Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Brittany Smith Date

Age at Cancer Diagnosis and Adverse Pregnancy Outcomes

By

Brittany Smith
Degree to be awarded: MPH

Epidemiology

_____

Penelope P. Howards, Ph.D.
Committee Chair

Age at Cancer Diagnosis and Adverse Pregnancy Outcomes

By

Brittany Smith

B.A. in Chemistry and Global Studies-Global Health
University of North Carolina at Chapel Hill
2018

Thesis Committee Chair: Penelope P. Howards, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2020

Abstract

Age at Cancer Diagnosis and Adverse Pregnancy Outcomes
By Brittany Smith

Studies have reported that cancer survivors are at an increased risk of preterm birth and low birth weight compared to women without history of cancer, but results for small for gestational age (SGA) are not consistent. Prior studies have not evaluated whether the risk of adverse pregnancy outcomes varies by age at cancer diagnosis although fertility outcomes have been reported to change with increasing age at cancer diagnosis. This study examines the relationship between age at cancer diagnosis and preterm birth, low birth weight and SGA while accounting for age at pregnancy. Georgia and North Carolina cancer registry data were linked to state birth records. We fit log-binomial models to estimate risk ratios (RR) comparing cancer survivors to cancer-free women matched on maternal age at delivery, parity, race/ethnicity, and education to women. Separate models were fit for four categories of age at cancer diagnosis: 20-24, 25-29, 30-34, and 35-45. Cancer survivors had an increased risk of preterm birth and low birth weight compared with cancer-free women, but the strength of the RRs did not vary across age at cancer diagnosis in a consistent pattern. Risk of preterm birth was increased for survivors diagnosed between ages 30 to 45 who were treated with chemotherapy compared with matched cancer-free women (RR = 1.94, $CI_{95\%}$: 1.23, 3.08). Most RRs for SGA were null, but when survivors treated with chemotherapy and invasive breast cancer survivors treated with chemotherapy were diagnosed between ages 30 and 45 there was an increased risk for SGA. These results suggest an opportunity for healthcare professionals to monitor cancer survivors for preterm birth and low birth weight, but age at cancer diagnosis does not appear to be an important predictor of adverse pregnancy outcomes.

Age at Cancer Diagnosis and Adverse Pregnancy Outcomes

By

Brittany Smith

B.A. in Chemistry and Global Studies-Global Health
University of North Carolina at Chapel Hill
2018

Thesis Committee Chair: Penelope Howards, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2020

Acknowledgements

I would like to begin with thanking my amazing thesis chair, Penelope Howards. Her class made me feel like I was prepared to tackle the analysis needed for a thesis and I appreciate the countless meetings, discussions, and edits as we went through the process. Additionally, I am thankful for the opportunity to explore this research question under her guidance. I am lucky to have found a great mentor in Dr. Howards.

I would also like to thank others who aided in my thesis process. Kathleen Hartnett lent her time and support during this project. I deeply appreciate her help with understanding the data and answering analysis questions. Her prior work put me in a great position to execute my thesis. I would also like to acknowledge and thank Dr. Michael Kramer for helping me think through additional analyses questions.

I am also grateful to Dr. Ward and the staff at the Georgia and North Carolina cancer registries for creating a data linkage protocol and linking cancer registry data and vital records. These registries helped to provide the data that made this thesis possible

I really could not have done this without support from my family, loved ones, and friends. They were always there to encourage me in completing my MPH and constantly checked in on me. I am grateful to have such compassionate and caring people in my life.

I would also like to thank the Lettie P. Whitehead scholarship foundation for their generosity and support in pursuing my graduate education.

Table of Contents

Chapter 1. Background

Introduction

A cancer diagnosis and the corresponding treatments among women prior to pregnancy can affect birth outcomes and fertility. As of 2016, there were an estimated 339,380 female cancer survivors ages 20-39 years old.[1] With approximately 57%-70% of patients 40 or younger wanting children after cancer, more research about this group is needed.[2–4] Prior research has focused on the differences in pregnancy outcomes related to length of time between the beginning of treatment and conception, and related to different cancer types and treatments. However, there is minimal research on the effect of age at cancer diagnosis and birth outcomes. We will evaluate whether age at cancer diagnosis plays a role in pregnancy outcomes, such as preterm birth, low birth weight, and small for gestational age. If there are cancer survivors at higher risk for poor pregnancy outcomes based on age of diagnosis, this could provide an opportunity for clinicians to monitor these women more carefully.

Cancer

Each year in the United States, more than 90,000 adolescents and young adults (AYA), ages 15 to 39, are diagnosed with cancer.[5] Many of the cancers diagnosed in AYA patients, such as lymphoma, testicular, and breast cancers have good survival outcomes.[6] There are almost 1 million cancer survivors of reproductive age living in the United States.[6] With medical developments and improvements, more are surviving cancer and this number will continue to increase. As of 2016, there were an estimated 339,380 female cancer survivors ages 20-39 years old.[1] The five year survival rate for women diagnosed with any invasive cancer before they are 45 years old is 85.8%.[5] For women diagnosed with invasive breast cancer before age 45, the five-year survival rate

is 88.1%.[5] Women diagnosed with invasive melanoma before age 45 have a 95.0% five-year survival rate.[5] With high survival rates in women before age 45, it is important to look at quality of life.

Cancer Survivorship Quality of Life

Female AYA cancer survivors often express concern about offspring health, personal health, pregnancy health, and partner disclosure when considering pregnancy.[7] Potential adverse pregnancy outcomes include preterm birth, low birth weight, and small for gestational age. Research has looked at the relationship between being a cancer survivor and these adverse birth outcomes. Some of these studies have focused on differential risks across cancer types and the impact of time between cancer treatment onset and conception. There is not sufficient research examining the relationship between age at cancer diagnosis and adverse pregnancy outcomes.

Pregnancy Outcomes

Preterm Birth

One birth outcome of interest is preterm birth, defined as delivery prior to 37 weeks of gestation. The rate of preterm birth in the United States has been declining since 2006 and as of 2013, the rate of preterm birth was 11.4%.[8] Factors associated with preterm birth include family history or personal history of preterm birth, African American race, stress and depression, low socioeconomic status, and maternal age.[8] In addition to these risk factors, cancer status could also affect preterm birth.

Studies have evaluated the relationship between cancer survivorship and preterm birth. In a study of childhood cancer survivors, risk of preterm birth for female cancer survivors was compared to risk of preterm birth for female siblings of the survivors.[9] Offspring of female cancer survivors had a higher risk of being born preterm

than offspring of female siblings (OR = 1.9, $CI_{95\%}$: 1.4, 2.4).[9] In another study comparing female cancer survivors diagnosed before age 35 (n=1,800) and siblings (n=7,137) in Finland, survivors were 51% more likely to deliver preterm that the sibling group ($p<0.001$).[10]

A study focusing on the effect of radiation on preterm birth used The British Childhood Cancer Survivor Study (BCCSS), a population-based cohort of those diagnosed between age 0 to 14 years, with birth records linked using Hospital Episode Statistics for England.[11] Wilms tumor cancer survivors treated with abdominal radiotherapy were more likely to deliver preterm than survivors treated without radiotherapy (RR = 1.89, $CI_{95\%}$: 1.30, 2.74).[11]

Another study looked at breast cancer survivors (n=338) who gave birth after cancer and their incidence of preterm birth compared to non-breast cancer survivors (n=6,760).[12] The risk of preterm birth was not meaningfully different (RR = 1.15, $CI_{95\%}$: 0.83, 1.59).[12] However, births to women with a history of ER- breast cancer were 1.97 times more likely to be preterm than births to women without a history of cancer ($CI_{95\%}$: 1.19, 3.26).[12]

Furthermore, there are different risks associated with the length of time between treatment onset and conception and preterm birth among women who conceived their first pregnancy after diagnosis between ages 20 and 45 compared to women without a history of cancer.[13] Women who waited less than a year to conceive after treatment onset had higher risks of preterm birth than women without a history of cancer ($RR_{chemotherapy\ alone}$ = 1.9, $CI_{95\%}$: 1.3 -2.7; $RR_{chemotherapy\ and\ radiation}$ = 2.4, $CI_{95\%}$: 1.6 -3.6).[13] Women who wait a year or more after chemotherapy alone or women who waited two years or more after beginning chemotherapy and radiation had similar risks of preterm birth to women without a history of cancer.[8]

These studies provide evidence about the effects of cancer and preterm birth in cancer survivors compared to siblings, specific cancer types, and survivors who waited longer to conceive after diagnosis compared to those who waited less time. However, these studies do not look at if these associations differ by age at cancer diagnosis. Additionally, the childhood cancer studies included women diagnosed before age 14. Associations could be different in a population treated before menarche compared to women treated after menarche.

Low Birth Weight

In 2012, 8% of babies born were low birth weight in the United States and 1.4% were very low birth weight.[14] Low birth weight babies mainly consist of babies born preterm although some low birth weight births are due to fetal growth restriction.[14] Additional risk factors affecting low birth weight include multiple gestation, substance abuse, chronic medical conditions such as high blood pressure, and race or ethnicity.[14]

In addition to these risk factors which are relevant to all women, research has evaluated the risk of low birth weight among cancer survivors. In a study of women with a history of breast cancer who were treated with chemotherapy compared to women without a history of breast cancer, the risk ratio of low birth weight was 1.92 ($CI_{95\%}$, 1.50–2.45).[15]

An additional study looked at breast cancer survivors (n=338) who gave birth after cancer and their incidence of low birth weight births compared to non-breast cancer survivors (n=6,760).[12] The risk of low birth weight was not meaningfully different (RR = 1.27, $CI_{95\%}$: 0.89, 1.81).[12] Births to women with a history of ER- breast cancer were 2.80 times more likely to be low birth weight than births to women without a history of cancer ($CI_{95\%}$: 1.73, 4.52).[12]

Reulen's study using the BCCSS cohort evaluated the effect of radiotherapy on low birth weight.[11] Wilms tumor survivors treated with abdominal radiotherapy had a higher risk of low birth weight offspring compared to offspring of survivors treated without radiotherapy (RR = 2.85, $CI_{95\%}$: 1.79, 4.48).[11]

In a study examining the relationship between time between cancer diagnosis and conception and birth outcomes, for women who conceived within less than one year from treatment onset, the risk of low birth weight was two times greater than women with no history of cancer ($CI_{95\%}$, 1.4 - 3.0).[13]

These studies support higher risks of low birth weight births in cancer survivors compared to women without a history of cancer. Incidence further varied by cancer treatments and cancer sites and subtypes. The studies did not account for age at diagnosis. In the study looking at treatment and Wilms tumors from the childhood cancer cohort, most participants were treated prior to menarche which could result in different associations from studies of women treated after menarche.[11] With some studies showing increased risks of low birth weight, it is important to understand if risks are uniform across age groups in women who are of reproductive age at diagnosis.

Small for Gestational Age

Small for Gestational Age (SGA) is an adverse pregnancy outcome defined as a birth weight less than the 10th percentile for gestational age, and it is associated with stillbirth and neonatal mortality.[16] The prevalence of SGA is approximately 8.6% - 9.6%. Risk factors for SGA are both genetic and environmental.[16] Some factors include maternal nutrition, substance use and/or abuse, maternal short stature, low weight, Indian or Asian ethnicity, nulliparity, and mother born SGA.[16]

A study comparing cancer survivors diagnosed at age 16-45 years identified through the Norwegian Cancer Registry to age-matched comparison women in the

Medical Birth Registry of Norway found no differences in risk of SGA between cancer survivors and the comparison women.[17] The researchers hypothesized this to be due to a lack of LBW or preterm infants resulting from small numbers that were eligible to meet SGA criteria.[17]

The risk of SGA has also been examined within cancer survivors.[18] Brain cancer survivors (RR = 1.7, $CI_{95\%}$: 1.1, 2.8) and extranodal non-Hodgkin lymphoma survivors (RR = 2.3, $CI_{95\%}$: 1.5, 3.6) were at a higher risk of SGA infants compared to women without a history of cancer, but risks weren't meaningfully different for other cancer types.[18] The risk of SGA was not meaningfully different (PR = 1.13, $CI_{95\%}$: 0.80, 1.60) in a study comparing breast cancer survivors (n=338) who gave birth after to non-breast cancer survivors (n=6,760).[12]

Looking at time between treatment onset and conception and SGA, cancer survivors who conceived closer to treatment onset had a lower risk of offspring who were SGA compared to women who waited longer between treatment onset and conception.[13] The risk of cancer survivors who waited at least five years after treatment onset before conception was twice that of women without a history of cancer ($CI_{95\%}$, 1.3 - 3.1).[13] Comparatively, the risk of cancer survivors who waited less than one year after treatment onset before conception was not meaningfully different from women without a history of cancer.[13]

These previous studies present mixed results on cancer and SGA with results varying when stratified by cancer type or timing between cancer diagnosis and conception. The Stensheim study identified small numbers as a possible cause for there being no meaningfully difference in risk of SGA for cancer survivors and women without a history of cancer.[17] The other studies that looked at SGA by cancer type or by timing did not account for age at diagnosis, but found inconsistent results.[12,13,18]

Age at Cancer Diagnosis

For the outcomes of interest; preterm birth, low birth weight, and SGA, studies have examined associations with general cancer survivorship, cancer types, and time to conception after cancer diagnosis. However, there is minimal research looking at the age at cancer diagnosis and fertility and pregnancy outcomes, and some of the studies offer conflicting results. If age at cancer diagnosis is associated with adverse pregnancy outcomes, doctors will better be able to treat and monitor these patients if they are at higher risk.

Regarding fertility, a study looked at age of diagnosis and acute ovarian failure in women from the Childhood Cancer Survivor Study cohort consisting of women diagnosed before the age of 21 years in the United States or Canada (n = 3,390).[19] Among the women who developed acute ovarian failure (n=215), women diagnosed between ages 13 and 20 were 1.8 times more likely to develop AOF ($CI_{95\%}$: 1.4-2.4).[19]

A review paper on ovarian aging and age at treatment looked at persistent menses, early menopause, and infertility for certain cancer sites compared to the general population.[20] They reported that the probability of early menopause after start of treatment decreases as age at treatment increased, but the chance of infertility increased as age of diagnosis increased.[20]

In a study of breast cancer survivors aged 40 or younger who were treated with chemotherapy and/or antihormonal therapy, becoming pregnancy was found to be associated with younger age at diagnosis.[21] However, this study was small sample with only 22 breast cancer survivors with a pregnancy and 281 survivors without a pregnancy.

In contrast, the childhood cancer study which compared cancer survivors diagnosed before age 21 to siblings, did not find a consistent association between age at diagnosis and reduced probability of becoming pregnant or having a live birth.[22]

The studies that considered age at cancer diagnosis as a potential reproductive risk factor focused on fertility and becoming pregnant. The fertility studies reported worsening fertility as age at cancer diagnosis increased.[19,20] The studies looking at age at cancer diagnosis and pregnancy after cancer presented mixed results possibly due to small sample sizes.[21,22] With reduced fertility at older ages of cancer diagnosis and mixed results on the potential effects of age at cancer diagnosis on giving birth after cancer, it is important to consider the potential effects of age at cancer diagnosis on pregnancy outcomes after cancer to best understand reproductive struggles of cancer survivors.

Conclusion

Understanding the relationship of cancer survivors and birth outcomes becomes increasingly important as the number of cancer survivors continues to increase and improvement in fertility planning improves for women undergoing cancer treatment. While there is research on some aspects of cancer survivors and birth outcomes, there remains gaps in other areas. In order to address these gaps, this study examines the relationship between age at cancer diagnosis and adverse birth outcomes such as preterm birth, low birth weight and small for gestational age while accounting for age at pregnancy.

Chapter 2. Age at Cancer Diagnosis and Adverse Pregnancy Outcomes

Introduction

In 2016, there were 339,380 female cancer survivors between 20 and 39 years old in the United States.[1] An estimated 57%-70% of cancer survivors age 40 or younger want children after cancer.[2–4] Thus, pregnancy health is a common concern among female adolescent and young adult cancer survivors.[7] In fact, studies have reported heightened risks of preterm birth and low birth weight in infants born to cancer survivors compared to women without a history of cancer.[9–13,15] However, the magnitude of association varied by cancer sites and timing between cancer diagnosis and conception. Most studies have not reported similar differences in having small for gestational age (SGA) births.[12,13,17]

Previous research has suggested that younger age at cancer diagnosis is associated with better fertility outcomes. A study from a childhood cancer survivor cohort found increased risks of acute ovarian failure in cancer survivors diagnosed between the ages of 13 and 20 compared with those diagnosed before age 13.[19] However, they did not find a meaningful association between age at cancer diagnosis and the ability to become pregnant or have a live birth.[22] Among young adult cancer survivors, a review reported that early menopause decreased as age at diagnosis increased, but infertility increased as age at diagnosis increased.[20] Additionally, a study reported an increased probability of becoming pregnant among breast cancer survivors diagnosed at younger ages compared to those diagnosed at older ages.[21] While these studies examine age at diagnosis and fertility or the ability to have a live birth, they do not evaluate the risk of adverse pregnancy outcomes such as preterm birth, low birth weight, or SGA.

The aim of this study was to assess whether the risk of adverse pregnancy outcomes differed by age at cancer diagnosis for women diagnosed with cancer as adults compared to women of the same age at pregnancy without a history of cancer.

We hypothesized that women diagnosed with cancer at younger ages would have similar risks of adverse birth outcomes to those without a history of cancer, and women diagnosed at older ages would be at higher risk of adverse birth outcomes.

Materials and Methods

Study Population

We identified women who had given birth after cancer by linking cancer registry data to birth certificate data in Georgia and North Carolina. Both state registries used the same linking protocol developed by the Georgia Cancer Registry. Women diagnosed with invasive cancer or ductal carcinoma in situ (DCIS) between the ages of 20 and 45 years were eligible. In Georgia, cancers diagnosed between August 23, 1993 and August 22, 2012 were linked to births between 1994 and 2012. In North Carolina, cancers diagnosed between August 23, 1999 and August 22, 2012 were linked to births between 2000 and 2013. Only first births after a cancer diagnosis were analyzed in this study. Women diagnosed with cancer during pregnancy were excluded.

Cancer survivors were matched to women without a history of cancer. The comparison women were eligible if they did not have a record of cancer in their state's cancer registry. Comparison women were matched to cancer survivors 5:1 within the same state on mother's age at delivery, race and ethnicity, parity, and maternal education. For sub-analyses with a smaller sample size; breast cancer survivors, melanoma survivors, and invasive breast cancer survivors treated with chemotherapy, comparison women were matched 20:1 to reduce random error. For both cancer survivors and comparison women, only singleton births between 20- and 44-weeks' gestation to mothers between the ages of 20 and 45 years were included.

Age at Diagnosis

Age at cancer diagnosis was obtained from the cancer registry records. We divided age at diagnosis into four categories; 20-24, 25-29, 30-34, and 35-45.

Outcomes

Adverse birth outcomes were identified in vital records and included: preterm birth, low birth weight, and SGA. Preterm birth was defined as a live birth before 37 weeks gestation. Low birth weight was defined as a live birth less than 2,500 g. Small for gestational age was defined as a live birth less than 10% of birth weight for gestational age and sex using national birthweight curves.[16]

Covariates

We identified potential confounders using a causal diagram drawn based on the literature. We matched on four potential confounders: maternal age at delivery, race/ethnicity, parity, and educational attainment. Smoking, an additional confounder of interest, was included in the model.

Statistical Methods

We describe the cancer survivors and all women without cancer (the pre-matching cohort) using frequencies, proportions, and risks. Log-binomial models were used to estimate risk ratios for women with a history of cancer compared with women without a history of cancer matched on maternal age at delivery, parity, education attainment, and race/ethnicity. Separate models were fit for the four age at diagnosis categories. Results were only reported if there were more than five cases.

Sub-analyses were conducted to estimate risk ratios for women by cancer type, including melanoma and breast cancer. Additionally, analyses were performed to examine associations in subgroups defined by treatment type (all cancers treated with chemotherapy and invasive breast cancer treated with chemotherapy), time from cancer

diagnosis to conception (less than 1 year and greater than 1 year), and parity (first birth only).

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

Results

From the cohort of 3,562 women with a history of cancer, the most common cancer types were melanoma (23.9%), thyroid (21.9%), and breast (18.5%) (Table 1). The majority of these women were diagnosed between the ages 25 and 34 (64.4%). Compared to eligible comparison women without a history of cancer, the women who gave birth after a cancer diagnosis were older, more educated, more likely to be married, and less likely to smoke. Additionally, cancer survivors were more likely to be classified as white, non-Hispanic.

Preterm Birth

Compared to women with no history of cancer diagnosis matched on maternal age at pregnancy, parity, race, and educational attainment, cancer survivors diagnosed with any cancer between ages 20 and 24 and women diagnosed at age 35 and older did not have a higher risk of preterm birth (RR = 1.15, $CI_{95\%}$: 0.91, 1.46; RR = 1.13, $CI_{95\%}$: 0.89, 1.43) (Table 2). Women diagnosed between ages 25 and 29 and women diagnosed between ages 30 and 34 had an increased risk of preterm birth (RR = 1.30, $CI_{95\%}$: 1.08, 1.55; RR= 1.35, $CI_{95\%}$: 1.14, 1.61). There were no meaningful differences in risk when restricting to the first births only.

Comparing women who had ductal carcinoma *in situ* (DCIS) or invasive breast cancer, to women with no history of cancer, women diagnosed between 25 and 29 were at an increased risk of preterm birth (RR = 1.92, $CI_{95\%}$: 1.37, 2.69). Breast cancer survivors diagnosed in the other age groups were not at increased risk.

Melanoma survivors diagnosed between ages 35 and 45 had a 45% higher risk of preterm birth ($CI_{95\%}$: 0.86, 2.44) than comparison women. Melanoma survivors diagnosed at other ages did not have meaningfully different risks.

Cancer survivors diagnosed between 35 and 45 years who underwent chemotherapy were at a higher risk for preterm birth (RR = 1.94, $CI_{95\%}$: 1.23, 3.08). Risks for survivors treated with chemotherapy diagnosed between 25 years and 34 years were slightly elevated, but the risk was not meaningfully different for those diagnosed between ages 20 and 24. Among invasive breast cancer survivors treated with chemotherapy, women diagnosed between ages 25 and 29 had the greatest increased risk of preterm birth (RR = 1.66, $CI_{95\%}$: 1.06, 2.61), but those diagnosed between ages 30 and 45 also had a modestly increased risk.

Cancer survivors who conceived within a year from cancer diagnosis were at a higher risk of preterm birth compared with matched comparison women, except for cancer survivors diagnosed between the ages 30 to 34. Among survivors who conceived after a year, only those diagnosed between ages 25 to 34 were at an increased risk compared with match cancer-free women.

Low Birth Weight

For low birth weight, cancer survivors diagnosed with any cancer were at increased risk of low birth weight compared to women without a history of cancer for all ages (Table 2). Women diagnosed between 25 and 29 had the strongest association (RR = 1.49, $CI_{95\%}$: 1.21, 1.84). The RRs did not change meaningfully when analyses were restricted to first births, except for women diagnosed with cancer between the ages of 20 and 24 for whom the RR moved towards the null.

The RR for low birth weight comparing DCIS and invasive breast cancer survivors diagnosed between ages 25 and 29 with matched cancer-free women was

stronger (RR = 2.49, $CI_{95\%}$: 1.72, 3.61) than the corresponding RR for all cancer survivors in that diagnosis age group. Results in other age groups were similar to results from survivors of any cancer. The low birth weight RR for melanoma survivors compared with cancer-free women was strongest for those diagnosed between the ages of 30 and 45.

Cancer survivors who underwent chemotherapy were at a higher risk of low birth weight births for all diagnosis age groups compared to matched comparison women. Those diagnosed between 20 and 24 years of age (RR = 1.42, $CI_{95\%}$: 0.91, 2.22), 25 and 29 years of age (RR=1.51, $CI_{95\%}$: 1.01,2.26) and 35 and 45 years of age (RR = 2.03, $CI_{95\%}$: 1.22, 3.39) had stronger RRs compared to the corresponding RRs for survivors of all cancers. Invasive breast cancer survivors treated with chemotherapy diagnosed between ages 25 and 29 were 2.19 times ($CI_{95\%}$: 1.36, 3.51) more likely to experience low birth weight than matched comparison women. This association was stronger than the RR for all cancer survivors treated with chemotherapy in the same diagnosis age group. Invasive breast cancer survivors treated with chemotherapy in the other diagnosis age groups were also at heightened risk of low birth weight compared to matched cancer-free women, and the results were similar to the results for survivors of all cancer types treated with chemotherapy.

Cancer survivors who conceived within a year of diagnosis were at a higher risk of low birth weight than matched comparison women for all ages at diagnosis. Survivors diagnosed between ages 25 and 29 who waited at least a year after diagnosis to conceive were a higher risk for having infants with low birth weight than comparison women, but the RR was weaker than for survivors diagnosed in the same age range who waited less than a year (RR = 1.40, $CI_{95\%}$: 1.09, 1.79 vs. RR=2.14, $CI_{95\%}$: 1.43, 3.20). The RRs comparing cancer survivors diagnosed at other ages who waited at least

a year after diagnosis to conceive with matched cancer-free women were closer to the null than the 25 to 29 diagnosis age group.

Small for Gestational Age

There were no meaningful differences in risk of SGA between all cancer survivors and matched comparison women (Table 2). However, when restricting to first births, survivors diagnosed between ages 30 and 34 were at an elevated risk of SGA (RR = 1.29, $CI_{95\%}$: 1.00, 1.65) compared with matched comparison women. Cancer survivors diagnosed in other age groups did not have different risks.

Cancer survivors diagnosed with DCIS or invasive breast cancer between ages 25 and 29 had a 31% higher risk of SGA than comparison women ($CI_{95\%}$: 0.84, 2.05). Breast cancer survivors diagnosed in other age groups were not at heightened risk. Melanoma survivors did not have meaningfully different risks.

Cancer survivors diagnosed between ages 30 and 45 who underwent chemotherapy were at elevated risk of SGA, but those 29 and younger were not at elevated risk. Invasive breast cancer survivors treated with chemotherapy followed the same pattern as all cancer survivors treated with chemotherapy.

There were no meaningfully differences in the risk of SGA for cancer survivors compared with women without a history of cancer when restricting to cancer survivors who conceived within a year of diagnosis or to those who waited a year after diagnosis to conceive.

Discussion

In this large population-based study, we analyzed the risks of adverse pregnancy outcome (preterm birth, low birth weight, and SGA) by age at cancer diagnosis for cancer survivors compared with matched cancer-free women. Risks of preterm birth varied across analyses. We did not observe a dose response relationship between age

at cancer diagnosis and preterm birth for any analysis. Invasive breast cancer survivors treated with chemotherapy and cancer survivors who conceived within a year of cancer diagnosis had heightened risks in all diagnosis age groups. However, cancer survivors diagnosed at age 30 and older who were treated with chemotherapy had elevated risks for preterm birth. The risk of low birth weight birth was higher in cancer survivors compared to matched women without a history of cancer for all cancer diagnosis age groups. In contrast, we did not observe an association between being a cancer survivor and SGA in most analyses. Among cancer survivors diagnosed at age 30 and older, who were treated with chemotherapy, both survivors of all cancer types and invasive breast cancer survivors had higher risks of SGA.

Previous studies have reported that cancer survivors are at an increased risk of having preterm and low birth weight births although the strengths of association varied.[9–13,15] We also found that cancer survivors had an elevated risk of preterm birth and low birth weight compared with cancer-free women, but we did not observe clear patterns in the strength of association related to age at cancer diagnosis. Previous studies yielded mixed results regarding the association of cancer history and SGA with some finding increased risks and some reporting null associations between cancer survivors and women with no cancer history.[12,13,17] Our study did not find meaningfully different risks of SGA for cancer survivors compared with cancer-free women except for cancer survivors diagnosed between ages 30 and 45 who were treated with chemotherapy and invasive breast cancer survivors in the same age groups treated with chemotherapy.

Prior research looking at age at cancer diagnosis as an exposure primarily has focused on its association with fertility, becoming pregnant, or having a live birth. Studies suggest that acute ovarian failure and infertility increase as age at diagnosis increases.[19,20] Additionally, early menopause may decrease as age at diagnosis increases.[20] The ability to get pregnant was reported to be associated with younger age

at diagnosis among cancer survivors diagnosed between ages 20 and 40.[21] However, a study comparing cancer survivors diagnosed before age 21 to siblings without a history of cancer found no meaningful difference in age at diagnosis and the ability to get pregnant or have a live birth.[22] None of these studies evaluate age at diagnosis and adverse birth outcomes specifically, but they highlight mixed findings in the association of age at cancer diagnosis and reproductive health after cancer suggesting the need for more research.

This study has important strengths including its multi-state, population-based design and large sample size of women with a history of cancer matched with women without a history of cancer. This population-based design helped to minimize selection bias. An additional strength is the use of cancer registry data which minimized the probability of misclassification of cancer status. A study found 96% sensitivity in cancer case detection and 95% accuracy in site-specific data calculated for 13 variables.[23] The use of birth certificate data also served as a strength. Reliability varies across certain birth certificate variables, but for our matching variables; maternal age, parity, education, and race/ethnicity, studies have reported good agreement with self-report.[24]

Despite its strengths, we have identified potential limitations in this study. Women diagnosed at later ages might have less time between diagnosis and conception compared to women diagnosed at younger ages. This could impact survivors whose treatments have short term effects on fertility or pregnancy outcomes, but not long-term effects.[13] We attempted to evaluate this by analyzing those who conceived within a year and those who conceived at least one year after diagnosis separately. Another limitation is that we were unable to perform sub-analyses on cancer types other than breast cancer and melanoma because of small numbers. An additional limitation is that our comparison women could include cancer survivors who were diagnosed with cancer in another state. However, cancer diagnosis in adolescent and young adult women is rare

(321.7 per 100,000 per year), and we do not hypothesize that misclassification of cancer diagnosis would be differential by the outcomes.[25]

In our study, we see that cancer survivors have a higher risk of having a preterm birth and low-birth weight birth compared with women without cancer. However, the strength of association does not appear to consistently increase with age at diagnosis. In contrast, cancer survivors and comparison women have similar risks for SGA births. The increased risks of preterm birth and low birth weight provide an opportunity for healthcare providers to closely monitor cancer survivors for low birth weight and preterm births, but age at cancer diagnosis does not appear to be an important predictor of adverse pregnancy outcomes.

Tables

Table 1. Characteristics of first eligible live singleton births to women diagnosed with cancer between ages 20 and 45 and all eligible comparison women without a history of cancer in Georgia and North Carolina. Births missing information on maternal age, race/ethnicity, education, and parity have been excluded.

Characteristic	All Cancers (n=3562)		All comparison women (n=3,351,259)	
	No.	%	No.	%
Maternal age at birth, yr				
20-24	196	5.5	1,041,557	31.1
25-29	882	24.8	1,036,603	30.9
30-34	1,262	35.4	825,870	24.6
35-39	960	27.0	373,461	11.1
40-45	262	7.4	73,768	2.2
Maternal race and ethnicity				
White, non-Hispanic	2,569	72.1	1,866,483	55.7
African American, non-Hispanic	716	20.1	912,189	27.2
Other, non-Hispanic	157	4.4	191,931	5.7
Hispanic, any race	120	3.4	380,656	11.4
Maternal education				
<High school	208	5.8	571,644	17.1
High school or GED	685	19.2	1,002,524	29.9
Some college or associate degree	1,066	29.9	892,713	26.6
≥4 Years of college	1,603	45.0	884,378	26.4
Parity, no. live births				
0	1,567	44.0	1,212,910	36.2
1	1,117	31.4	1,158,675	34.6
2	565	15.9	605,336	18.1
≥3	313	8.8	374,338	11.2
Married				
Yes	2,891	81.3	2,223,109	66.3
No	667	18.8	1,126,759	33.6
Missing	4		1,391	
Smoker				
Yes	193	5.4	315,692	9.4
No	3,365	94.6	3,030,222	90.4
Missing	4		5,345	
Age at Diagnosis, yr				
20-24	751	21.1		

25-29	1,187	33.3
30-34	1,106	31.1
35-45	518	14.5
Cancer Type		
Breast	659	18.5
Cervical	113	3.2
Hodgkin lymphoma	238	6.7
Melanoma	850	23.9
Thyroid	779	21.9
Other	923	25.9
Time from Cancer Diagnosis Until Conception		
<1 year	906	25.4
≥1 year	2,656	74.6

Table 2. Risk ratios comparing risks of preterm birth, low birth weight, and small for gestational age by age at diagnosis in first birth after cancer diagnosis to risks of women without a history of cancer.

		Preterm Birth		Low Birth Weight		Small for Gestational Age	
Age at Diagnosis	**Total Births[1]**	**N[1]**	**RR ($CI_{95\%}$)**	**N[1]**	**RR ($CI_{95\%}$)**	**N[1]**	**RR ($CI_{95\%}$)**
All Cancers							
20-24	751	77	1.15(0.91,1.46)	62	1.24(0.95,1.62)	72	0.91 (0.72,1.15)
25-29	1187	132	1.30(1.08,1.55)	102	1.49(1.21,1.84)	109	0.97 (0.73, 1.17)
30-34	1106	139	1.35(1.14,1.61)	95	1.27(1.03,1.57)	114	1.09 (0.90,1.31)
35-45	518	74	1.13(0.89,1.43)	62	1.37(1.05,1.78)	59	1.07 (0.83,1.39)
First births only							
20-24	433	41	1.09(0.79,1.50)	34	1.09(0.77,1.56)	41	0.84(0.61,1.14)
25-29	593	64	1.17(0.91,1.52)	50	1.33(0.99,1.79)	56	0.94(0.72,1.23)
30-34	397	50	1.18(0.89,1.58)	46	1.33(0.98,1.81)	64	1.29(1.00,1.65)
35-45	144	16	0.84(0.51,1.37)	20	1.38(0.88,2.16)	17	0.97(0.61,1.54)
Breast only							
20-24	37	4	–	3	–	3	–
25-29	148	30	1.92(1.37,2.69)	26	2.49(1.72,3.61)	18	1.31(0.84,2.05)
30-34	275	35	1.13(0.83,1.56)	28	1.28(0.89,1.84)	33	1.17(0.84,1.62)
35-45	199	26	1.09(0.76,1.58)	24	1.39(0.95,2.03)	23	1.05(0.71,1.55)
Melanoma only							
20-24	168	10	0.75(0.41,1.38)	5	–	9	0.59(0.31,1.11)
25-29	324	29	1.20(0.84,1.72)	18	1.23(0.77,1.95)	20	0.85(0.55,1.31)
30-34	269	23	1.10(0.73,1.64)	16	1.45(0.88,2.36)	16	0.84(0.52,1.36)
35-45	89	14	1.45(0.86,2.44)	10	1.79(0.95,3.36)	8	1.09(0.53,2.26)
Chemotherapy only							
20-24	190	23	1.02(0.67,1.56)	22	1.42(0.91,2.22)	22	1.02(0.66,1.57)
25-29	258	30	1.15(0.79,1.67)	28	1.51(1.01,2.26)	26	1.01(0.68,1.51)

30-34	291	42	1.24(0.91,1.70)	31	1.20(0.83,1.75)	40	1.49(1.08,2.08)
35-45	110	21	1.94(1.23,3.08)	18	2.03(1.22,3.39)	15	1.29(0.77,2.17)
Invasive breast cancer treated with chemotherapy only							
20-24	17	2	–	1	–	3	–
25-29	98	17	1.66(1.06,2.61)	16	2.19(1.36,3.51)	9	0.94(0.50,1.78)
30-34	168	22	1.21(0.81,1.80)	16	1.44(0.71,1.84)	26	1.38(0.96,1.99)
35-45	69	11	1.27(0.73,2.23)	10	1.77(0.98,3.20)	10	1.38(0.77,2.48)
<=1 year from diagnosis to pregnancy							
20-24	150	22	1.67(1.06,2.62)	20	2.19(1.33,3.60)	19	1.14(0.72,1.81)
25-29	280	31	1.34(0.92,1.95)	30	2.14(1.43,3.20)	25	1.06(0.71,1.60)
30-34	277	30	1.18(0.81,1.72)	21	1.30(0.82,2.05)	23	0.87(0.57,1.32)
35-45	199	34	1.37(0.97,1.93)	26	1.66(1.11,2.48)	23	1.03(0.68,1.57)
>1 year from cancer diagnosis to pregnancy							
20-24	601	55	1.04(0.79,1.37)	42	1.07(0.78,1.47)	53	0.94(0.71,1.25)
25-29	907	101	1.31(1.06,1.61)	72	1.40(1.09,1.79)	84	1.07(0.86,1.34)
30-34	829	109	1.25(1.03,1.52)	74	1.21(0.95,1.55)	91	1.16(0.94,1.44)
35-45	319	40	1.00(0.73,1.39)	36	1.18(0.83,1.66)	36	0.93(0.67,1.30)

[1]Counts represent cancer survivor cohort and are not inclusive of matched comparison women.

References

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289. doi:10.3322/caac.21349

2. Letourneau JM, Ebbel EE, Katz PP, et al. Pre-treatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer*. 2012;118(6):1710-1717. doi:10.1002/cncr.26459

3. Partridge AH, Gelber S, Peppercorn J, et al. Web-Based Survey of Fertility Issues in Young Women With Breast Cancer. *J Clin Oncol*. 2004;22(20):4174-4183. doi:10.1200/JCO.2004.01.159

4. Schover LR. Patient attitudes toward fertility preservation. *Pediatr Blood Cancer*. 2009;53(2):281-284. doi:10.1002/pbc.22001

5. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2017. *Natl Cancer Inst*. https://seer.cancer.gov/csr/1975_2017/.

6. Tang M, Webber K. Fertility and pregnancy in cancer survivors. *Obstet Med*. 2018;11(3):110-115. doi:10.1177/1753495X18757816

7. Irene Su H, Lee YT, Barr R. Oncofertility: Meeting the Fertility Goals of Adolescents and Young Adults With Cancer. *Cancer J Sudbury Mass*. 2018;24(6):328-335. doi:10.1097/PPO.0000000000000344

8. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Semin Fetal Neonatal Med*. 2016;21(2):68-73. doi:10.1016/j.siny.2015.12.011

9. Signorello LB, Cohen SS, Bosetti C, et al. Female Survivors of Childhood Cancer: Preterm Birth and Low Birth Weight Among Their Children. *JNCI J Natl Cancer Inst*. 2006;98(20):1453-1461. doi:10.1093/jnci/djj394

10. Melin J, Heinävaara S, Malila N, Tiitinen A, Gissler M, Madanat-Harjuoja L. Adverse Obstetric Outcomes Among Early-Onset Cancer Survivors in Finland: *Obstet Gynecol*. 2015;126(4):803-810. doi:10.1097/AOG.0000000000001035

11. Reulen RC, Bright CJ, Winter DL, et al. Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. *JNCI J Natl Cancer Inst*. 2017;109(11). doi:10.1093/jnci/djx056

12. Anderson C, Engel SM, Anders CK, Nichols HB. Live birth outcomes after adolescent and young adult breast cancer. *Int J Cancer*. 2018;142(10):1994-2002. doi:10.1002/ijc.31227

13. Hartnett KP, Mertens AC, Kramer MR, et al. Pregnancy after cancer: Does timing of conception affect infant health? *Cancer*. 2018;124(22):4401-4407. doi:10.1002/cncr.31732

14. Jin J. Babies With Low Birth Weight. *JAMA*. 2015;313(4):432-432. doi:10.1001/jama.2014.3698

15. Black KZ, Nichols HB, Eng E, Rowley DL. Prevalence of preterm, low birthweight, and small for gestational age delivery after breast cancer diagnosis: a population-based study. *Breast Cancer Res*. 2017;19(1):11. doi:10.1186/s13058-017-0803-z

16. McCowan L, Horgan RP. Risk factors for small for gestational age infants. *Best Pract Res Clin Obstet Gynaecol*. 2009;23(6):779-793. doi:10.1016/j.bpobgyn.2009.06.003

17. Stensheim H, Klungsøyr K, Skjærven R, Grotmol T, Fosså SD. Birth outcomes among offspring of adult cancer survivors: A population-based study. *Int J Cancer*. 2013;133(11):2696-2705. doi:10.1002/ijc.28292

18. Hartnett KP, Ward KC, Kramer MR, et al. The risk of preterm birth and growth restriction in pregnancy after cancer. *Int J Cancer*. 2017;141(11):2187-2196. doi:10.1002/ijc.30914

19. Chemaitilly W, Mertens AC, Mitby P, et al. Acute Ovarian Failure in the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2006;91(5):1723-1728. doi:10.1210/jc.2006-0020

20. Letourneau J, Chan SW, Rosen MP. Accelerating Ovarian Age: Cancer Treatment in the Premenopausal Woman. *Semin Reprod Med*. 2013;31(6):462-468. doi:10.1055/s-0033-1356482

21. McCray DKS, Simpson AB, Flyckt R, et al. Fertility in Women of Reproductive Age After Breast Cancer Treatment: Practice Patterns and Outcomes. *Ann Surg Oncol*. 2016;23(10):3175-3181. doi:10.1245/s10434-016-5308-y

22. Chow EJ, Stratton KL, Leisenring WM, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol*. 2016;17(5):567-576. doi:10.1016/S1470-2045(16)00086-3

23. Thoburn KK, German RR, Lewis M, Nichols P "Janie," Ahmed F, Jackson-Thompson J. Case completeness and data accuracy in the Centers for Disease Control and Prevention's National Program of Cancer Registries. *Cancer*. 2007;109(8):1607-1616. doi:10.1002/cncr.22566

24. Northam S, Knapp TR. The Reliability and Validity of Birth Certificates. *J Obstet Gynecol Neonatal Nurs*. 2006;35(1):3-12. doi:10.1111/j.1552-6909.2006.00016.x

25. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492