplementation with the hormone thyroxine to replace the function of the thyroid gland and might be at higher risk of these pregnancy complications if they do not sustain optimal thyroxine levels during pregnancy.

In this study, African-American survivors of breast, reproductive, and thyroid cancers had higher risks of adverse outcomes after cancer than white women. But these higher risks reflected the high baseline risks of adverse outcomes in African-American women, rather than a larger increase in risk after cancer diagnosis. Our observation of an increased risk of low birth weight risk after reproductive cancer among white women, but not among African-American women, is largely consistent with results from the only other paper examining risks by race.[38] However, for breast cancer, the study using linked records from Florida found higher risks of low birth weight after breast cancer in African-American women, but not in white women. In contrast, we observed nearly identical small increases in risk among women of both races. One key difference is that the Florida study included women diagnosed with cancer during the pregnancy or immediately after delivery (who thus may have had undetected cancer during the pregnancy), while our study was limited to pregnancies that began after diagnosis.

This study has important strengths, including its population-based design and large sample of African-American women. With more than 4,000 first births after cancer, our study is the largest of pregnancy outcomes in cancer survivors to date.

The quality of cancer diagnosis information in U.S. cancer registries is high, with a study finding 96% sensitivity for detection of cancer cases and a mean of 95% accuracy across 13 variables.[90] Although the quality of birth certificate data differs by variable and state, studies of U.S. vital records have consistently shown that the pregnancy outcomes of low birth weight, Apgar score, and delivery method, as well as all four matching factors (maternal age, race/ethnicity, parity, and education), have excellent agreement with both medical records and maternal self-report.[91-94] Preterm delivery from the obstetric estimate of gestational age has

generally good agreement with medical records,[92,95,96] although both birth certificates and medical records may misclassify preterm delivery, particularly in women who did not plan their pregnancies.[97] However, our observed association between thyroid cancer and gestational diabetes and possibly hypertension should be interpreted with caution, because both complications are underreported in vital records. Validation studies of vital records in U.S. states have found sensitivities ranging from 34% to 66% for gestational hypertension and 49% to 76% for gestational diabetes. Specificity for these outcomes is excellent, however, at 99% in three different states.[91,93,98]

One limitation of the study is that the U.S. does not have a national cancer registry, so cancer diagnosis information is specific to each state. Thus, to be correctly identified, a woman's first birth after cancer must have occurred in the same state as her diagnosis. Women who were diagnosed in one state and then gave birth in another state are missing from this analysis. We are also unable to correctly identify cancer survivors diagnosed before the years covered by the study. It is thus likely that we are missing a disproportionate number of survivors who had a long interval between diagnosis and the first birth after cancer, because these women are more likely to have been diagnosed in years before we have registry data and because they had more time to move to a different state before delivery. While having cancer data only from recent years is thus a limitation of the study, it is also a strength, because the survivors identified in our study all received modern cancer treatments. Previous population-based studies of pregnancy in cancer survivors included women diagnosed as long ago as the 1940s-1970s,[33,35,36] when both cancer treatment and obstetric management of pregnancy were very different.

Future studies should use medical records to verify our observation of increased risk of gestational diabetes and hypertension in thyroid cancer survivors, and use other data sources to examine other outcomes including early pregnancy losses, birth defects, and stillbirth. Future studies should also focus on risks after less common cancers that our sample size was not large enough to analyze. Our study suggests that survivors of some cancers need closer monitoring and

management in pregnancy. However, the results are reassuring for many survivors of cancer diagnosed in young adulthood; we did not observe an increased risk of adverse pregnancy outcomes after many cancer diagnoses.

3.7 Acknowledgments

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3.8 Supplement

Our protocol for linking cancer diagnoses from the cancer registry to pregnancy outcomes in vital records was developed by the Georgia Cancer Registry and applied uniformly

across all three states. The goal was to develop a linking strategy that limited the number of possible matches requiring manual review to a manageable number, while still allowing women's birth and cancer records to link with slight variations such as different spellings of the same name or transposition of digits in the Social Security number. The Georgia Cancer Registry developed a two-step method that first used a deterministic link to narrow the population to likely matches, then a probabilistic link that scored pairs of records on their likelihood of being a true match.

Cancer registry staff in each state used Link Plus, a record linkage program developed by the U.S. Centers for Disease Control and Prevention, to conduct the link. Registries were only able to link pregnancies to cancer records within their state. Thus, we could correctly identify a cancer survivor who delivered in Georgia and was diagnosed in Georgia, but not a woman who delivered in Georgia and was diagnosed in Tennessee.

Before the match, live birth and stillbirth files were concatenated into one file, which allowed us to identify all pregnancies that reached 20 weeks, whether or not it ended in live birth. For the initial deterministic step of the link, cancer registries assigned an identification number (ID) to each woman that took the format: first two letters of first name, first two letters of surname, last two letters of surname, and 8-digit date of birth. For example, the ID for a fictional woman named Ada Lovelace, born October 23, 1980, would be adloce10231980. Because we wanted to capture women who changed their surnames between the time of cancer diagnosis and birth, staff created two separate IDs for women who had more than one surname listed in vital records. For example, a woman with a married name of Ada Lovelace and family name of Ada Smith would be assigned two IDs: adloce10231980 and adsmth10231980.

In the first, deterministic step, we required women's vital record and cancer record to match exactly on either ID or Social Security number. Women whose records were an exact match on either of these two variables were retained for the second step, which was a probabilistic link. In the second step, the population was limited to women who matched in the first deterministic step. These women were then linked probabilistically on their date of birth,

Social Security number, first name, middle name, and all last names (family name in vital records to family name in cancer record, and married name in vital record to family name in cancer record).

Link Plus scores the probability that each linked pair is a true match. We accepted all pairs scored >=16 as true matches and rejected those with scores <7 or below. For matches with scores between 7 and 16, cancer registry staff did a manual review considering census tract, zip code, race, ethnicity, and for deceased women, date of last contact. For deceased women, if the date of last contact was before the before the birth or fetal death, the match was determined to be false.

Identifying data including names, Social Security numbers and geographic identifiers were removed before cancer registries released the data to for analysis.

3.9 Tables

Table 3.1. Characteristics of the first eligible live singleton birth to women ages 20-45 conceived after cancer diagnosis (N=4,203), for the most common cancer types and all cancers, compared with all eligible live, singleton births to women ages 20-45 without a previous diagnosis, using birth certificate data linked to cancer registries in Georgia, North Carolina, and Tennessee. Births missing data for the four matching variables (maternal age, race/ethnicity, education, and parity) have been removed.

	Breast		Cervix uteri		Hodgkin lymphoma		Melanoma		Thyroid		All Cancers		Comparison births	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preterm birth														
≥37 weeks gestation	644	85	94	72	264	90	896	91	869	90	3,712	88	3,642,000	90
<37 weeks gestation	110	15	37	28	29	9.9	85	8.7	101	10	491	12	389,349	9.7
Birth weight														
≥2,500g	658	87	103	79	274	94	927	95	906	93	3,831	91	3,752,452	93
1,500-<2,500g	72	9.5	18	14	17	5.8	41	4.2	48	5.0	284	6.8	227,305	5.6
<1,500g	24	3.2	10	7.6	2	0.7	9	0.9	15	1.7	88	2.1	51,592	1.3
Small for gestational age														
No	665	88	121	92	266	91	920	94	888	92	3,783	90	3,596,951	89
Yes	89	12	10	7.6	27	9.2	61	6.2	82	8.5	420	10	434,378	11
Maternal age at birth														
20-24	8	1.1	5	3.8	25	8.5	48	4.9	67	6.9	250	5.9	1,271,379	32
25-29	89	12	40	31	118	40	260	27	265	27	1,084	26	1,256,448	31
30-34	206	27	52	40	98	33	396	40	358	37	1,479	35	978,443	24
35-39	321	43	31	24	47	16	226	23	227	23	1,091	26	438,243	11
40-45	130	17	3	2.3	5	1.7	51	5.2	53	5.5	299	7.1	86,836	2.2
Maternal race and ethnicity														
White, non-Hispanic	419	56	92	70	201	67	959	98	729	75	3,074	73	2,333,454	58
African American, non-Hispanic	266	35	33	25	73	25	4	0.4	132	14	810	19	1,039,528	26
Asian, non-Hispanic	22	3	2	1.5	3	1.0	2	0.2	43	4.4	101	2.4	119,298	3.0
Native American, non-Hispanic	4	0.5	0	0.0	1	0.3	1	0.1	5	0.5	18	0.4	20,681	0.5
Pacific Islander, non-Hispanic	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	3	0.1	1,729	0.0
Multiracial, any ethnicity	17	2.3	1	0.8	5	1.7	6	0.6	18	1.9	69	1.6	127,706	3.2
Hispanic, any race	26	3.5	3	2.3	10	3.4	7	0.7	42	4.3	128	3.0	388,953	9.6

Table 3.1. *Continued*

	Breast		Cervix uteri		Hodgkin lymphoma		Melanoma		Thyroid		All Cancers		Comparison births	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Maternal education														
Less than high school	44	5.8	17	13	23	7.8	18	1.8	47	4.8	259	6.2	681,696	17
High school or GED	169	22	16	12	67	23	138	14	174	18	801	19	1,194,965	30
Some college or associate degree	193	26	39	30	95	32	270	28	325	34	1,278	30	1,100,788	27
At least 4 years of college	348	46	59	45	108	37	555	57	424	44	1,865	44	1,053,900	26
Parity														
0	283	38	61	47	127	43	497	51	380	39	1,825	43	1,459,220	36
1	248	33	43	33	95	32	305	31	319	33	1,313	31	1,391,980	35
2	124	16	15	12	52	18	134	14	175	18	677	16	726,821	18
3 or more	99	13	12	9.2	19	6.5	45	4.6	96	9.9	388	9.2	453,328	11
Smoking during pregnancy														
No	684	93	116	92	255	91	887	95	879	95	3,763	93	3,380,485	89
Yes	49	6.7	10	7.9	26	9.3	44	4.7	45	4.9	267	6.6	417,691	11
Missing	21	-	5	-	12	-	50	-	46	-	173	-	233,173	-
Mother married														
Yes	576	76	107	82	213	73	904	92	809	83	3,380	81	2,650,219	66
No	178	24	24	18	80	28	75	7.7	161	17	819	20	1,379,500	34

Table 3.2. Risk ratios for preterm birth, low birth weight (LBW) and small for gestational age (SGA) for the first live singleton birth conceived after diagnosis with each cancer, compared with births to matched comparison women without a previous cancer diagnosis.

Cancer	Total births	Preterm birth < 37 weeks		Preterm birth < 32 weeks		LBW (< 2,500g)		Very LBW (< 1,500g)		LBW at term		SGA	
		N	RR	N	RR	N	RR	N	RR	N	RR	N	RR
Brain	104	11	1.1 (0.6, 1.9)	1	-	7	-	2	-	1	-	16	1.7 (1.1, 2.8)
Breast, all	754	110	1.3 (1.1, 1.6)	22	1.5 (1.0, 2.5)	96	1.4 (1.2, 1.8)	24	1.8 (1.1, 2.8)	23	1.1 (0.7, 1.7)	89	1.1 (0.9, 1.3)
Breast, invasive (no DCIS)	598	94	1.3 (1.1, 1.7)	18	1.7 (1.0, 2.8)	82	1.6 (1.3, 2.0)	20	2.1 (1.3, 3.6)	21	1.4 (0.9, 2.2)	78	1.2 (0.9, 1.5)
Breast, DCIS only	156	16	0.9 (0.6, 1.5)	4	-	14	1.2 (0.7, 2.0)	4	-	2	-	11	0.7 (0.4, 1.3)
Cervix uteri	131	37	2.8 (2.1, 3.7)	13	5.4 (3.1, 9.6)	28	2.8 (2.0, 4.0)	10	4.3 (2.3, 8.2)	1	-	10	0.8 (0.4, 1.4)
Hodgkin lymphoma	293	29	1.1 (0.7, 1.5)	1	-	19	0.9 (0.6, 1.5)	2	-	4	-	27	1.0 (0.7, 1.4)
Leukemia	62	13	2.0 (1.2, 3.3)	3	-	9	-	2	-	1	-	10	1.4 (0.8, 2.6)
Melanoma	981	85	0.9 (0.8, 1.2)	15	1.7 (0.9, 3.0)	50	0.9 (0.7, 1.3)	9	-	14	0.9 (0.5, 1.5)	61	0.8 (0.6, 1.1)
Non-Hodgkin lymphoma, nodal	94	10	1.1 (0.6, 2.1)	3	-	9	-	2	-	2	-	5	-
Non-Hodgkin lymphoma, extranodal	65	7	-	1	-	11	2.0 (1.1, 3.5)	0	-	5	-	17	2.4 (1.6, 3.7)
Thyroid	970	101	1.0 (0.8, 1.2)	14	1.0 (0.6, 1.9)	64	1.0 (0.7, 1.3)	16	1.4 (0.8, 2.4)	19	0.9 (0.6, 1.5)	82	0.9 (0.7, 1.1)

**Risk Ratios are presented for all outcomes with N >= 10 in cancer survivors.*

**Comparison women without cancer were matched 5:1 to breast, melanoma, and thyroid cancer survivors and 25:1 to survivors of all other cancers on exact age at birth (single-year category), parity (0, 1, 2, 3+), race and ethnicity (Hispanic, non-Hispanic white, African American, Asian, Pacific Islander, Native American, and multiracial of any ethnicity), maternal education (college graduate yes or no), and state of residence (GA, NC, TN).*

Table 3.3. Risk ratios for pregnancy complications, admission to the neonatal intensive care unit (NICU), 5-minute Apgar score < 7, and Cesarean section for the first live singleton birth conceived after diagnosis with each cancer, compared with births to matched comparison women without a previous cancer diagnosis.

	Gestational hypertension		Gestational diabetes		Admission to NICU		Apgar score < 7 at 5 minutes		C-section	
Cancer	**N**	**RR**	**N**	**RR**	**N**	**RR**	**N**	**RR**	**N**	**RR**
Brain	1/34	-	1/34	-	2/34	-	4/103	-	40/104	1.2 (1.0, 1.6)
Breast, all	11/182	0.9 (0.5, 1.6)	18/182	1.2 (0.8, 1.9)	17/182	1.3 (0.8, 2.2)	26/751	1.7 (1.1, 2.7)	329/754	1.1 (1.0, 1.2)
Breast, invasive (no DCIS)	10/149	0.8 (0.4, 1.6)	14/149	1.3 (0.8, 2.3)	15/149	1.5 (0.9, 2.6)	22/595	1.8 (1.1, 2.9)	255/598	1.2 (1.0, 1.3)
Breast, DCIS only	1/33	-	4/33	-	2/33	-	4/156	-	74/156	1.2 (1.0, 1.4)
Cervix uteri	4/28	-	4/28	-	6/28	-	5/131	-	66/130	1.5 (1.3, 1.8)
Hodgkin lymphoma	4/90	-	3/90	-	3/90	-	3/293	-	108/293	1.1 (1.0, 1.3)
Leukemia	0/19	-	2/19	-	1/19	-	1/61	-	27/62	1.3 (1.0, 1.8)
Melanoma	16/240	1.2 (0.7, 2.1)	9/240	-	7/240	-	15/974	1.0 (0.6, 1.7)	345/977	1.1 (1.0, 1.2)
Non-Hodgkin lymphoma, nodal	2/29	-	2/29	-	1/29	-	5/95	-	35/95	1.1 (0.8, 1.4)
Non-Hodgkin lymphoma, extranodal	1/13	-	2/13	-	1/13	-	2/65	-	29/65	1.3 (1.0, 1.7)
Thyroid	25/313	1.5 (0.9, 2.3)	34/313	1.8 (1.2, 2.6)	18/313	0.9 (0.5, 1.4)	17/965	1.0 (0.6, 1.6)	340/969	1.1 (1.0, 1.2)

**Comparison women without cancer were matched 5:1 to breast, melanoma, and thyroid cancer survivors and 25:1 to survivors of all other cancers on exact age at birth (single-year category), parity (0, 1, 2, 3+), race and ethnicity (Hispanic, non-Hispanic white, African American, Asian, Pacific Islander, Native American, and multiracial of any ethnicity), maternal education (college graduate yes or no), and state of residence (GA, NC, TN).*

Table 3.4. Risks, risk differences, and risk ratios for preterm birth, low birth weight, and small for gestational age in the first live singleton birth conceived after diagnosis with breast, reproductive, and thyroid cancers, compared with births to matched comparison women without a previous cancer diagnosis, stratified by race.

	Breast	Reproductive*	Thyroid
Preterm birth			
White women			
Risk, cancer survivors	12% (9%, 15%)	18% (13%, 24%)	9% (7%, 12%)
Risk, matched comparison births	9% (8%, 10%)	8% (8%, 9%)	9% (7%, 9%)
Risk Difference	3% (-1%, 6%)	9% (4%, 15%)	0% (-2%, 3%)
Risk Ratio	1.3 (1.0, 1.8)	2.1 (1.6, 2.9)	1.1 (0.8, 1.7)
African-American women			
Risk, cancer survivors	20% (15%, 25%)	22% (14%, 32%)	20% (13%, 28%)
Risk, matched comparison births	15% (13%, 17%)	14% (13%, 16%)	17% (14%, 20%)
Risk Difference	4% (-1%, 10%)	8% (-1%, 17%)	2% (-5%, 10%)
Risk Ratio	1.3 (1.0, 1.7)	1.6 (1.0, 2.4)	1.1 (0.8, 1.7)
Interaction Contrast	0.02 (-0.04, 0.08)	-0.01 (-0.12, 0.10)	-0.01 (-0.10, 0.07)
Low birth weight			
White women			
Risk, cancer survivors	9% (7%, 12%)	14% (9%, 20%)	5% (4%, 7%)
Risk, matched comparison births	7% (6%, 8%)	5% (5%, 6%)	6% (5%, 7%)
Risk Difference	2% (-1%, 5%)	9% (4%, 14%)	0% (-2%, 1%)
Risk Ratio	1.4 (1.0, 1.9)	2.7 (1.9, 3.9)	0.9 (0.7, 1.3)
African-American women			
Risk, cancer survivors	18% (14%, 24%)	14% (7%, 24%)	17% (11%, 24%)
Risk, matched comparison births	13% (11%, 15%)	13% (11%, 14%)	11% (9%, 14%)
Risk Difference	6% (-1%, 11%)	2% (-6%, 10%)	5% (-2%, 12%)
Risk Ratio	1.4 (1.1, 1.9)	1.1 (0.6, 2.0)	1.5 (0.9, 2.3)
Interaction Contrast	0.03 (-0.03, 0.09)	-0.07 (-0.17, 0.02)	0.02 (-0.06, 0.10)
Small for gestational age			
White women			
Risk, cancer survivors	8% (6%, 11%)	8% (5%, 13%)	8% (6%, 10%)
Risk, matched comparison births	9% (8%, 10%)	9% (8%, 9%)	8% (7%, 9%)
Risk Difference	-1% (-4%, 2%)	0% (-4%, 4%)	0% (-2%, 2%)
Risk Ratio	0.9 (0.6, 1.3)	1.0 (0.6, 1.6)	1.0 (0.7, 1.3)
African-American women			
Risk, cancer survivors	17% (13%, 22%)	13% (6%, 23%)	12% (7%, 19%)
Risk, matched comparison births	14% (12%, 16%)	15% (14%, 17%)	15% (12%, 18%)
Risk Difference	3% (-2.1, 7.7%)	-2% (-10%, 5%)	-3% (-9%, 3%)
Risk Ratio	1.2 (0.9, 1.6)	0.9 (0.5, 1.5)	0.8 (0.5, 1.3)
Interaction Contrast	0.04 (-0.02, 0.09)	-0.02 (-0.11, 0.07)	-0.02 (-0.09, 0.04)

**Reproductive cancers include cervix uteri, corpus uteri, ovary, vulva, and all other female genital cancers. Comparison women without cancer were matched 5:1 to breast and thyroid cancer survivors and 25:1 to reproductive cancer survivors on exact age at birth (single-year category), parity (0, 1, 2, 3+), race and ethnicity (Hispanic, non-Hispanic white, African American, Asian, Pacific Islander, Native American, and multiracial of any ethnicity), maternal education (college graduate yes or no) and state of residence (GA, NC, TN).*

3.10 Appendix Table

Appendix Table 3.A1. Cancer type for the first eligible singleton birth conceived after a cancer diagnosis (N=4,203).

Cancer type	N	%
Melanoma	981	23%
Thyroid	970	23%
Breast	754	18%
Hodgkin lymphoma	293	7.0%
Cervix uteri	131	3.1%
Colorectal	106	2.5%
Brain	104	2.5%
Non-Hodgkin lymphoma, nodal	95	2.3%
Ovary	90	2.1%
Oral and pharynx	84	2.0%
Soft tissue	84	2.0%
Kidney and bladder	64	1.5%
Leukemia	63	1.5%
Non-Hodgkin lymphoma, extranodal	63	1.5%
Non-epithelial skin, other than melanoma	58	1.4%
Digestive	43	1.0%
Other reproductive	37	0.9%
Lung and other respiratory	32	0.8%
Bones and joints	30	0.7%
Corpus uteri	22	0.5%
Vulva	22	0.5%
Other	77	1.8%

3.11 Figure

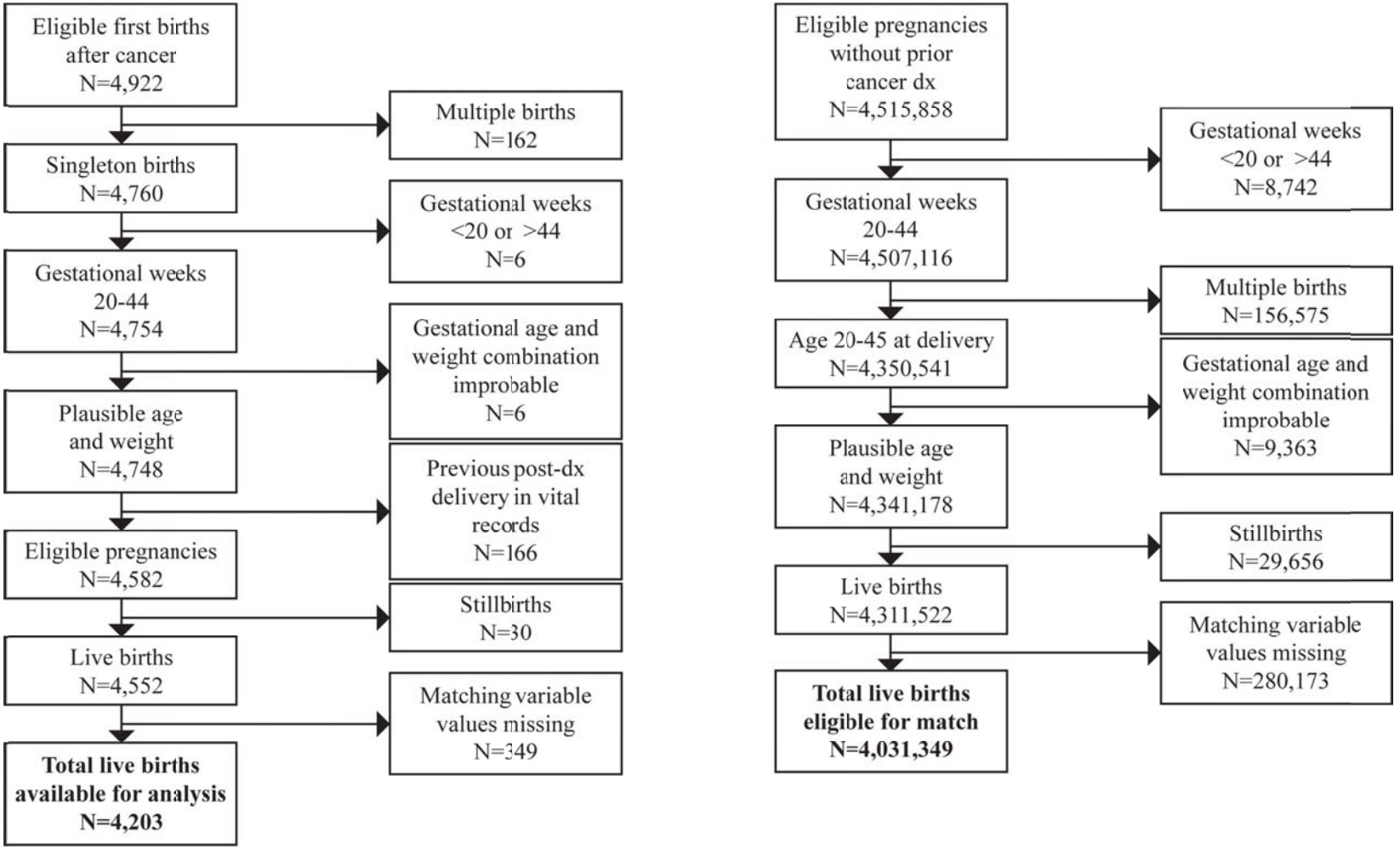

Figure 3.1. Exclusions and total N for first births after cancer and comparison groups.

4. AIM 2: PREGNANCY OUTCOMES IN WOMEN TREATED FOR CANCER BEFORE CONCEPTION

4.1 Manuscript information

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4.2 Abstract

4.2.1 Background
Although some cancer treatments are known to reduce fertility, less is known about outcomes in women who get pregnant after treatment. Our aim was to assess whether cancer survivors have higher risks of preterm birth, low birth weight, and small for gestational age infants in pregnancies conceived after treatment.

4.2.2 Methods
Diagnosis and treatment data from cancer registries were linked to pregnancy outcomes from birth certificates in three U.S. states. Analyses were limited to the first, live singleton birth conceived after diagnosis. Log-binomial models were used to estimate risk ratios comparing risks of adverse pregnancy outcomes after cancer treatments to risks in women without a cancer history, matched to cancer survivors on age at delivery, parity, race/ethnicity, and education. A probabilistic bias analysis used validation data from medical records to assess the extent to which registry treatment misclassification affected the estimates.

4.2.3 Results
Chemotherapy for breast cancer was associated with having a low birth weight infant, regardless of whether the women received radiation (RR for chemotherapy without radiation=1.7, 95% CI: 1.2, 2.6; RR for chemotherapy with radiation=1.8, 95% CI: 1.3, 2.6). The bias analysis did not meaningfully change these results. Radioactive iodine for thyroid cancer and chemotherapy for Hodgkin lymphoma were not associated with adverse pregnancy outcomes.

4.2.4 Conclusions
These results are reassuring for women who receive radioactive iodine for thyroid cancer. Pregnancy outcomes may depend on chemotherapy regimen, as infants born to women who received chemotherapy for breast cancer but not Hodgkin lymphoma had higher risks.

4.3 Introduction

Improvements in cancer treatment have dramatically increased the number of long-term survivors.[4] Because maternal age at first birth has also risen,[82] a growing number of women want to have children after cancer. Some cancer treatments, particularly alkylating chemotherapy and pelvic radiation, have been associated with lower ovarian reserve, infertility, and early menopause.[15,24,65,99-103] But less is known about whether these treatments cause adverse pregnancy outcomes in survivors who do conceive.

Much of the evidence to date on pregnancy after cancer treatments has come from long-term cohorts of survivors diagnosed in childhood. Data from the Childhood Cancer Survivor Study, a large multicenter cohort of survivors in the U.S., showed slightly higher odds of preterm birth in deliveries to women who received alkylating chemotherapy in childhood,[25] while data from a cohort of childhood survivors in Britain did not.[27] Although the results of these studies provide important evidence about the effects of cancer treatment at a young age, they may not be generalizable to survivors diagnosed as adults. Some side effects of treatment may be more harmful in children or adolescents during critical windows of development, while others, like chemotherapy-induced immunosuppression, may be more pronounced in adults.[104] One population-based study of survivors in Finland observed higher odds of preterm birth in women who received chemotherapy for any cancer, both with and without radiation, than in their sisters.[33] However, the study grouped women diagnosed both as children and adults.

Studies on radiation exposure in childhood survivors have consistently found higher risks of preterm birth, miscarriage, fetal malposition, and stillbirth after pelvic radiation.[15,26,28,29] One study also found higher miscarriage risks after cranial and spinal radiation, but there is less evidence on whether radiation to a field that includes the hypothalamus and pituitary causes adverse outcomes in pregnancy.[29] Although clinical studies have reported no increased risk of

adverse pregnancy outcomes after radioactive iodine treatment for thyroid cancer, most of the sample sizes have been small, with fewer than 100 pregnancies in survivors.[77]

Thus, the aim of this study was to use a population-based cohort of births across three U.S. states to assess whether chemotherapy and/or radiation for cancers diagnosed in adulthood increase the risk of adverse outcomes in subsequent pregnancies. A validation study with medical records for a subset of women allowed us to conduct a bias analysis examining the extent to which misclassification of treatment in state cancer registries affected the results.

4.4 Methods

4.4.1 Study populations

We used two different populations for this study: 1) women identified in the state cancer registries of Georgia, North Carolina and Tennessee linked to vital records, with a matched comparison cohort sampled from birth certificates 2) a subset of Georgia cancer survivors who participated in the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study. For the main analyses, we used treatment data from state cancer registries. The subset of Georgia cancer survivors, who had treatment information abstracted from medical records, served as validation for a bias analysis.

Population for main analysis: Registry data linked to birth records in three states

Cancer registry staff in Georgia, North Carolina, and Tennessee linked registry data to vital records to identify women who had a birth after a cancer diagnosis. Women diagnosed between the ages of 20 and 45 with any reportable invasive cancer[83] or ductal carcinoma in situ (DCIS) were included. In each state, we identified the first birth that was conceived after a cancer diagnosis. The sample included cancers diagnosed August 23, 1993-August 22, 2012 linked to births from 1994-2012 in Georgia (cancer diagnoses prior to 1999 were from metropolitan Atlanta only), cancers diagnosed August 23, 1999-August 22, 2012 linked to births from 2000-

2013 in North Carolina, and cancers diagnosed Jan. 1, 2004-August 22, 2013 linked to births from May 20, 2004-2013 in Tennessee.

The comparison group included births from the same period to women with no previous record of cancer in the state's registry during the years covered by the study. Comparison women were matched 25:1 to cancer survivors in the same state on four primary confounders recorded on the birth certificate: 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 women of any ethnicity), parity (0, 1, 2, and ≥3), maternal education (college graduate yes or no). For both cancer survivors and comparison women, analyses were limited to live, singleton births between 20 and 44 weeks gestation to women who were ages 20-45 at the time of delivery. Analysis was limited to births conceived after cancer diagnosis, with date of pregnancy conception calculated date by subtracting the clinical estimate of gestational age from the date of birth in vital records. Although stillbirths were included to determine the first pregnancy after cancer, these deliveries were excluded from analysis because a high proportion of stillbirths had missing values for matching variables. Women diagnosed during pregnancy were excluded.

Population for validation of treatment data and bias analysis: FUCHSIA Women's Study

Medical records were abstracted for participants in the FUCHSIA Women's Study, which included women diagnosed at ages 20-35 with any reportable malignant cancer[83] or in situ breast cancer during the years 1990-2009 in metro Atlanta or 1999-2009 in the rest of Georgia. The study was limited to women who had survived for at least two years after diagnosis and were ages 22-45 at the time of recruitment into the study. Abstractors gathered data for the primary cancer diagnosis, any relapses, and additional primary cancers. Medical records were included from all locations available, including those reported by women during telephone interviews, recorded by the Georgia Cancer Registry, or mentioned in her medical records (for example, a clinic

administering chemotherapy said radiation treatment was given elsewhere). Among women whose medical records were abstracted, 60 were breast cancer survivors who were also in the linked dataset for the main analysis because they became pregnant after cancer. Women who had treatment recorded in the registry, or self-reported treatment that could not be confirmed due to abstractors having incomplete medical records, were coded as missing and not included in sensitivity and specificity calculations.

4.4.2 Exposures

The exposure was cancer treatment as recorded in the cancer registry, including chemotherapy, beam radiation, and radioactive iodine. Women who had treatment recorded as received or recommended were coded as exposed. For the subset of Georgia cancer survivors who participated in the FUCHSIA Women's Study, treatment data came from medical records. Analyses were limited to women who started treatment before conception; we excluded 17 cancer survivors who were diagnosed before conception but had a treatment start date that was during or after pregnancy. We classified women into treatment categories including chemotherapy without beam radiation, chemotherapy with beam radiation, beam radiation without chemotherapy, and head and neck radiation (defined as beam radiation for a cancer of the head or neck). For survivors of breast cancer, there was sufficient sample size (≥10 adverse pregnancy outcomes in the exposed) to analyze chemotherapy both with and without beam radiation. We also had sufficient sample size to estimate the effect of any chemotherapy (with or without beam radiation) for survivors of Hodgkin lymphoma and radioactive iodine in thyroid cancer survivors. Cancer type was classified by primary site and histology, using site recode values from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

4.4.3 Outcomes

Birth outcomes from vital records included preterm birth (<37 weeks gestation), very preterm birth (<32 weeks gestation), low birth weight (<2,500g), very low birth weight

(<1,500g), and low birth weight at term (<2,500g at ≥37 weeks gestation). An external national distribution was used to determine which infants were small for gestational age (<10% of birth weight for gestational age and sex) and to exclude a small number of infants with implausible combinations of birth weight and gestational age.[85]

4.4.4 Covariates

We identified likely potential confounders of the association between cancer treatment and adverse pregnancy outcomes using a causal diagram, which was informed by both the literature and data. In addition to the variables that we controlled for through matching (mother's age at delivery, education, race/ethnicity, and parity), we considered variables from vital records including the mother's marital status and self-reported smoking during pregnancy. These covariates did not change our estimates of effect, so we did not include them in our models.

4.4.5 Statistical methods

We used frequencies and proportions to describe the study population and calculated risks of each adverse pregnancy complication or outcome by cancer treatments. Separate log binomial models for each treatment category and outcome were used to estimate risk ratios (RRs) comparing the risk in cancer survivors to matched comparison women without a history of cancer. RRs were estimated for pregnancy outcomes with n≥10 cancer survivors.

Of the cancer types in our study, only breast cancer had sufficient a validation data sample size to include in the bias analysis. The sensitivity, specificity, positive predictive value, negative predictive value for chemotherapy and beam radiation in the registry were calculated among breast cancer survivors who were in both the registry and the validation study, using medical records as the gold standard. Of the 60 breast cancer survivors in both the registry and the validation study, 9 were excluded from the sensitivity analysis for chemotherapy because treatment type or start date was not available in medical records; 1 was excluded because treatment type was missing in the registry; 2 were excluded because the registry and medical

records agreed that the woman received chemotherapy, but it was during pregnancy; and 2 were excluded because we were unable to obtain complete medical records confirming the woman's self-report that she was treated with chemotherapy. This left 46 women available for chemotherapy sensitivity analysis. For radiation, 11 of the 60 breast cancer survivors were excluded because treatment type or start date was not available in medical records, and 1 because treatment type was missing in the registry, leaving 48 women for radiation sensitivity analysis.

The positive and negative predictive values calculated from sensitivity analyses informed a probabilistic, record-level bias analysis assessing the extent to which misclassification of treatment in registry data affected the results. A Monte Carlo simulation produced 10,000 individual datasets, with chemotherapy and radiation values for breast cancer survivors changing independently in each, as informed by the validation study. For example, if the negative predictive value for chemotherapy was 70%, a woman unexposed to chemotherapy remained unexposed in 70% of iterations, on average, and changed to exposed in 30% of iterations. From these datasets, we calculated 10,000 simulated RRs comparing the risks for each exposure (chemotherapy with radiation and chemotherapy without radiation) to the risks in matched comparison women without cancer. The median of these 10,000 RRs represents the estimate adjusted for misclassification of exposure, assuming that the bias model is accurate. The bounds of the Simulation Interval were calculated using a standard error that included both random and systematic error.

All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

4.5 Results

Women who conceived after any treatment for cancer were older, better educated, and more likely to be having their first child than women without cancer (Table 4.1). More than half of the women in the study treated with chemotherapy were survivors of breast cancer or Hodgkin lymphoma.

Among breast cancer patients, which included women with DCIS, 25% had chemotherapy without beam radiation, 10% had beam radiation without chemotherapy, 30% received both, and 35% received neither (Appendix Table 4.A1). Among women with Hodgkin lymphoma, 40% received chemotherapy without beam radiation and 36% had chemotherapy with beam radiation. Nearly half of thyroid cancer survivors (46%) were treated with radioactive iodine. The largest populations of women who received neither chemotherapy nor radiation were survivors of melanoma (n=932) and thyroid cancer (n=473).

In the main analysis examining pregnancy risks after registry-reported chemotherapy for any cancer, we observed higher risks of low birth weight in women who had chemotherapy both with and without beam radiation, but not for beam radiation without chemotherapy (Table 4.2). The increased risks of adverse pregnancy outcomes were not uniform across cancer type. In analyses limited to breast cancer survivors, chemotherapy both with and without radiation was also associated with higher risks of low birth weight (RR for chemotherapy with radiation=1.8, 95% CI: 1.3, 2.6; RR for chemotherapy without radiation=1.7, 95% CI: 1.2, 2.6) than women without cancer (Table 4.2). This increase in low birth weight was likely explained at least in part by an increase in the risk of preterm birth (RR for chemotherapy with radiation=1.2, 95% CI: 1.0, 1.5; RR for chemotherapy without radiation=1.3, 95% CI: 1.1, 1.7).

In contrast to breast cancer survivors, women treated with chemotherapy for Hodgkin lymphoma did not have higher risks of any adverse pregnancy outcomes. The RR for low birth weight in women who received beam radiation to the head and neck was 1.5 (95% CI: 0.9, 2.8). Treatment with radioactive iodine did not increase thyroid cancer patients' risk of having an infant born preterm, low birth weight, or small for gestational age (Table 4.2).

The validation study showed high agreement between registry treatment data and medical records. Among breast cancer survivors, the registry had 92% sensitivity for chemotherapy and 88% sensitivity for radiation (Appendix Table 4.A2). There were no women for whom the

registry recorded treatment but medical records did not, resulting in perfect specificity for both chemotherapy and radiation. The RRs we estimated using treatment data in the registry did not meaningfully change in the bias analysis designed to adjust for misclassification of chemotherapy and radiation (Table 4.3).

4.6 Discussion

This large population-based cohort study allowed us to estimate risks stratified by cancer treatment. In analyses that grouped all cancer survivors, we observed slightly higher risks of preterm birth and low birth weight in pregnancies conceived after chemotherapy with or without radiation, suggesting that any increases in risk after treatment are likely small or limited to certain cancer types or subgroups of survivors. We observed higher risks of low birth weight infants in women treated with chemotherapy for breast cancer both with and without radiation, but did not see any risk of adverse outcomes associated with chemotherapy for Hodgkin lymphoma. Treatment with radioactive iodine for thyroid cancer was not associated with higher risks of infants born preterm, low birth weight, or small for gestational age. We did not observe an increase in any adverse pregnancy outcomes in the total population of women who received beam location at any location, although there was possible evidence of a slightly elevated risk of low birth weight infants in the subset of women treated with radiation for cancers of the head and neck.

Differences in the chemotherapy regimens by cancer type may explain our observation of higher risks in survivors of breast cancer but not Hodgkin lymphoma. Because registries do not report specific agents, we were unable to compare the risks of different chemotherapy regimens or classes of drug. However, among Georgia survivors for whom we had medical records, most with Hodgkin lymphoma received the ABVD regimen of doxorubicin (Adriamycin), bleomycin, vinblastine, and the alkylating agent dacarbazine, so it is likely that this regimen predominated

among Hodgkin survivors in the registry. In contrast, among breast cancer survivors for whom we had medical records, most received a regimen including the alkylating agent cyclophosphamide.

Patients treated with cyclophosphamide have a high risk of amenorrhea and ovarian failure,[105-107] whereas the evidence of ABVD gonadotoxicity is mixed, with several studies showing only small increases in risk or no increased risk of amenorrhea or infertility after treatment.[108-111] However, the mechanism by which chemotherapy increases the risk of a low birth weight infant might not be through ovarian injury but by other mechanisms such as chronic anemia or immunosuppression that are common in chemotherapy patients[17,18] and have been linked to preterm birth.[19,20] Some studies have found immunosuppression persisting months or years after chemotherapy, with CD4+ counts as low as 50% of pretreatment levels 12-14 months after treatment,[112,113] and weaker vaccine response in survivors with a mean of 2.6 years since treatment with cytotoxic chemotherapy.[114] It is also plausible that chemotherapy increases the risk of low birth weight through other mechanisms in some patients, such as growth restriction due to insufficient weight gain in pregnancy. In our study, chemotherapy exposure before pregnancy was weakly associated with both preterm birth and infants born small for gestational age.

Chemotherapy and radiation are not perfectly reported in cancer registries, in part because registries record only the first course of treatment. Treatment received for relapse or a second treatment because initial treatment was unsuccessful are not available in registry data. Our bias analysis showed that while chemotherapy and radiation are slightly underreported in cancer registries, the positive predictive value of both treatments in the registry is excellent. In our validation study of women diagnosed in Georgia, medical records confirmed treatment for all women that the registry recorded as having chemotherapy and radiation. The estimated effects of chemotherapy with and without radiation did not change meaningfully in the bias analysis, although the analysis had certain limitations. We had insufficient data to calculate negative and

positive predictive values for treatment by cancer stage or by pregnancy outcome. Thus, some of the women changed from unexposed to exposed at random in the bias analysis are unlikely to have been truly exposed. In contrast, because the positive predictive value of treatment in the registry was perfect, nearly all of the women used in the original estimate using the registry data truly were exposed. This may be the reason that the point estimates moved slightly down and toward the null in the bias analysis.

Our study has some limitations, including our inability to distinguish all the women who had pelvic radiation. Of the women in our study who conceived after radiation for an abdominopelvic cancer, 45% (of 11) had a preterm birth. However, because the registries do not record radiation location, we were unable to identify women who had total body radiation or local radiation for lymphoma that included the pelvic field. A second limitation is that to be correctly identified as a cancer survivor, a woman had to give birth in the same state as her cancer diagnosis, during the years of the study. We are thus likely to be disproportionately missing some survivors with a long interval between diagnosis and birth, because these women are more likely to have been diagnosed before registries began collecting data or to have moved to a different state before the birth. However, for these missing women to bias the study, they would need to be systematically different from the women who were diagnosed and gave birth in the same state. Finally, while our overall sample study was large, we had insufficient sample size to examine the effects of treatment separately for cancer types less common than breast, Hodgkin, and thyroid.

This study also has important strengths, including its population-based design and inclusion of comprehensive medical records for a subset of survivors. Studies evaluating the quality of U.S. vital records have found excellent agreement between birth certificate data and medical records for our covariates, as well as infant birth weight, and generally good agreement for preterm birth.[92,95,96] There was also good agreement between registry data and medical records in the validation study.

In conclusion, we observed an increased risk for low birth weight infants after chemotherapy for breast cancer but not for Hodgkin lymphoma. Radioactive iodine for thyroid cancer was not associated with adverse outcomes. Although there was a suggestion of increased pregnancy risk after radiation to the head and neck, the estimated RR for this outcome was not strong or precise. Studies with medical records for a larger population of women would clarify the pregnancy risks after radiation to fields that include the pituitary, hypothalamus, or pelvis, as well as treatments we had insufficient sample size to analyze, including stem cell transplant, immunotherapy, and brachytherapy. Future studies should focus on identifying the subsets of breast cancer survivors who may be at the highest risk of adverse pregnancy outcomes, and how long these risks may persist after chemotherapy.

4.7 Acknowledgments

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4.8 Tables

Table 4.1. Characteristics of the first eligible live singleton birth to women ages 20-45 conceived after cancer diagnosis (N=4,203), for different cancer treatments, compared with all live singleton births to women ages 20-45 without a previous cancer diagnosis, using birth certificate data linked to cancer registries in Georgia, North Carolina, and Tennessee. Births missing data for the four matching variables (maternal age, race/ethnicity, education, and parity) have been removed.

	Comparison births		All Cancers		Chemo only		Beam radiation only		Chemo and beam radiation		Radio-active iodine		No chemo or radiation	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cancer type														
Breast	-	-	754	18	174	33	73	43	208	52	0	0	242	12
Cervix uteri	-	-	131	3	0	0	1	1	1	0	0	0	123	5
Hodgkin lymphoma	-	-	293	7	117	22	10	6	106	26	0	0	36	1
non-Hodgkin lymphoma	-	-	158	4	63	12	8	5	33	8	0	0	40	2
Melanoma	-	-	981	23	5	1	1	1	1	0	0	0	932	39
Thyroid	-	-	970	23	0	0	7	4	0	0	448	100	473	20
Other	-	-	916	22	172	32	69	41	52	13	0	0	571	24
Maternal age at birth														
20-24	1,271,379	32	250	6	38	7	8	5	18	4	31	7	139	6
25-29	1,256,448	31	1,084	26	154	29	40	24	89	23	118	26	619	26
30-34	978,443	24	1,479	35	177	33	46	27	131	33	169	38	878	36
35-39	438,243	11	1,091	26	134	25	49	29	138	34	115	26	595	25
40-45	86,836	2	299	7	28	5	26	15	25	6	15	3	186	8
Maternal race and ethnicity														
White, non-Hispanic	2,333,454	58	3,074	73	325	61	103	61	249	62	340	76	1,901	79
African American, non-Hispanic	1,039,528	26	810	19	171	32	48	28	117	29	52	12	366	15
Asian and Pacific Islander, non-Hispanic	121,027	3	104	2	6	1	7	4	10	2	22	5	52	2
Native American, non-Hispanic	20,681	1	18	0	2	0	1	1	3	1	3	1	7	0
Multiracial, any ethnicity	127,706	3	69	2	9	2	5	3	6	1	8	2	34	1
Hispanic, any race	388,953	10	128	3	18	3	5	3	16	4	23	5	57	2

Table 4.1. *Continued*

	Comparison births		All Cancers		Chemo only		Beam radiation only		Chemo and beam radiation		Radio-active iodine		No chemo or radiation	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Maternal education														
Less than high school	681,696	17	259	6	51	10	12	7	20	5	17	4	139	6
High school or GED	1,194,965	30	801	19	130	24	39	22	90	22	68	15	418	17
Some college or associate degree	1,100,788	27	1,278	30	171	32	50	32	119	30	148	33	714	30
At least 4 years of college	1,053,900	26	1,865	44	179	34	68	39	172	43	216	48	1,146	47
Parity														
0	1,459,220	36	1,825	43	211	39	63	37	184	46	192	43	1,076	45
1	1,391,980	34	1,313	31	158	30	57	34	129	32	140	31	752	31
2	726,821	18	677	16	95	17	35	21	58	14	81	18	376	16
3 or more	453,328	11	388	9	67	14	14	8	30	7	35	8	213	9
Smoking during pregnancy														
No	3,380,485	89	3,763	93	471	92	155	94	362	93	415	97	2,162	93
Yes	417,691	11	267	7	42	8	10	6	29	7	15	3	154	7
Mother married														
Yes	2,650,219	66	3,380	80	355	67	128	76	295	75	384	86	2,542	84
No	1,379,500	34	819	20	176	33	40	24	99	25	65	14	496	16

Table 4.2. Risk ratios comparing the risk of preterm birth, low birth weight (LBW), and small for gestational age (SGA) for the first pregnancy conceived after cancer treatment with the risk of adverse pregnancy outcomes in women without a previous cancer diagnosis.

	Total births	Preterm birth < 37 weeks		Preterm birth < 32 weeks		LBW (< 2,500g)		Very LBW (< 1,500g)		LBW at term		SGA	
		N	RR	N	RR	N	RR	N	RR	N	RR	N	RR
All cancers													
Chemotherapy without beam radiation	531	68	1.2 (1.0, 1.5)	14	1.5 (0.9, 2.5)	65	1.6 (1.3, 2.1)	15	1.8 (1.1, 3.0)	15	1.3 (0.8, 2.1)	73	1.3 (1.1, 1.6)
Chemotherapy with beam radiation	401	57	1.3 (1.1, 1.7)	8	-	45	1.4 (1.1, 1.9)	10	1.3 (0.7, 2.4)	12	1.3 (0.7, 2.3)	50	1.2 (0.9, 1.6)
Beam radiation without chemotherapy	168	20	1.1 (0.7, 1.7)	3	-	15	1.2 (0.7, 1.9)	2	-	13	1.0 (0.6, 1.6)	21	1.2 (0.8, 1.8)
Head and neck radiation	110	14	1.3 (0.8, 2.2)	2	-	11	1.5 (0.9, 2.8)	3	-	3	-	12	1.0 (0.6, 1.8)
Breast cancer													
Chemotherapy without beam radiation	174	24	1.3 (0.9, 1.8)	4	-	24	1.7 (1.2, 2.6)	4	-	5	-	26	1.4 (0.9, 2.0)
Chemotherapy with beam radiation	208	35	1.6 (1.2, 2.2)	4	-	29	1.8 (1.3, 2.6)	7	-	8	-	31	1.4 (1.0, 1.9)
Hodgkin lymphoma													
Chemotherapy with or without beam radiation	223	19	0.9 (0.6, 1.3)	1	-	12	0.8 (0.5, 1.4)	2	-	3	-	22	1.0 (0.7, 1.5)
Thyroid cancer													
Radioactive iodine	470	33	0.8 (0.6, 1.1)	4	-	25	0.9 (0.6, 1.3)	4	-	11	1.1 (0.6, 2.0)	37	0.9 (0.6, 1.2)

Table 4.3. Change in estimates of the risk ratio comparing risk of preterm birth, low birth weight (LBW), and small for gestational age (SGA) in breast cancer survivors to matched comparison women, after bias analysis addressing misclassification of treatment in the registry.

	Preterm birth		**LBW**		**SGA**	
	Original data	**Simulated data adjusting for misclassification**	**Original data**	**Simulated data adjusting for misclassification**	**Original data**	**Simulated data adjusting for misclassification**
	RR (95% CI)	**median RR (95% SI)**	**RR (95% CI)**	**median RR (95% SI)**	**RR (95% CI)**	**median RR (95% SI)**
Chemotherapy without radiation	1.3 (0.9, 1.8)	1.2 (0.7, 2.0)	1.7 (1.2, 2.6)	1.7 (1.1, 2.7)	1.4 (0.9, 2.0)	1.2 (0.8, 1.8)
Chemotherapy with radiation	1.6 (1.2, 2.2)	1.5 (1.0, 2.2)	1.8 (1.3, 2.6)	1.7 (1.2, 2.5)	1.4 (1.0, 1.9)	1.3 (0.9, 1.9)

4.9 Appendix Tables

Appendix Table 4.A1. N for each treatment type by cancer type, for the first eligible live singleton birth conceived after diagnosis.

		Chemotherapy only		Beam radiation only		Radioactive iodine		Chemotherapy and beam radiation		No chemotherapy or radiation		Missing
Cancer type	**Total**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**
Bones and joints	30	12	41	0	0	0	0	0	0	17	59	1
Brain	104	2	2	19	20	0	0	22	23	54	56	7
Breast	754	174	25	73	10	0	0	208	30	242	35	57
Cervix uteri	131	0	0	1	1	0	0	1	1	123	98	6
Colorectal	106	30	30	0	0	0	0	2	2	69	68	5
Hodgkin lymphoma	293	117	43	10	4	0	0	106	39	36	13	24
Kidney and bladder	64	2	3	0	0	0	0	0	0	61	97	1
Leukemia	63	50	83	0	0	0	0	1	2	9	15	3
Lung and other respiratory	32	2	6	4	13	0	0	2	6	23	74	1
Melanoma	981	5	1	1	0	0	0	1	0	932	99	42
Non-Hodgkin lymphoma, extranodal	63	18	31	6	10	0	0	10	17	24	41	5
Non-Hodgkin lymphoma, nodal	95	45	52	2	2	0	0	23	27	16	19	9
Oral and pharynx	84	0	0	12	16	0	0	14	18	50	66	8
Non-epithelial skin, other than melanoma	58	1	2	3	5	0	0	0	0	52	93	2
Other reproductive	171	58	36	0	0	0	0	1	1	102	63	10
Soft tissue	84	5	6	21	27	0	0	4	5	47	61	7
Thyroid	970	0	0	7	1	448	48	0	0	473	51	42
Other	120	10	9	10	9	0	0	6	5	87	77	7

Appendix Table 4.A2. Comparison of treatment prior to pregnancy conception in medical records from the FUCHSIA Women's Study to registry values for breast cancer survivors in Georgia.

	Medical Records		
Registry	**Total**	**Yes**	**No**
Chemotherapy			
Yes	36	36	0
No	10	3	7
Total	46	39	7
Sensitivity		92%	
Specificity		100%	
Positive Predictive Value		100%	
Negative Predictive Value		70%	
Radiation			
Yes	30	30	0
No	18	4	14
Total	48	34	14
Sensitivity		88%	
Specificity		100%	
Positive Predictive Value		100%	
Negative Predictive Value		78%	

5. AIM 3: PREGNANCY AFTER CANCER: DOES TIMING OF CONCEPTION AFFECT INFANT HEALTH?

5.1 Manuscript information

Pregnancy after cancer: Does timing of conception affect infant health?

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Concise abstract: Cancer survivors who conceived their pregnancies more than 1 year after starting chemotherapy without radiation and 2 years after starting chemotherapy with radiation had no higher risks of preterm birth than comparison women without cancer. The preterm birth risk was slightly higher in cervical cancer survivors who conceived within a year of diagnosis than for those who conceived ≥1 year after diagnosis.

5.2 Abstract

5.2.1 Background
The aim of this study was to determine whether women who conceive soon after treatment have higher risks of adverse pregnancy outcomes.

5.2.2 Methods
Vital records data were linked to cancer registry diagnosis and treatment information in three U.S. states. The first pregnancy conceived after diagnosis between ages 20-45 years with any invasive cancer or ductal carcinoma in situ was 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.

5.2.3 Results
Women who conceived ≤1 year after starting chemotherapy for any cancer had higher risks of preterm birth than comparison women (RR for chemotherapy alone=1.9, 95% CI: 1.3, 2.7; RR for chemotherapy with radiation=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 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 (RR for pregnancies conceived ≤1 year after diagnosis=3.5, 95% CI: 2.2, 5.4; RR for pregnancies conceived >1 year=2.4, 95% CI: 1.6, 3.5).

5.2.4 Conclusions
In women who received chemotherapy, the higher risk of preterm birth was limited to those survivors with short intervals between treatment and conception.

5.3 Introduction

Women who want to have children after cancer diagnosis face difficult decisions about pregnancy timing after treatment. Organizations including the American Cancer Society, American Society of Clinical Oncology, and National Comprehensive Cancer Network offer advice on how long women should wait before getting pregnant, but caution that there is not enough evidence to inform guidelines.[50,51,53] Although conceiving after a cancer diagnosis does not appear to increase risk of cancer recurrence,[43,44] 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 6-12 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.[51,53] - Other side effects of chemotherapy, including immunosuppression, anemia, fatigue, or cardiovascular damage, might increase the risk of having an infant born preterm or small for gestational age. Some have observed an increased risk of preterm birth and/or growth restriction in infants born to cancer survivors,[33,35] but it is not clear whether these risks depend on the time since treatment.

Cervical cancer survivors and other women who have procedures to diagnose and remove abnormal cervical tissue are at particularly high risk of early delivery.[115] Although some studies have found higher risks of preterm birth and miscarriage in women with shorter intervals between cervical surgeries and conception,[73] others have not.[72,116] Pregnancy timing after cancer may also 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,[117] the American Thyroid Association recommends that patients wait 6-12 months before conceiving to establish the optimal dose of thyroid hormone.[78]

Although many organizations offer advice to women who hope to get pregnant after treatment, it is unknown how many cancer patients talk with their doctors about pregnancy timing, and if so, what recommendations they receive. Thus, our aims were to determine whether the risks of adverse pregnancy outcomes differ by time since diagnosis and treatment for different cancer types, and to characterize pregnancy advice received by women diagnosed during their reproductive years.

5.4 Methods

5.4.1 Study populations

Two different populations were used for this study. In order to assess whether pregnancy timing after cancer is associated with adverse pregnancy outcomes, we used diagnosis and treatment data from state cancer registries linked to birth data from vital records in the U.S. states of Georgia, North Carolina, and Tennessee. To characterize recommendations that women received from their doctors and impute treatment end dates for breast cancer survivors, we used information from Georgia cancer survivors diagnosed at ages 20-35 who participated in the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study.

Pregnancy timing analyses: Cancer registry data linked to vital records in three states

Cancer registry diagnosis and treatment data from Aug. 23, 1994-2012 in Georgia, Aug. 23, 1999-2013 in North Carolina, and Jan. 1, 2004-2013 in Tennessee was linked to vital records. Births to women ages 20-45 diagnosed with any reportable invasive cancer[83] and ductal carcinoma in situ (DCIS) were eligible. We identified the first birth at greater than 20 weeks

gestation that was conceived after a cancer diagnosis reported in vital records from Jan. 1, 1994-2012 in Georgia, Jan. 1, 2000-2013 in North Carolina, and May 20, 2004-2013 in Tennessee.

We identified the first pregnancy reaching 20 weeks that was conceived after a cancer diagnosis in each state. Although stillbirths were included to determine the first pregnancy after cancer, these deliveries were excluded from analysis because a high proportion of stillbirths had missing values for matching variables. Women diagnosed during pregnancy were excluded.

Live 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 on births to cancer survivors on four variables from vital records: 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).

For both cancer and comparison births, analyses were limited to live, singleton births between 20 and 44 weeks gestation to mothers aged 20-45 at the time of delivery.

Pregnancy recommendations and medical record data: FUCHSIA Women's Study

For analyses of pregnancy timing recommendations that women received from healthcare providers, we used responses from participants in the FUCHSIA Women's Study. Participants were eligible for the study if they were diagnosed with any reportable invasive cancer[83] or DCIS during the years 1990-2009 in metro Atlanta or 1999-2009 in the rest of Georgia and survived for at least two years after diagnosis. The study was limited to women aged 20-35 at diagnosis and 22-45 at the time of recruitment. Survivors completed a telephone interview in English between May 2012 and February 2013. Cancer diagnosis and treatment information was abstracted from medical records.

The FUCHSIA Women's Study (N=1,282) included all cancer survivors, whether or not they were able to get pregnant or wanted children after diagnosis. For this analysis, the study population was limited to 1,066 survivors who were potentially able to get pregnant after cancer, meaning that they did not have a hysterectomy and/or bilateral oophorectomy before or during cancer treatment. Participants were asked: "Did a healthcare professional tell you how long to wait after your cancer treatment ended before attempting to get pregnant?" and if yes, "How long were you told to wait?"

5.4.2 Exposures

Treatment type and start date were based on the first course of treatment in the cancer registry. For the subset of survivors who also participated in the FUCHSIA Women's Study, treatment type and start date from medical records were used if they differed from the 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 that happen around the time of diagnosis, the exposure for these cancers was categorized time since diagnosis. For women who received chemotherapy and/or radiation, the exposure for the main analysis was categorized time from treatment start date in the registry to conception. For women treated with both chemotherapy and radiation, treatment start was defined as the day that the patient initiated chemotherapy or radiation, whichever came first.

In a secondary analysis limited to breast cancer survivors, we used time since treatment completion. Because treatment end date is unavailable in cancer registries, we imputed treatment end date for breast cancer patients by assigning each woman the median treatment duration length (105 days for chemotherapy without radiation and 211 days for chemotherapy with radiation) using data abstracted from medical records in the FUCHSIA Women's Study. This allowed an estimation of pregnancy risk by time since treatment completion in breast cancer survivors.

5.4.3 Outcomes

Outcomes from birth certificate data were preterm birth (<37 weeks gestation), low birthweight (<2,500g), and small for gestational age (<10% of birthweight for gestational age and sex based on a national distribution[84]).

5.4.4 Statistical analyses

Proportions were used to describe the study population and risks of adverse pregnancy outcomes in each time period after cancer. Log-binomial models were used to estimate risk ratios comparing 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 SAS 9.4 (SAS Institute, Inc., Cary, NC).

5.5 Results

Cancer survivors in the linked registry study were likely to be married (80%), have a 4-year college degree (44%) and in their 30s at the time of the first birth after cancer diagnosis (61% between ages 30 and 39). Pregnancy timing after cancer was strongly associated with age at diagnosis. Among births to women 40 or older at diagnosis, 55% were conceived within a year, compared with 21% among women who were 20–24 at diagnosis (Table 5.1). Pregnancy timing also differed by cancer type. Cervical cancer patients were the most likely to conceive soon after diagnosis, with 32% of births in this study conceived within a year.

Among survivors of any cancer treated with chemotherapy but not radiation, the risks of preterm birth and low birthweight were highest in pregnancies conceived within a year of starting treatment (Table 5.2). The preterm birth risk in these pregnancies was twice as high as in comparison women, with a Risk Ratio (RR) of 1.9 (95% 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 breast cancer patients who had chemotherapy with and without radiation mirrored the risks for all survivors, with the highest risks of preterm birth and low birthweight in pregnancies conceived within a year

of starting treatment (Table 5.2). In contrast, survivors who conceived at least one year after starting chemotherapy without radiation and more than two years after chemotherapy with radiation did not have higher risks of having an infant born preterm, low birthweight, or small for gestational age (SGA) than women without a cancer history. This was true in both analyses that included all survivors and those limited to breast cancer survivors (Table 5.2).

In analyses with imputed treatment end dates for breast cancer survivors, infants born to women who conceived within a year of completing chemotherapy with or without radiation had higher risks of preterm birth and low birthweight (preterm birth RR for chemotherapy without radiation=2.4, 95% CI: 1.5, 3.9; RR for chemotherapy with radiation=2.1, 95% CI: 1.3, 3.2) than comparison women (Appendix Table 4.A2). Infants born to breast cancer survivors who conceived at least one year after the estimated treatment end date had no higher risk than comparison women without a history of cancer.

The risk of having an infant born SGA was highest in women with the longest intervals between treatment start and conception (Table 5.2). The SGA risk was twice as high in births to chemotherapy patients who waited at least 5 years to conceive than those without cancer, and this difference was not explained by age at diagnosis (Appendix Table 5.A1). Thyroid cancer survivors did not have higher risks of any adverse outcome, regardless of when they conceived.

Among participants in the FUCHSIA Women's Study who did not have a hysterectomy or bilateral oophorectomy during or before treatment, 37% were counseled about how long to wait before becoming pregnant (Figure 5.1). The percent of women receiving a recommendation was highest among survivors of thyroid cancer (59%), cervical cancer (49%), and breast cancer (43%). Among thyroid cancer survivors, the most common recommendation was to wait 1-2 years after completing treatment (66%), with a wide range of 2 months to 5 years (Figure 5.2a). Breast cancer patients who were not prescribed Tamoxifen were most commonly told to wait a year after finishing treatment, while the most common recommendation for women taking

Tamoxifen was 5 years (Figure 5.2b). The most common recommendation for Hodgkin lymphoma patients was to wait between 1 and 2 years after treatment before conceiving. Among the 17 cervical cancer patients given a recommendation, 11 were told to wait less than a year before attempting to conceive.

5.6 Discussion

In this study, the elevated risks of preterm birth and low birthweight in infants born to cancer survivors were limited to pregnancies conceived soon after treatment. Infants born to women who conceived more than a year after starting chemotherapy without radiation and more than two 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 a year after finishing treatment. Breast cancer patients with at least a year after treatment and pregnancy did not have higher risks than matched women without cancer. We observed higher risks of infants born small for gestational age after chemotherapy, with or without radiation, in women who conceived more than 5 years after starting treatment. Thyroid cancer patients did not have higher risks for preterm birth or infants born low birthweight, or small for gestational age at any time after diagnosis.

Many women diagnosed during their reproductive years are talking with their doctors about family planning after cancer. In this population of Georgia cancer survivors aged 20-35 at diagnosis, which included women who did not plan to have children, more than a third remembered receiving a recommendation about how long to wait before getting pregnant. Cervical cancer patients were the most likely to be told to wait less than a year and to conceive soon after diagnosis. It is possible that some women with more invasive cancers or positive margins after surgery are being counseled to get pregnant quickly so that they can have a hysterectomy after delivery. We observed a slightly higher RR for preterm birth in cervical

cancer survivors who conceived within a year of diagnosis (RR=3.5, 95% CI: 2.2, 5.4) than in those who conceived after 1 year (RR=2.4, 95% CI: 1.6, 3.5), but because the confidence intervals for these RRs overlapped, this may be a chance finding. Some have hypothesized that conceiving too soon after cervical cancer could increase the risk of preterm birth due to inflammation from incomplete wound healing, but it is also possible that the slightly higher risk in women who conceive soon after cancer are due to other underlying differences between the patients who conceive quickly and those who wait, such as type of cervical procedure or risk of recurrence.

The mechanism by which chemotherapy might cause a temporary increase in preterm birth might be through transient effects such as immunosuppression[17,18] associated with preterm birth.[19,20] Studies have found that immunosuppression in breast cancer patients persists months or years after chemotherapy, with CD4+ counts at half of pretreatment levels 12-14 months after treatment,[112,113] and weaker vaccine response in breast cancer survivors with a mean of 2.6 years since chemotherapy.[114] 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 with long intervals between cancer and conception are not due to the wait time itself, but underlying differences such as poorer cancer prognosis or underlying reproductive conditions that cause both infertility and adverse pregnancy outcomes.

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, miscarriage, and stillbirth, which we could not assess. A second limitation is that while the effects of chemotherapy likely depend on regimen and dose, these 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 round of treatment failed. As a result, we underreport time to conception in women who conceived after a second course of treatment. To assess the extent of treatment misclassification, we compared registry data to medical records for the subset of women who also participated in the FUCHSIA study. In this population, the sensitivity for treatment with chemotherapy at any time before conception was 92%, with perfect specificity; radiation before pregnancy had 88% sensitivity and perfect specificity. Only 1 out 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 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 shown that vital record accuracy is excellent for birthweight and our matching variables,[91-94] and generally good for clinical estimate 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 two years of diagnosis, when the risk of relapse is highest, to lower the risk of needing more cancer treatment during pregnancy. Others may not have time to wait, because cancer treatments such as alkylating chemotherapy can accelerate ovarian aging.[118] 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 diagnosed with cancer during their reproductive years.

5.7 Acknowledgments

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5.8 Tables

Table 5.1. Characteristics of the first eligible live singleton birth to women ages 20-45 conceived after cancer diagnosis, by time between diagnosis and conception.

	All	≤1 year		>1-2 years		>2-5 years		>5 years	
Characteristics	**N**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cancer type									
Breast	754	168	22	212	28	273	36	101	13
Cervical	131	42	32	33	25	41	31	15	11
Hodgkin lymphoma	293	55	19	67	23	114	39	57	19
Melanoma	981	282	29	252	26	321	33	126	13
Thyroid	970	263	27	244	25	352	36	111	11
Other	1,074	291	27	270	25	376	35	137	13
Age at diagnosis									
20-24	910	192	21	188	21	332	36	198	22
25-29	1,412	337	24	359	25	511	36	205	15
30-34	1,283	336	26	365	28	457	36	125	10
35-39	532	200	38	146	27	167	31	19	3.6
40-45	66	36	55	20	30	10	15	0	-
Maternal age at birth									
20-24	251	128	51	76	30	47	19	0	-
25-29	1,084	305	28	299	28	390	36	90	8.3
30-34	1,480	359	24	396	27	525	36	200	14
35-39	1,089	237	22	257	24	408	37	187	17
40-45	299	72	24	50	17	107	36	70	23
Maternal race and ethnicity									
White, non-Hispanic	3,074	782	25	786	26	1,101	36	405	13
African American, non-Hispanic	810	234	29	212	26	262	32	102	13
Other non-Hispanic	191	53	28	52	27	64	34	22	12
Hispanic, any race	128	32	25	28	22	50	39	18	14
Maternal education									
Less than high school	259	89	34	68	26	75	29	27	10
High school or GED	801	207	26	239	30	270	34	85	11
Some college or associate degree	1,278	348	27	298	23	462	36	170	13
At least 4 years of college	1,865	457	25	473	25	670	36	265	14
Mother married									
Yes	3,380	860	25	878	26	1,206	36	436	13
No	819	241	29	199	24	270	33	109	13
Missing	4	0	-	1	-	1	-	2	-

Table 5.2. Risk and risk ratios by time between treatment start date and conception of the first live birth after cancer, compared with the risk in matched women who have never had cancer.

		Preterm birth			Low birth weight			Small for gestational age		
	Live births	N	Risk (%)	RR	N	Risk (%)	RR	N	Risk (%)	RR
All cancers, chemotherapy without radiation										
≤1 year	121	26	21 (15, 29)	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 years	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 years	179	17	10 (6, 15)	0.9 (0.6, 1.4)	17	10 (6, 15)	1.3 (0.8, 2.1)	21	12 (7, 17)	1.2 (0.8, 1.9)
>5 years	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 year	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 years	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 years	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 years	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 year	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 years	60	6	10 (4, 21)	1.0 (0.4, 2.0)	5	8 (3, 18)	1.3 (0.6, 3.1)	4	5 (2, 16)	0.8 (0.3, 1.8)
>2 years	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 year	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 years	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 years	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*										
≤1 year	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 year	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*										
≤1 year	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)

Table 5.2. *Continued*

		Preterm birth			Low birth weight			Small for gestational age		
	Live births	N	Risk (%)	RR	N	Risk (%)	RR	N	Risk (%)	RR
Thyroid cancer*										
>1-2 years	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 years	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 years	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)

**For cervical and thyroid cancer, the timing categories reflect time from diagnosis to conception, rather than treatment start to conception.*

5.9 Appendix Tables

Appendix Table 5.A1. Risks and risk ratios for small for gestational age (SGA) births by the mother's age at cancer diagnosis and time between start of treatment and conception, for women treated with chemotherapy (with or without radiation).

	Diagnosis age 20-29				Diagnosis age ≥30			
Treatment start to conception	**N**	**SGA N**	**Risk (%)**	**RR**	**N**	**SGA N**	**Risk (%)**	**RR**
≤1 year	103	13	13 (7, 21)	1.1 (0.7, 1.9)	90	14	16 (9, 25)	1.4 (0.8, 2.3)
>1-2 years	124	16	13 (8, 20)	1.1 (0.7, 1.8)	134	15	11 (6, 18)	1.1 (0.7, 1.9)
>2-5 years	178	15	8 (5, 14)	0.9 (0.5, 1.5)	159	21	13 (8, 19)	1.4 (0.9, 2.2)
>5 years	99	18	18 (11, 27)	2.1 (1.3, 3.2)	45	11	24 (13, 40)	1.8 (1.0, 3.1)

Appendix Table 5.A2. Risk of preterm birth, low birth weight, and small for gestational age infants by time from imputed end of treatment to conception of first pregnancy among breast cancer patients.

		Preterm birth			Low birth weight			Small for gestational age		
	Live births	N	Risk (%)	RR	N	Risk (%)	RR	N	Risk (%)	RR
Chemotherapy without radiation										
≤1 year	48	13	27 (15, 42)	2.4 (1.5, 3.9)	11	23 (12, 37)	2.6 (1.5, 4.5)	6	13 (5, 25)	1.1 (0.5, 2.5)
>1-2 years	51	3	6 (1, 16)	0.5 (0.2, 1.7)	3	6 (1, 16)	0.8 (0.3, 2.3)	6	12 (4, 24)	1.3 (0.6, 2.7)
>2 years	71	7	10 (4, 19)	0.7 (0.4, 1.5)	9	13 (6, 23)	1.3 (0.7, 2.5)	12	17 (9, 28)	1.4 (0.8, 2.4)
Chemotherapy and radiation										
≤1 year	62	16	26 (16, 39)	2.1 (1.3, 3.2)	12	19 (10, 31)	2.0 (1.2, 3.4)	11	18 (9, 30)	1.7 (1.0, 2.9)
>1-2 years	53	8	15 (7, 28)	1.4 (0.7, 2.7)	5	9 (3, 21)	1.3 (0.6, 3.2)	6	11 (4, 23)	1.0 (0.5, 2.2)
>2 years	88	9	10 (5, 19)	0.9 (0.5, 1.7)	9	10 (5, 19)	1.2 (0.6, 2.2)	13	15 (8, 24)	1.3 (0.8, 2.3)

5.10 Figures

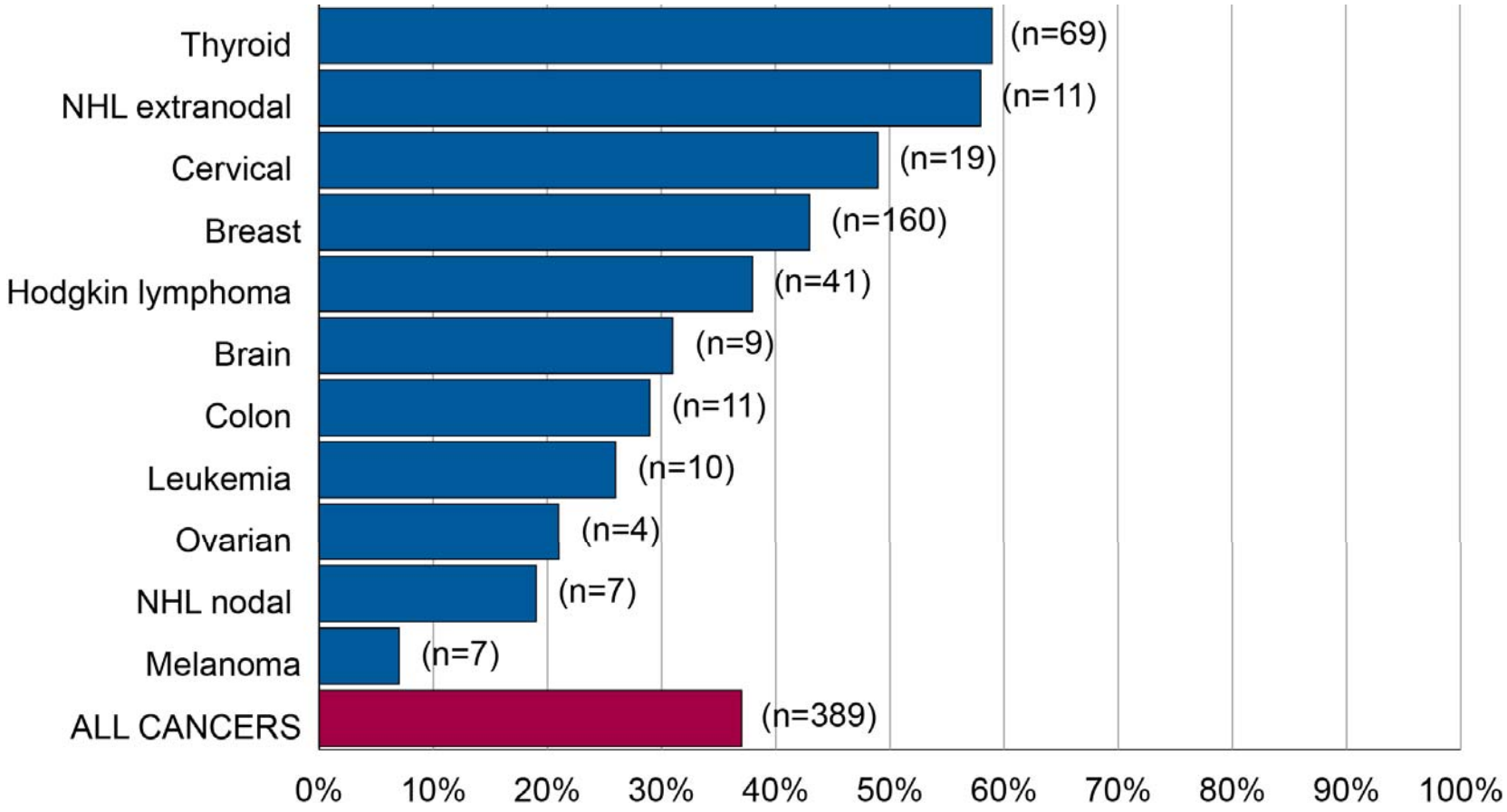

Figure 5.1. Percent (and number) of cancer survivors in the FUCHSIA Women's Study who reported receiving a recommendation from a healthcare professional about how long to wait after their treatment ended before attempting pregnancy, by cancer type.

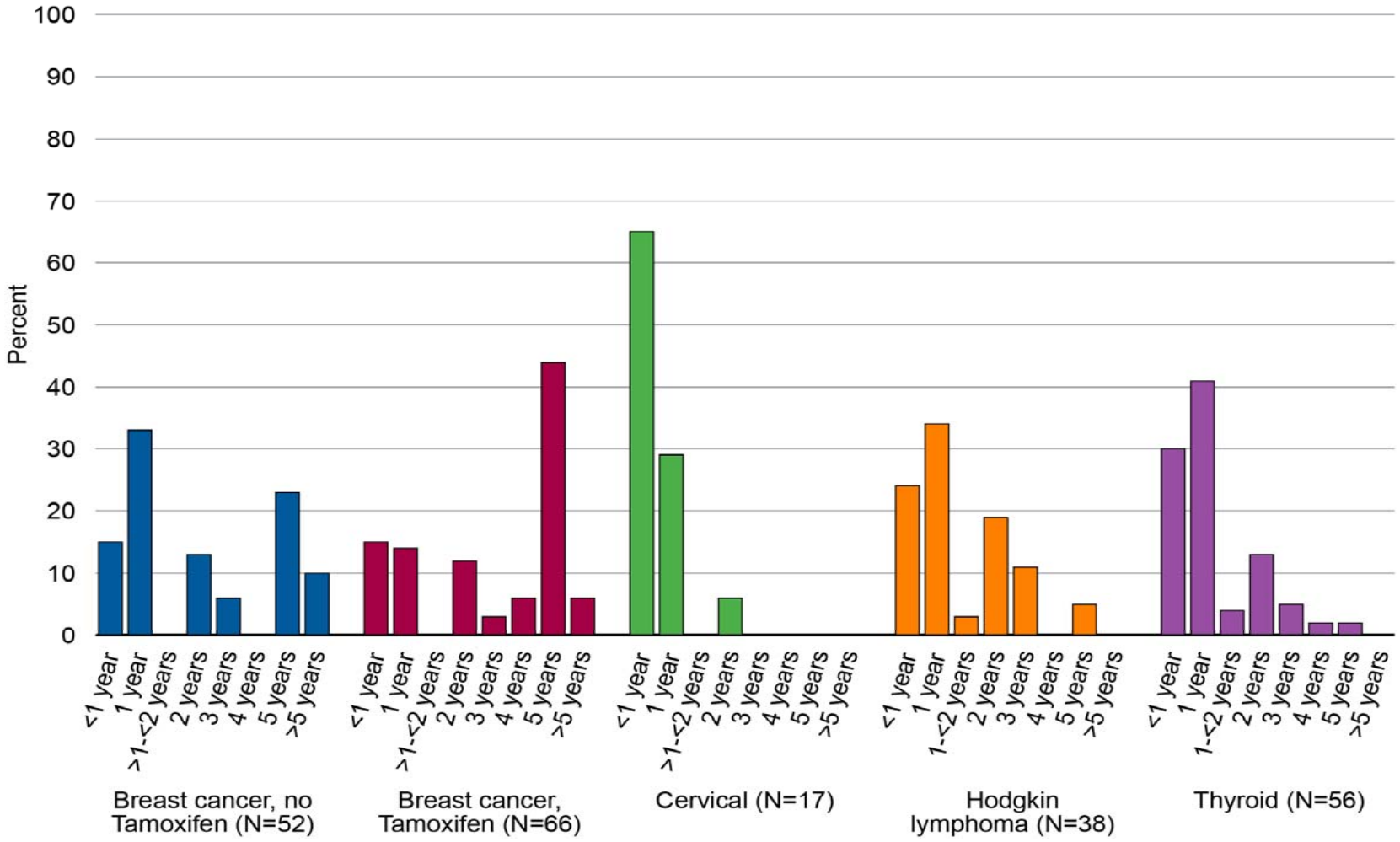

Figure 5.2a. Length of time that cancer survivors in the FUCHSIA Women's Study said they were told to wait after treatment before attempting pregnancy, by cancer type.

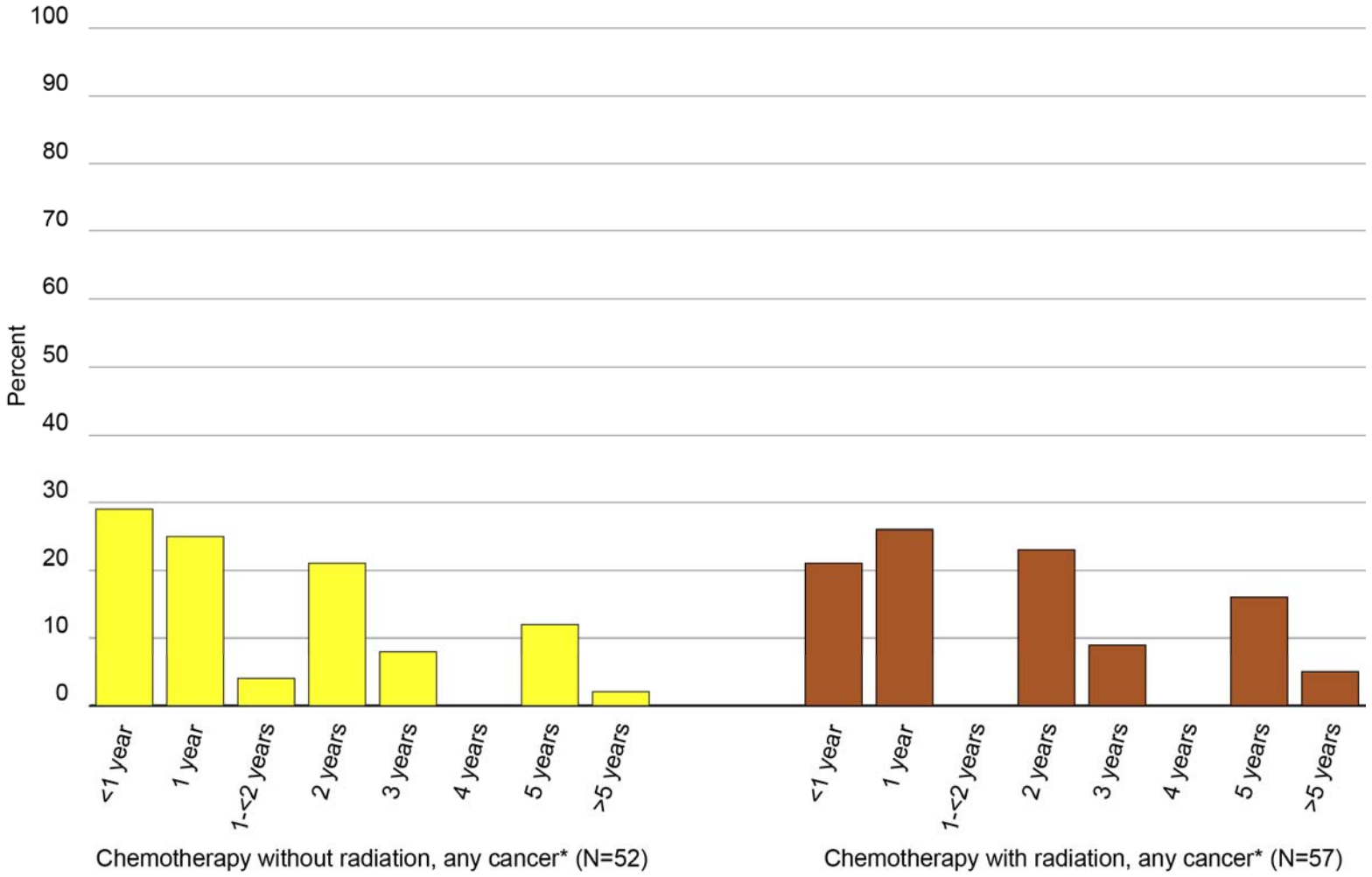

Figure 5.2b. Length of time that cancer survivors in the FUCHSIA Women's Study said they were told to wait after treatment before attempting pregnancy, by treatment type.
**Excluding women prescribed Tamoxifen.*

6. CONCLUSION AND FUTURE DIRECTIONS

6.1 Summary of Findings

This population-based study across three U.S. states is the largest of its kind to date. It provided an opportunity to examine whether women have higher risks of adverse outcomes in pregnancies conceived after cancer, and how these risks differ by race, cancer type, treatment, or pregnancy timing after cancer.

In infants born to survivors of invasive breast cancer, we observed higher risks of preterm delivery and related outcomes such as low birth weight, but only in those conceived soon after treatment. For breast cancer survivors who conceived >1 year after starting chemotherapy without radiation or >2 years after chemotherapy with radiation, the risks of having a preterm or low birth weight infant were no higher than in matched women without a history of cancer. In the sample of women who participated in the FUCHSIA Women's Study, more than 40% of all of breast cancer survivors said that they received a recommendation from a health care provider about how long to wait before attempting to conceive. These conversations provide an opportunity for clinicians to counsel women that pregnancy risks may be highest in the first 1-2 years after starting treatment.

Cervical cancer survivors had a high risk of preterm birth in pregnancies conceived the first year after cancer, with 36% of infants delivered before 37 weeks. Although the risk of preterm birth was slightly lower in pregnancies conceived >1 year after diagnosis, it remained elevated at 25%. Leukemia survivors also had a higher risk of preterm birth in pregnancies conceived after diagnosis, but there was insufficient sample size to determine whether the risks differed by type of treatment or timing of conception.

Some cancer diagnoses were associated with a higher risk of infants born small for gestational age in subsequent pregnancies. Infants born to survivors of brain cancer, extranodal

non-Hodgkin lymphoma, and possibly leukemia had higher risks of SGA. Because the sample sizes for these cancers were small, we were unable to assess whether the risks are limited to survivors who received certain treatments or vary by time since treatment. Infants born to women treated with beam radiation for any cancer for the head or neck might have higher risks of SGA, although our results for this outcome were not precise. Thyroid cancer survivors had higher risks of gestational diabetes and possibly gestational hypertension complicating the first pregnancy after diagnosis, but no higher risk of any other pregnancy outcomes we examined.

Infants born to survivors of ductal carcinoma in situ, melanoma, and nodal non-Hodgkin lymphoma did not have higher risks of preterm birth, low birth weight, or SGA. In contrast to infants born to breast cancer survivors treated with chemotherapy, infants born to survivors of Hodgkin lymphoma did not have higher risks of adverse outcomes, regardless of whether the women had chemotherapy. This difference suggests that the risks of chemotherapy likely differ sharply by regimen. Although African-American women had slightly higher risks of preterm birth and small for gestational age infants after cancer than white women, this was largely due to the higher baseline risk of these outcomes in African-American women, rather than a larger increase in risk attributable to cancer.

The validation sub-study of FUCHSIA Women's Study participants with medical records allowed us to assess whether the misclassification of treatment in the cancer registry affected the results. Most of the associations we estimated using treatment data in the registry did not meaningfully change in the bias analysis designed to correct for incomplete reporting of chemotherapy and radiation.

6.2 Study Limitations

This study design linking cancer registry data to vital records has certain limitations. One is that the U.S. does not have a national cancer registry, so women who gave birth in a different state than where they were diagnosed are missing from this analysis. We were also unable to

identify cancer survivors who were diagnosed before the years of the study. Thus, we are missing a disproportionate number of survivors with a long interval between diagnosis and the first birth after cancer, because these women are more likely to have been diagnosed in years before we have registry data and had more time to move out of state between the diagnosis and birth. However, for this missing data to bias the study, the women who did not link because they moved out of state or who had longer intervals would have to be systematically different than women who remained. A further limitation is that cancer registries record radiation type but not location, so we were unable to distinguish women who had total body radiation that included the pelvic field. Finally, cancer registries record the start but not the end date of treatment, so we had to analyze outcomes by time since treatment initiation rather than completion. Because treatment duration can vary even among women with the same treatment type, we were unable to pinpoint exact dates of treatment completion.

Vital records have limitations of their own. Although the study covariates and outcomes including birth weight, Apgar score, and NICU admission are well-reported in vital records, birth certificates often underreport complications of pregnancy. Thus, the observed association between thyroid cancer and gestational diabetes and hypertension should be interpreted with caution. Vital records also have poor sensitivity for birth defects, particularly those that are not evident at delivery, which prevented us from including this outcome. We were also unable to analyze stillbirth as an outcome because of the high number of these records that were missing values for our matching variables, or spontaneous abortion, because vital records do not report pregnancies ending before 20 weeks.

Finally, we did not have sufficient sample size to analyze risks for less common treatments, such as stem cell transplant or brachytherapy. For cancers including brain, leukemia, and non-Hodgkin lymphoma, we had insufficient sample size to stratify by treatment type or timing of conception.

6.3 Study Strengths

This study had important strengths, including its population-based design and representation of African-American women. It is the first large study to include medical records for a subset of women, which allowed us to assess the potential bias introduced by misclassification of treatment in the registry. Importantly, it was limited to women treated in the modern era; previous studies have had to include cases as far back as the 1940s-1970s, when management of cancer and pregnancy were very different. This study was also the first population-based study to consider the timing of conception after diagnosis, allowing us to distinguish transient from long-term effects of treatments. Importantly, we were able to calculate separate risks for different cancer types and treatments. Our results improved on previous studies by showing that elevated risks are likely limited to certain cancers and treatments, and for cancers such as breast, only in women who conceive soon after treatment.

6.4 Future Directions

Our observation that risks may be lower in women with longer intervals between chemotherapy treatment and conception has important implications for future studies. The mechanism by which certain chemotherapeutic drugs could increase pregnancy risks for 1-2 years after treatment initiation include side effects such as anemia, inadequate weight gain during pregnancy, and immunosuppression, which have been associated with preterm birth.[19,20] Recent studies in breast cancer patients treated with cyclophosphamide have found evidence that reduced immune function may persist more than a year after treatment.[112-114] Future studies should thus measure immune markers to determine whether lower immunity after treatment with chemotherapy is associated with preterm birth. Identification of a meaningful biomarker that mediates the association between cancer treatment and preterm delivery could allow clinicians to gauge whether a woman's immune function has recovered before she conceives. This would

allow clinicians to better pinpoint the optimal time for cancer survivors to wait before attempting pregnancy and better tailor recommendations to individual patients.

In this study, we observed a 36% risk of preterm birth in pregnancies conceived ≤1 year of cervical cancer diagnosis, and 25% for pregnancies conceived at >1 year after diagnosis. Because the confidence intervals for RRs in pregnancies conceived ≤1 and >1 year after diagnosis were wide and overlapping, we could not rule out that the difference is a chance finding. Some authors have suggested that the risk of early delivery may be especially high in the first year after cervical surgery due to incomplete wound healing,[73] but the results of small clinical studies have been mixed.[71-73,116,119,120] Interviews with participants of the FUCHSIA Women's Study suggest most cervical cancer patients say they were told to wait less than a year before conceiving, so it is important for future studies to assess whether the evidence on pregnancy outcomes aligns with this recommendation. Studies should examine timing of conception in cervical patients by type of cervical procedure to assess whether the risks of conceiving soon after surgery may outweigh the benefits for some women.

To our knowledge, this is the first study to examine whether thyroid cancer survivors are at increased risk of gestational diabetes and hypertension. Future studies incorporating medical records and markers of thyroid function could help clarify the risks in these patients and assess whether earlier screenings or closer management could improve pregnancy outcomes. We had insufficient sample size to examine these complications by time since treatment, but future studies could assess whether the risks, if confirmed, might be limited to thyroid patients who conceive soon after treatment or have not yet established optimal levels of thyroid hormone.

Our observation of higher risks after chemotherapy in infants born to survivors of breast cancer, most of whom receive cyclophosphamide, but not in infants born to survivors of Hodgkin lymphoma, most commonly treated with the regimen of doxorubicin (Adriamycin), bleomycin, vinblastine, and the alkylating agent dacarbazine, suggests that pregnancy outcomes may be

highly dependent on drug. Future studies can incorporate medical records to assess whether particular drugs are associated with higher risks of preterm or growth-restricted infants in other cancer types. We observed higher risks for some adverse pregnancy outcomes after leukemia, brain cancer, and extranodal non-Hodgkin lymphoma. Future research should assess whether certain treatments might increase the risks in these patients, whether the risks depend on pregnancy timing, and if women who receive similar treatments for less common cancers may share these risks. It is possible that the higher risk of infants born small for gestational age in brain cancer patients is due to radiation to a field including the hypothalamus or pituitary. The estimates for beam radiation to the head and neck were suggestive of an association between cranial radiation and low birth weight, but were not precise.

Our results underscore that pregnancy outcomes vary by cancer type, treatment, and timing of conception. While survivors of extranodal non-Hodgkin lymphoma, thyroid cancer, brain cancer and cervical cancer may need closer management during pregnancy, the results were reassuring for women diagnosed with DCIS, melanoma, Hodgkin lymphoma, and nodal non-Hodgkin lymphoma. Critically, some risks of cancer treatment appear to be transient; breast cancer survivors who waited more than 1-2 years after starting treatment had no higher risk of preterm birth than women without a history of cancer. Interviews with cancer survivors in the FUCHSIA Women's Study suggest that many are talking with their health care providers about pregnancy. The results from this study provide critical evidence that can enhance counseling of these survivors, inform recommendations on how long they should wait before they conceive, and improve obstetric care for women who are able to get pregnant after cancer.

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