The Potential Effect of Cancer on the Birth Outcomes of Female Cancer Survivors

By

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Abstract

Objectives: To determine if women who become pregnant after a cancer diagnosis are more likely to have adverse birth outcomes than women who had a pregnancy prior to being diagnosed with cancer. ***Methods:*** The study population included 15,662 women who were diagnosed with cancer and had a live birth in North Carolina during the years of 1990-2009. The exposure of interest was one of eleven cancer diagnoses. The outcomes investigated were preterm birth (PTB) and low birthweight (LBW). Logistic regression was run using *Stata 11.1*. ***Results:*** Women who were diagnosed with cancer before a pregnancy were 1.37 times as likely to deliver a PTB infant and 1.36 times as likely to deliver a LBW infant than women who were diagnosed with cancer after a pregnancy. ***Conclusions:*** The findings suggest that women in North Carolina who were diagnosed with cancer prior to giving birth had a slightly higher risk of experiencing PTB and LBW deliveries.

Introduction

Although the cancer incidence rate has declined by 1% every year since 1999 (and the cancer death rate has declined by 1.6% per year between 2001 and 2006) (1), cancer remains prevalent in the United States. The cancer incidence rate for women is 407.9 per 100,000 (2); moreover, there is a clear disparity between the cancer survival rates of non-Hispanic black and non-Hispanic white women. Even though white women have a higher incidence rate of cancer diagnoses than black women (407.4 per 100,000 vs. 377.2), black women have a higher death rate than white women (176.9 per 100,000 vs. 153.4).(2) Among all women in the United States, the three most common cancers are breast cancer (117.7 per 100,000), lung cancer, (55.2), and colorectal cancer (41.9).(3)

Due to the advancement of treatment options for cancer, more people are able to live fruitful lives after a cancer diagnosis. Yet, for pre-menopausal women the effects of the disease and treatment on their reproductive capacity and potential pregnancy outcomes continues to be a justified concern. Although cancer is considered a disease of the aging population, the number of pre-menopausal women afflicted by cancer is not a small group. As of January 2007, nearly 6.4 million women who had ever been diagnosed with cancer in the United Stated were still living and about 15% of these women were between the ages of 10 and 49 at diagnosis.(4) When comparing the overall cancer incidence rate for women by state, North Carolina has the 23rd highest rate with an overall age-adjusted cancer incidence rate of 411.7 per 100,000 (see Figure 1).(5) The ten most frequently diagnosed cancers for women in North Carolina are: breast, lung/bronchus, colon/rectum, corpus uteri, endocrine, non-Hodgkin Lymphoma, melanoma (skin), ovary, kidney, and pancreas (see Table 1). The most frequently diagnosed cancers among women of color (i.e., minority women) run parallel with those diagnosed among the general female population in North Carolina. However, white women are more likely to be diagnosed with Melanoma of the skin in their lifetime and minority women are more likely to be diagnosed with bone, kidney, and pancreas cancer.(6) When considering the potential pregnancies that may occur among women of reproductive age, ages 15-49, after a diagnosis and subsequent treatment for cancer, the question is: *are female cancer survivors in North Carolina who experience a live birth after their diagnosis more likely to have adverse birth outcomes (e.g., preterm birth, low birthweight) than North Carolinian women who have experienced a live birth prior to being diagnosed with cancer?* In order to address this question, it is important to determine if these adverse birth outcomes vary by any relevant maternal characteristics or risk factors, including age at time of cancer diagnosis, age at time of pregnancy, race/ethnicity, and socioeconomic status.

Figure 1: Cancer Incidence Rates Ranked by State: 2003-2007, Female, All Cancer Sites Combined (5)

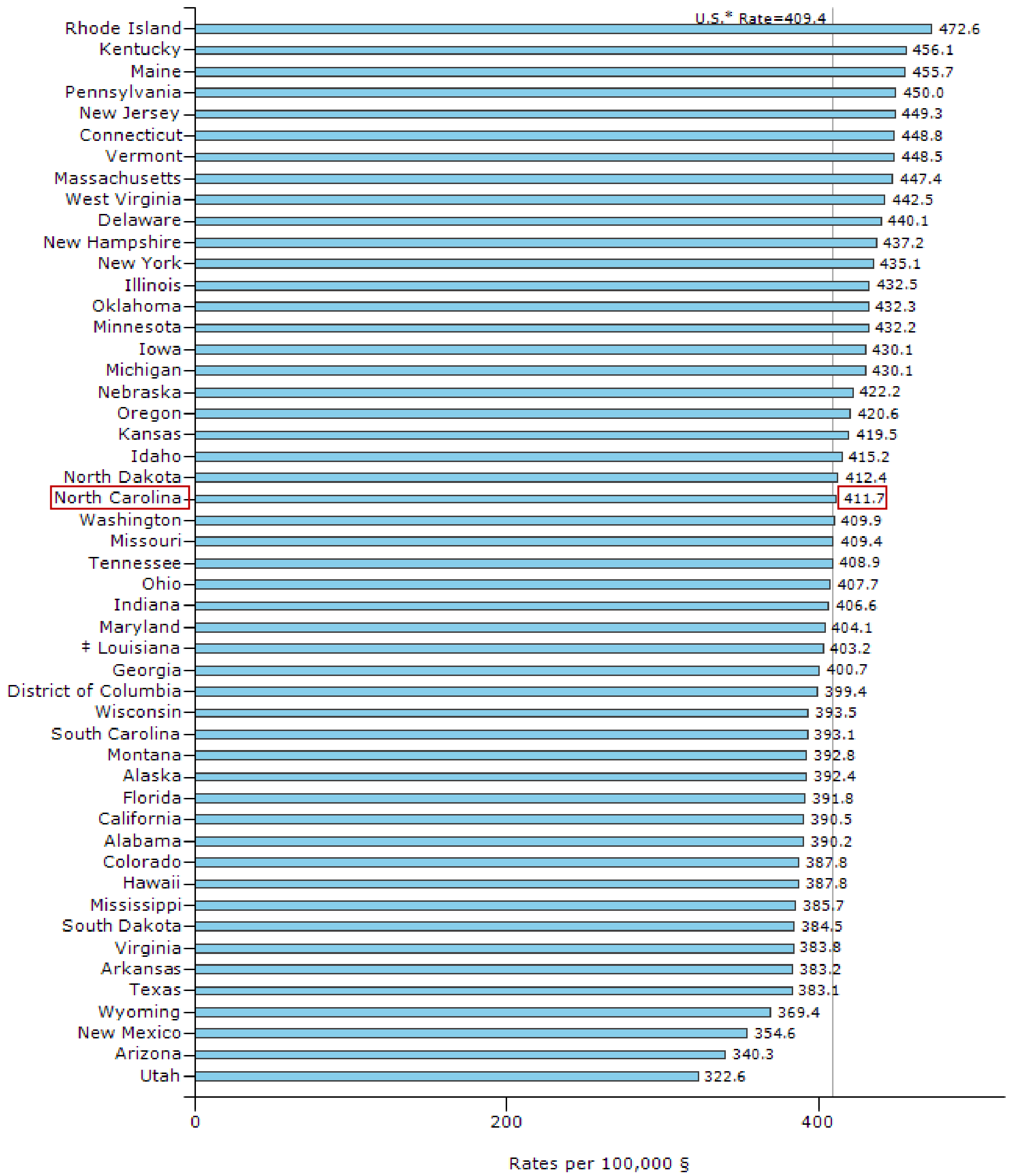
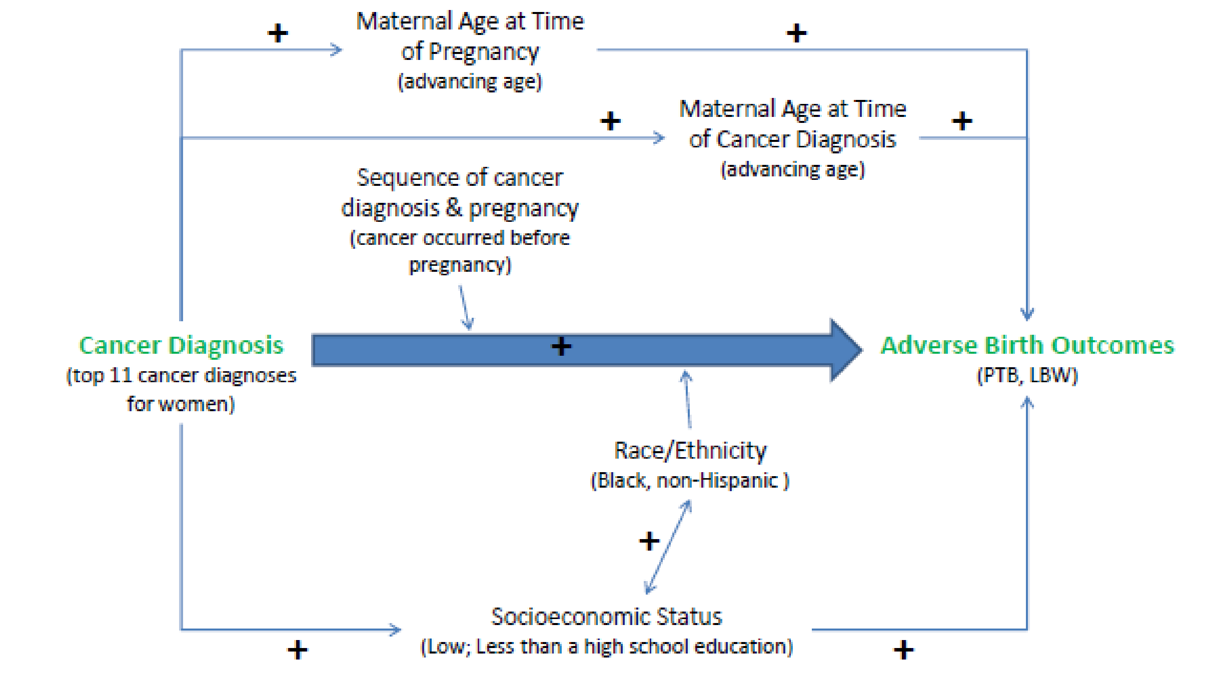


Table 1 – 2003-2007 Ten Most Frequently Diagnosed Cancers for Females (of all Races/Ethnicities) in North Carolina (6)		
Cancer	**Cases**	**Incidence Rate[a]**
Female Breast	36,562	149.6
Lung/Bronchus	14,340	57.6
Colon/Rectum	10,249	40.9
Corpus Uteri	5,210	20.9
Endocrine	3,889	16.9
Non-Hodgkin Lymphoma	3,801	15.4
Melanoma (Skin)	3,617	15.3
Ovary	2,998	12.2
Kidney	2,658	10.8
Pancreas	2,600	10.3
[a] Incidence rates are per 100,000 population and are age-adjusted to the 2000 U.S. Census. In situ cancers except those of the urinary bladder and female breast are excluded.		

Conceptual Model

Figure 2 presents a conceptualization of the association between cancer and subsequent birth outcomes. In this model, the pathway between the exposure (cancer diagnosis) and the outcome [adverse birth outcomes; preterm birth (PTB) and low birthwieght (LBW)] is moderated and therefore will vary by two key variables: 1) sequence of cancer diagnosis and pregnancy and 2) race/ethnicity. Three additional variables are mediators in the relationship between the exposure and outcome: maternal age at time of diagnosis, maternal age at time of pregnancy, and socioeconomic status (SES). I believe that maternal age at the time of the cancer diagnosis, maternal age at the time of pregnancy, and SES are influential factors that must be considered in the pathway between the exposure and outcome variables. In general, cancer has not been associated with the diminishment of a woman's reproductive capacity.(7-9) Yet, this conceptual model presents the hypothesis that the birth outcomes of female cancer survivors will vary by whether they experienced a live birth before or after their cancer diagnosis after controlling for factors associated with PTB and LBW, such as race/ethnicity and education level. Additionally, this model explores the potential underlying effect that maternal age at time of cancer diagnosis and maternal age at time of pregnancy have on the relationship between cancer and adverse birth outcomes (PTB and LBW).

Figure 2 – Conceptual Model of the Association Between Cancer and Adverse Birth Outcomes



Pregnancy After Cancer Treatment

There are very few published studies that have examined the potential association between cancer diagnosis and treatment and birth outcomes.(7-13) Moreover, most of these studies have not focused on the variables displayed in the conceptual model presented in this paper (Figure 2). These studies have examined how pregnancy and birth outcomes have varied by type of cancer and the cancer treatment method/dosage by comparing this population to women who had not been diagnosed with cancer.

Most studies concluded that in general cancer treatments (e.g., chemotherapy, radiation therapy, surgery) are not associated with an increased risk of adverse pregnancy or poor birth outcomes among women treated for cancer. This lack of an association held for both women who became pregnant naturally and women who underwent assisted reproductive technology (ART). However, some studies did find that certain types of cancer treatments were associated with preterm birth (PTB) and low birthweight (LBW). Patients who had received radiation therapy in the abdominal/pelvic region were more likely to deliver infants who were born before 37 weeks gestation (PTB) and who weighed less than 2500 g at birth (LBW) in comparison to the identified cohort group (i.e., siblings of cancer survivors who had ever given birth). An increased risk of experiencing a miscarriage was also seen among patients who received radiation therapy in this particular region of the body.(7,10,12,13) This body of knowledge suggests that the severity, and more specifically the type of treatment and its impact on reproductive capacity, may serve as a moderator in the relationship between cancer diagnosis/treatment and adverse birth outcomes.

Limitations in Current Research

The studies cited have paved the way for further exploration of the determinants of adverse pregnancy outcomes among women who have undergone cancer treatment. A majority of the studies that I reviewed sampled from the North American or European Childhood Cancer Survivors Studies' established databases of 5-year (or longer) childhood and adolescent survivors (7,10,12-15) and two of them report much smaller populations from single location sources (8,9), yet all of the studies have notable limitations. The three main limitations that are apparent throughout most of the studies are the sole use of childhood cancer survivors as the study population, the lack of maternal characteristics in the statistical analysis models, and the use of self-reported pregnancy outcomes.

One of the main limitations of this collection of studies is that a majority of them (five out of seven) focus on childhood and adolescent survivors.(7,10-13,16) The most widely used data in these studies were from the North American or British Childhood Cancer Survivors Studies (four out of seven of the studies).(7,10-13,16) From this wealth of data about patients who were diagnosed before the age of 21, survived for five or more years, and have reported on their health status and socio-demographic information as adults, the researchers have been able to extract information about the pregnancy outcomes of female survivors and the partners of male survivors. However, one major concern about using only childhood cancer survivors when examining pregnancy outcomes is that by the time most of these survivors begin to have children, their pregnancies are often years after their cancer diagnosis and treatment. In the only two studies that focused on female cancer survivors who were diagnosed with cancer during their reproductive years, the studies' populations consisted of only 16 and 40 women who received care at a specific facility.(8,9) The statistical significance and strength of the studies with smaller and single site study populations are insufficient to determine an association between cancer diagnosis/treatment and poor pregnancy outcomes that have a low/moderate prevalence. Furthermore, the time interval between cancer diagnosis and pregnancy may be an important variable that may impact the risk of adverse pregnancy outcomes for female cancer survivors and this variable has not been thoroughly examined.

Another important limitation that should be addressed is the lack of maternal characteristics and risk factors that were included in the statistical models of these studies. Only a few researchers considered factors that may be associated with the pregnancy outcomes of female cancer survivors that were beyond type of cancer and cancer treatment regimen.(10,11,13) Some of the additional variables included in the analyses of these studies were substance use during pregnancy (tobacco, alcohol, & recreational drugs), high blood pressure, diabetes, vitamin supplement usage, age at diagnosis, and race/ethnicity. It is possible that some of these factors, especially race/ethnicity, may present themselves as confounders or moderators when added to the analyses of these research questions. Studies that have focused on disparities in medical treatment and health outcomes have demonstrated that racial/ethnic and socioeconomic status (SES) disparities are particularly apparent among cancer patients.(17-19) Therefore, race/ethnicity and SES are important variables to include in models that analyze factors that may be associated with cancer. An analysis model that includes identified maternal characteristics and risk factors may potentially shed light on how adverse pregnancy outcomes among female cancer survivors can be addressed via interventions that occur between cancer treatment and subsequent pregnancies.

Lastly, due to the nature of case-control studies, the information is collected retrospectively and in the case of the studies examined in this paper, the pregnancy outcome information is all self-reported. Self-reported data is usually subject to recall bias and the questionable reliability of this data is therefore an important limitation to mention. It is especially of concern in this instance, when women are asked if they experienced a range of pregnancy outcomes, including miscarriage, stillbirth, preterm delivery, and low birthweight; some of these outcomes, particularly miscarriage and stillbirth, are not easily discerned by non-medical professionals. Therefore, the fact that the pregnancy outcomes are self-reported and the cancer diagnosis and treatment information is obtained from medical records, means the reliability of these two sources are not equitable, which may have the potential to skew the results if a portion of the participants under- or over-reported events of miscarriage, stillbirth, preterm delivery, or low birthweight infants.

The Childhood Cancer Survivors Studies, conducted in both North America and Europe, have been the catalysts for exploring the health outcomes of child and adolescent survivors. Most importantly, these studies have recruited the largest study populations on this topic to date. However, this topic area warrants more research that will provide additional insight into the lives and health of women, men, and children after being treated for cancer. The incidence of cancer in the United States has been on the decline since 1999 and moreover, the treatment options for those diagnosed with cancer has led to more survivors of cancer surviving for longer periods of time after a bout with cancer. As cancer survivors continue on with their lives, the medical and public health communities need to be prepared to address the numerous health issues that may differ between cancer survivors and the general population. The potential risk of adverse pregnancy outcomes of female cancer survivors still needs further exploration and I believe more reliable and complete data sources may assist in the process of resolving this important research question.

The ideal method for addressing my proposed research question is to link cancer registry information with birth certificate record data. Mueller, et al. (11) was the only study that I reviewed that used this method to analyze childhood and adolescent cancer survivors' pregnancy outcomes. Contrary to the results from studies that used the Childhood Cancer Survivors Study data, Mueller et al. did find an association between cancer and pregnancy outcomes. This study determined that infants born to female child and adolescent cancer survivors were more likely to be preterm (< 37 weeks gestation) and low birthweight (<2,500 g).(11) This stark difference in the findings based on self-reported data versus clinically-based and systematically gathered information leads me to believe that the data that has been used to determine the pregnancy outcomes of female cancer survivors in past studies has not provided us with the full picture on the effects of cancer on subsequent pregnancy outcomes.

Methods

Design & Sampling

The cancer registry data that is currently available in North Carolina is from 1990 to 2009, which helped to define the years of data that I focused on as a part of my analysis. The cancer registry data was linked to birth record data to identify the subjects: female cancer survivors who were diagnosed with cancer and gave birth during the years of 1990-2009. Inclusion criteria for the cases were female/woman, of any age, all races/ethnicities, delivered a live birth in North Carolina during the years of 1990-2009, and was diagnosed for one of the following eleven cancers prior to their pregnancy: breast, lung/bronchus, colon/rectum, corpus uteri, cervix uteri, endocrine, non-Hodgkin Lymphoma, melanoma (skin), ovary, kidney, and pancreas.[1] Subjects that experienced a stillbirth, miscarriage, or other adverse pregnancy outcome that did not result in a live birth during the years of 1990-2009 were excluded from this study. The control group included all female cancer survivors who gave birth in North Carolina from 1990-2009 and were diagnosed with cancer after their pregnancy. The exposure of interest was a cancer diagnosis before live birth delivery and the outcomes of interest were preterm birth (PTB; <37 weeks gestation) and low birthweight (LBW; <2,500 g). The additional independent variables that were included in the data analysis and controlled for are maternal age at time of cancer diagnosis (in years), maternal age at time of pregnancy (in years), sequence of cancer diagnosis and pregnancy (by date), race/ethnicity, and socioeconomic status (using education level as a proxy).

Data Collection

The cancer registry and birth record data that was used in my analysis were collected by the North Carolina State Center for Health Statistics. Both of these data sources are routinely collected.

It is a requirement by North Carolina State Law for all health care providers to report information about newly diagnosed cancer patients to the Central Cancer Registry (CCR), which "collects, process, and analyzes data on all cancer cases diagnosed among North Carolina residents."(20) Most cancer cases are reported by the hospital where the patient was diagnosed or treated; however, laboratories, clinics, and medical offices are also required to report cancer cases to supplement the information that is obtained from hospitals. All cancer

[1] The eleven cancer diagnoses that were used in this analysis included the ten most frequently diagnosed cancers for women (of all ages) in North Carolina and cervix uteri, which was added because it is one of the five most frequently diagnosed cancers among women ages 20-44.(6)

cases diagnosed in North Carolina are reported to the CCR, including benign brain/central nervous system tumors, yet it is important to note that some skin cancers and *in situ* cancers are excluded.

Within ten days of a delivery, a hospital administrator or person attending a non-hospital delivery (e.g., midwife) must file a birth certificate or fetal death report to the Department of Health and Human Services and then each State Center for Health Statistics houses and manages these vital statistics records.(21) Therefore, the available birth record data on North Carolina should accurately account for all deliveries that have occurred within the state in a given time period.

Data Analysis

Stata 11.1 was used to analyze the relationships between the independent and dependent variables through the use of logistic regression. Three models were used to determine if there are any statistically significant relationships between the established variables (Table 2). In Model 1, I looked at the relationship between the exposure variable (cancer; any of eleven cancer diagnoses) and each of the outcome variables (PTB, LBW) separately. In Model 2, I completed a logistic model for each maternal characteristic (i.e., maternal age at time of cancer diagnosis (in years), maternal age at time of pregnancy (in years), maternal race/ethnicity, and maternal education level) to the two versions of Model 1 to determine if each variable is a confounder. I followed up the analyses of these two models with Model 3, where I added all of the maternal characteristics to Model 1 to examine the impact they had on the initial (unadjusted) odds ratios in Model 1. After estimating the odds ratios and confidence intervals from each of these models, I compared the data to my established hypotheses.

Table 2 – Logistic Regression Modeling for Cancer before Pregnancy and Adverse Birth Outcomes		
MODEL 1	**MODEL 2**	**MODEL 3**
Gestational Age Cancer before Pregnancy **Birthweight** Cancer before Pregnancy	**Gestational Age** Cancer before Pregnancy + Maternal Age at Time of Diagnosis Cancer before Pregnancy + Maternal Age at Time of Pregnancy Cancer before Pregnancy + Maternal Race/Ethnicity Cancer before Pregnancy + Maternal Education Level **Birthweight** Cancer before Pregnancy + Maternal Age at Time of Diagnosis Cancer before Pregnancy + Maternal Age at Time of Pregnancy Cancer before Pregnancy + Maternal Race/Ethnicity Cancer before Pregnancy + Maternal Education Level	**Gestational Age** Cancer before Pregnancy + ALL Variables **Birthweight** Cancer before Pregnancy + ALL Variables

Results

My study population included 15,662 women who were diagnosed with one of the eleven most frequently diagnosed cancers for women (i.e., breast, lung/bronchus, colon/rectum, corpus uteri, cervix uteri, endocrine, non-Hodgkin Lymphoma, melanoma (skin), ovary, kidney, and pancreas) and delivered a live birth between the years of 1990 and 2009 in North Carolina. At the time of their cancer diagnosis, the women ranged in age from less than one year old to 61 years old. At the time of delivery of their live-born infant, the women ranged in age from thirteen to 51. A vast majority of the women were diagnosed with cancer (97.75%; 15,310) and became pregnant (99.95%; 15,654) during their reproductive years, ages 15-49. Furthermore, 63.61% (9,963) of the women experienced a live birth before they were diagnosed with cancer, 36.16% (5,663) experienced a live birth after being diagnosed with cancer, and the date of cancer diagnosis and delivery date were equivalent for 0.23% (36) of the study population. The 36 women that had cancer diagnosis and delivery dates that were equivalent were excluded from the final analysis for two reasons: 1) there are multiple additional complications that may occur when an untreated cancer occurs during pregnancy or when cancer is being treated during a pregnancy and these issues were beyond the scope of this paper and have been addressed in previous studies; and 2) since the cancer diagnosis date and the delivery date could not be ordered, these subjects did not fit into the analysis model established for this study. A majority of the sample population was White/non-Hispanic

(75.46%), had greater than a high school education (63.69%), had a full term pregnancy (86.90%), and delivered a normal birthweight infant (89.72%) (Table 3).

Table 3 – Characteristics of Study Population, North Carolina Central Cancer Registry & Birth Record Data, 1990-2009

Characteristic[a]	Unweighted Count	Percent (%)
Maternal Characteristics		
Maternal Age at Time of Diagnosis (years)		
≤ 14	193	1.23%
15-19	843	5.38%
20-29	5,257	33.57%
30-39	6,630	42.33%
40-49	2,580	16.47%
≥ 50	159	1.02%
Maternal Age at Time of Pregnancy (years)		
≤ 14	6	0.04%
15-19	597	3.81%
20-29	6,233	39.80%
30-39	8,056	51.44%
40-49	768	4.90%
≥ 50	2	0.01%
Race/Ethnicity		
Black/non-Hispanic	3,021	19.29%
White/non-Hispanic	11,818	75.46%
Hispanic (any race)	407	2.60%
Other[c]	413	2.64%
Missing	3	0.02%
Education Level		
Less than high school	1,718	10.97%
High school	3,969	25.34%
Greater than high school	9,975	63.69%
Maternal Medical Condition		
Sequence of Diagnosis & Pregnancy[b] (by date)		
Cancer Diagnosis before Pregnancy	5,663	36.16%
Cancer Diagnosis date equal to Delivery Date	36	0.23%
Cancer Diagnosis after Pregnancy	9,963	63.61%
Infant Characteristics[d]		
Gestational Age		
PTB (< 37 weeks)	2,048	13.08%
Term (≥ 37 weeks)	13,611	86.90%
Missing	3	0.02%
Birthweight		
LBW (< 2,500 g)	1,610	10.28%
Normal (≥ 2,500 g)	14,052	89.72%
TOTAL	**15,662**	**100%**

[a] All of the characteristics were either captured in the cancer registry, birth record data, or calculated using these two sources
[b] This information is based off of the cancer diagnosis date and the delivery date
[c] The "Other" race/ethnicity category includes all races besides Black and White that are non-Hispanic (i.e., American Indian, Chinese, Japanese, Hawaiian, Filipino, & other Asian); this information was obtained from the birth record data
[d] PTB = preterm birth; LBW = low birthweight

When comparing the demographics of the women who were diagnosed with cancer before their delivery date versus those who were diagnosed with cancer after their delivery date

(9,963 vs. 5,663 women for a total of 15,626 subjects) (Table 4), the maternal characteristics were quite similar, except for the women who were diagnosed with cancer before their pregnancy tended to be younger at the age of diagnosis compared to women who were diagnosed with cancer after their pregnancy. However, a greater percentage of the group of women who had a bout with cancer before their pregnancy experienced a preterm birth (15.42% vs. 11.72%) and delivered a low birthweight infant (12.15% vs. 9.20%) than women who were diagnosed with cancer after a pregnancy.

The logistic regression analysis of the linked Central Cancer Registry and birth record data demonstrated that women who were diagnosed with cancer before delivering a live-born infant were 1.37 times as likely to deliver a PTB infant (95% CI 1.25-1.51) and 1.36 times as likely to deliver a LBW infant (95% CI 1.23-1.51) than women who were diagnosed with cancer after experiencing a live birth. When each maternal characteristic was controlled for none of them presented themselves as true confounders in the relationship between being diagnosed with cancer before a pregnancy and adverse birth outcomes; none of the maternal characteristics significantly decreased the odds ratio when added to the Model 1 version of the logistic regression model. Yet, the odds ratios for PTB and LBW significantly increased for women who were Black/non-Hispanic (PTB OR 1.53 and LBW OR 2.07) and had less than a high school education (1.45 and 1.95). Therefore, women who were diagnosed with cancer, became pregnant afterwards, and were Black/non-Hispanic or had less than a high school education had a greater chance of having a preterm birth or delivering a low birthweight infant compared to women who were diagnosed with cancer after a pregnancy and were White/non-Hispanic or had greater than a high school education. Furthermore, when controlling for all maternal characteristics (Model 3), women diagnosed with cancer before a pregnancy were 1.42 times as likely to deliver a PTB infant (95% CI 1.26-1.62) and 1.41 times as likely to deliver a LBW infant

(95% CI 1.23-1.63) than women who were diagnosed with cancer after a live birth (Table 5). Therefore, being diagnosed with cancer before experiencing a pregnancy and subsequent live birth was significantly associated with PTB and LBW and this association became slightly stronger when maternal characteristics were accounted for.

Table 4 – Participants with Cancer Diagnosis before and after Pregnancy by Selected Factors, North Carolina Central Cancer Registry & Birth Record Data, 1990-2009

Characteristic[a]	Cancer Diagnosis before Pregnancy[e,g] [n *(%)*[f]]	Cancer Diagnosis after Pregnancy[e,h] [n *(%)*[f]]
Maternal Characteristics		
Maternal Age at Time of Diagnosis (years)		
≤ 14	192 *(3.39%)*	1 *(0.01%)*
15-19	740 *(13.07%)*	101 *(1.01%)*
20-29	3,121 *(55.11%)*	2,124 *(21.32%)*
30-39	1,470 *(25.96%)*	5,138 *(51.57%)*
40-49	51 *(0.90%)*	2,529 *(25.38%)*
≥ 50	89 *(1.57%)*	70 (0.70%)
Maternal Age at Time of Pregnancy (years)		
≤ 14	2 *(0.04%)*	4 *(0.04%)*
15-19	185 *(3.27%)*	410 *(4.12%)*
20-29	2,377 *(41.97%)*	3,844 *(38.58%)*
30-39	2,839 *(50.13%)*	5,195 *(52.14%)*
40-49	260 *(4.59%)*	508 *(5.10%)*
≥ 50	0 *(0%)*	2 *(0.02%)*
Race/Ethnicity		
Black/non-Hispanic	1,081 *(19.09%)*	1,933 *(19.40%)*
White/non-Hispanic	4,333 *(76.51%)*	7,459 *(74.87%)*
Hispanic (any race)	123 *(2.17%)*	281 *(2.82%)*
Other[c]	125 *(2.21%)*	288 *(2.89%)*
Missing	1 *(0.02%)*	2 *(0.02%)*
Education Level		
Less than high school	615 *(10.86%)*	1,095 *(10.99%)*
High school	1,471 *(25.98%)*	2,492 *(25.01%)*
Greater than high school	3,577 *(63.16%)*	6,376 *(64.00%)*
Infant Characteristics[d]		
Gestational Age		
PTB (< 37 weeks)	873 *(15.42%)*	1,168 *(11.72%)*
Term (≥ 37 weeks)	4,789 *(84.57%)*	8,793 *(88.26%)*
Missing	1 *(0.02%)*	2 *(0.02%)*
Birthweight		
LBW (< 2,500 g)	688 *(12.15%)*	917 *(9.20%)*
Normal (≥ 2,500 g)	4,975 *(87.85%)*	9,046 *(90.80%)*
TOTAL	**15,626**[i]	**100%**

[a] All of the characteristics were either captured in the cancer registry, birth record data, or calculated using these two sources
[b] This information is based off of the cancer diagnosis date and the delivery date
[c] The "Other" race/ethnicity category includes all races besides Black and White that are non-Hispanic (i.e., American Indian, Chinese, Japanese, Hawaiian, Filipino, & other Asian); this information was obtained from the birth record data
[d] PTB = preterm birth; LBW = low birthweight
[e] The cancer diagnoses that were included are breast, lung/bronchus, colon/rectum, corpus uteri, cervix uteri, endocrine, non-Hodgkin Lymphoma, melanoma (skin), ovary, kidney, and pancreas
[f] n= unweighted count, % = column percentage
[g] Date of the cancer diagnosis occurred before the delivery date; [h] Date of the cancer diagnosis occurred after the delivery date
[i] The 36 subjects who had a date of cancer diagnosis that was equivalent to the delivery date were excluded from this analysis

Table 5 – Unadjusted & Adjusted Odds Ratios (ORs) by Selected Factors for Preterm Birth (PTB) and Low Birthweight (LBW), North Carolina Central Cancer Registry & Birth Record Data, 1990-2009		
Characteristic[a]	**PTB OR[b] (95% CI)[c]**	**LBW OR (95% CI)**
	MODEL 1 (Unadjusted)	
Cancer before Pregnancy[d]	1.37 (1.25-1.51)	1.36 (1.23-1.51)
	MODEL 2	
Cancer before Pregnancy + Each Maternal Characteristic		
Maternal Age at Time of Diagnosis (years)	1.40 (1.25-1.57)	1.33 (1.17-1.51)
≤ 14*		
15-19	0.79 (0.52-1.20)	0.91 (0.59-1.42)
20-29	0.84 (0.57-1.23)	0.75 (0.50-1.13)
30-39	0.88 (0.60-1.30)	0.74 (0.49-1.12)
40-49	0.87 (0.58-1.31)	0.80 (0.52-1.23)
≥ 50	0.95 (0.54-1.69)	0.91 (0.49-1.69)
Maternal Age at Time of Pregnancy (years)	1.38 (1.25-1.51)	1.37 (1.23-1.52)
≤ 14	6.99 (1.40-34.84)	8.76 (1.76-43.67)
15-19	1.10 (0.86-1.41)	1.20 (0.93-1.56)
20-29*		
30-39	1.01 (0.92-1.12)	0.89 (0.80-0.99)
40-49	1.41 (1.15-1.73)	1.72 (1.40-2.11)
≥ 50[#]		
Race/Ethnicity	1.38 (1.25-1.51)	1.37 (1.24-1.53)
Black/non-Hispanic	1.53 (1.37-1.71)	2.07 (1.84-2.32)
White/non-Hispanic*		
Hispanic (any race)	0.80 (0.57-1.11)	0.76 (0.51-1.13)
Other[e]	1.29 (0.98-1.71)	1.50 (1.11-2.03)
Education Level	1.37 (1.25-1.51)	1.36 (1.23-1.51)
Less than high school	1.45 (1.26-1.67)	1.95 (1.68-2.27)
High school	1.21 (1.08-1.34)	1.47 (1.31-1.66)
Greater than high school*		
	MODEL 3 (Adjusted)	
Cancer before Pregnancy + All Variables	1.42 (1.26-1.62)	1.41 (1.23-1.63)
Maternal Age at Time of Diagnosis (years)		
15-19	0.84 (0.54-1.28)	0.99 (0.62-1.56)
20-29	0.99 (0.66-1.49)	1.00 (0.65-1.55)
30-39	1.07 (0.69-1.65)	1.07 (0.67-1.72)
40-49	0.98 (0.61-1.57)	1.04 (0.62-1.74)
≥ 50	1.03 (0.56-1.90)	1.04 (0.54-2.02)
Maternal Age at Time of Pregnancy (years)		
≤ 14	4.53 (0.86-23.70)	4.37 (0.82-23.21)
15-19	0.91 (0.69-1.20)	0.83 (0.62-1.11)
30-39	1.08 (0.95-1.23)	1.03 (0.89-1.19)
40-49	1.51 (1.18-1.94)	1.94 (1.49-2.53)
≥ 50[#]		
Race/Ethnicity		
Black/non-Hispanic	1.48 (1.32-1.66)	1.88 (1.67-2.13)
Hispanic (any race)	0.69 (0.49-0.97)	0.59 (0.40-0.89)
Other	1.22 (0.93-1.62)	1.36 (1.01-1.85)
Education Level		
Less than high school	1.52 (1.30-1.78)	1.96 (1.66-2.31)
High school	1.19 (1.07-1.34)	1.40 (1.23-1.58)

* Each of these categories were designated as the comparison group under its indicated category and were treated as such in the logistical regression model
[#] This category was omitted because it predicts failure perfectly and is equal to zero, so these observations were dropped from the model
[a] All of the characteristics were either captured in the cancer registry, birth record data, or calculated using these two sources
[b] Unadjusted odds ratio
[c] 95% confidence interval
[d] Date of the cancer diagnosis occurred before the delivery date
[e] The "Other" race/ethnicity category includes all races besides Black and White that are non-Hispanic (i.e., American Indian, Chinese, Japanese, Hawaiian, Filipino, & other Asian); this information was obtained from the birth record data

Public Health Implications

The association between cancer and adverse pregnancy outcomes has yet to be fully determined. The current literature on this exposure-outcome relationship is not in complete agreement about the potential risk of adverse pregnancy outcomes among female cancer survivors. Earlier studies on this topic have focused on childhood cancer survivors, who usually have a significant interval between their cancer diagnosis/treatment and subsequent pregnancies. The results from these studies cannot be appropriately applied to the population of female cancer survivors who are diagnosed with cancer during their reproductive years (15-49 years old), over the age of 21 (the age cut off for the childhood cancer studies), and become pregnant within relatively shorter time spans following their cancer diagnosis.

The long- and short-term effects of cancer on a woman's reproductive capacity are not completely understood. Furthermore, it is difficult to determine to what extent cancer (diagnosis and treatment) attributes to adverse pregnancy outcomes in comparison to other known risk factors (e.g., race/ethnicity, socio-economic status, maternal age, etc.). Comparable to other studies that focus on a relatively rare event, studies on the pregnancy outcomes of female cancer survivors need to establish larger sample populations in order to examine other variables that may impact the association between cancer treatment and adverse pregnancy outcomes.

Conclusion

The results from this study suggest that women in North Carolina who were diagnosed with cancer prior to giving birth had a higher risk of experiencing PTB and LBW deliveries. Women diagnosed with cancer prior to a pregnancy had a 42-percent increased risk of experiencing a PTB and a 41-percent increased risk of having a LBW delivery, which leads me to believe that cancer is one of many exposures that may lead to PTB and LBW. In fact, the association between cancer diagnosis and adverse birth outcomes increased when maternal factors were adjusted for in the analysis. Therefore, the impact of being diagnosed with cancer prior to a pregnancy and its potential effect on birth outcomes should not be disregarded. All chronic diseases and co-morbidities that occur during the preconception or interconception periods, that is, prior to or in between pregnancies, should be considered as potential risk factors for future adverse pregnancy outcomes.

As strategies for screening and treatment continue to advance, survival rates for cancer will simultaneously increase; therefore, the quality of life issues that arise for female cancer survivors who are of reproductive age need to be sufficiently addressed. I hoped that the preliminary study introduced in this paper has added to the existing research by exploring additional factors that may influence the association between cancer and subsequent poor birth outcomes. The current gap in the literature lies in the lack of maternal characteristics and risk factors that are examined in studies regarding the issue described. Through the use of linked cancer registry and birth record data from the North Carolina State Center for Health Statistics, I explored an underutilized avenue for examining the birth outcomes of female cancer survivors. Moreover, I attempted to add a layer to this pertinent discussion by highlighting the social determinants of health (i.e., race/ethnicity, education level) that may be potential contributing factors to this complex issue.

Despite the strengths of this study, there are seven distinct limitations that should be mentioned. First, after the process of linking the cancer registry and birth record data was completed it was discovered that if a woman had delivered more than one child during the given time period and was diagnosed with a different cancer after her first diagnosis that the pregnancies would only be linked to the first cancer diagnosis. Therefore, multiple bouts with cancer and placement of pregnancies may not be clearly defined in this linked data set and may have skewed the results in either direction. Second, the pregnancies of women who were beyond the 15-49 reproductive age range (age 14 or younger and age 50 or older) were included in this analysis. Although they represented a small portion of the total study population, women who are younger and older than the typical reproductive age group tend to have high risk pregnancies. This was definitely apparent in the results of the data where young women who were age 14 or younger and were diagnosed with cancer prior to giving birth had extremely high odds ratios and wide confidence intervals for experiencing a preterm birth and delivering a low birthweight infant. The impact of including this small sub-set of women on the study's results has not been analyzed. Third, pregnancies that occurred during the cancer treatment period were not easily discernable and were decidedly included in the analysis. The effects of cancer treatment on some of the pregnancies could have skewed the odds ratios to be higher than they would have been if these types of pregnancies were excluded from the analysis. Fourth, all of the women had the same exposure (cancer) during the given time period, yet the timing of their pregnancies was either before or after their diagnosis date. Restricting the analysis to only women who had ever been diagnosed with cancer during the years of 1990-2009 focuses solely on a vulnerable population and a better comparison group may be women who had never been diagnosed with cancer, but gave birth during the designated time period. Fifth, pregnancies that were the result of In Vitro Fertilization (IVF) were not controlled for. These pregnancies tend have a higher prevalence of multiple births and a higher risk for PTB and LBW deliveries. The inclusion of IVF pregnancies may have skewed the results by impacting the prevalence of PTB and LBW pregnancies and therefore increasing the odds ratios. Sixth, to produce a cleaner analysis, the study's population should be limited to women's first births and single births. By limiting the population by these factors, the analysis would not be impacted by the higher risk of PTB and LBW deliveries that occur among births that occur after a woman's first birth and among multiple births (i.e., twins, triplets, etc.). Seventh, several cancers are associated with tobacco use, including lung and cervical cancers. Therefore, tobacco use is an additional maternal factor that should have been accounted for in this study's analysis models. All of these limitations are key issues that were not resolved during the scope of this preliminary study, but should be considered in any future studies that pertain to this same topic area.

The information and knowledge acquired through this research project may inform the type of reproductive, preconception, and interconception health care that female cancer survivors receive. This knowledge could assist with developing interventions that will aim to prevent the occurrence of adverse birth outcomes among this particularly vulnerable population by not only addressing their medical needs, but considering how particular social determinants impact their health status (i.e., race/ethnicity, SES). In turn, this means that more female cancer survivors could experience healthy pregnancies and deliver healthy newborns. Since there is limited information on the pregnancy outcomes of female cancer survivors, especially women who are diagnosed at ages 21 and older, I believe adding to this body of knowledge has the potential to contribute to medical and public health entities' ability to holistically serve this population.

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