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Seth Mitchell Penley Date

Female, Young Adult Cancer Survivors and Cardiometabolic Health

By

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Master of Public Health

Epidemiology

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Female, Young Adult Cancer Survivors and Cardiometabolic Health

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B.S.
The University of Virginia
2016

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Abstract

Female, Young Adult Cancer Survivors and Cardiometabolic Health

By Seth Mitchell Penley

Due to improvements in cancer treatments and new technologies, the survival rate for individuals diagnosed with cancer has increased. Thus, there is a growing population of cancer survivors. While some studies have focused on the health of childhood cancer survivors after treatment has ended, there is a need for research related to the long-term cardiometabolic health of reproductive-aged women in the U.S. We used data from the Furthering Understanding of Cancer Health and Survivorship in Adult (FUCHSIA) Women's Study. The FUCHSIA Women's Study includes 1282 cancer survivors and 1073 women who were never diagnosed with cancer. We considered three outcomes in the study: any cardiovascular outcome (chronic hypertension or high blood pressure, congestive heart failure or cardiomyopathy, or heart attack or myocardial infarction), diabetes, and any cardiometabolic outcome (any cardiovascular outcome or diabetes). We performed adjusted logistic regression to examine the relationship between cancer diagnosis and development of the three outcomes. We controlled for potential confounders including: race, education, income, cigarette smoking, and age at interview. We repeated these analyses restricted to 1) breast cancer survivors, 2) survivors who had radiation to the chest (described as survivors who were diagnosed with breast cancer or lung cancer and received radiation), 3) survivors who were treated with chemotherapy, and 4) survivors who had both radiation to the chest and chemotherapy treatment. In the unadjusted model for all cancer survivors compared with those who were never diagnosed with cancer, the odds ratio (OR) for diabetes was 1.26 (95% CI:0.83, 1.90), for any cardiovascular outcome was 1.24 (95% CI:0.98, 1.57), and for any cardiometabolic outcome was 1.22 (95% CI:0.97, 1.52). The adjusted results for all models were null. Among those treated with chemotherapy, in the unadjusted model, the odds of all outcomes was slightly greater among cancer survivors, compared to those who were never diagnosed with cancer. However, after adjusting for confounders, the OR for all outcomes were null among those treated with chemotherapy. These results should be interpreted with caution but provide modest reassurance that cancer and its treatments broadly may not increase the risk of cardiometabolic outcomes in reproductive-aged women.

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I would also like to thank my family and friends for their advice and unwavering support and love.

Seth Mitchell Penley

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Chapter 1

Background

Introduction

The development of cancer treatment regimens and new technologies in the late 20th century and early 21st century have helped increase the likelihood of survival among cancer patients (1-10). The increasing population of cancer survivors has led to a growing research interest in cancer survivorship (2-8, 10). Some types of cancer have deleterious effects on the health of cancer survivors long after treatment has ended (3). Specifically, survivors of childhood cancers such as leukemia, neuroblastoma, and Wilms tumor, are at greater risk of developing risk factors that could lead to cardiometabolic diseases and conditions, such as diabetes mellitus (5). Further, several cancer treatments and the lifestyle changes that accompany cancer treatment can lead to the development of risk factors associated with cardiometabolic diseases (1). While some studies have examined the cardiometabolic health of cancer survivors, few have focused on young adult women. Therefore, there is a need to consider whether young adult female cancer survivors are at higher risk of developing cardiometabolic risk factors that might increase their chance of developing a cardiometabolic disease.

Cancer in Young Adult Women

Currently, one in three women will develop cancer in their lifetime (11). The incidence and prevalence of cancer varies among races, ethnicities, and age groups (12). As of January 1, 2012, an estimated 4 percent of women diagnosed with cancer were 20

to 39 years of age at the time of diagnosis (11). For the same year, the age-standardized incidence rate for cancer in women worldwide aged 20-39 years was 57.0 per 100,000 (13). At the time, the five most common types of new cancer cases among these women included: breast, cervix uteri, thyroid, leukemia, and ovarian (13).

At the beginning of 2012, an estimated 3 million women living in the United States (U.S.) had a history of breast cancer diagnosis and about 20% of breast cancers occurred in women aged younger than 50 years (11). In 2015, among women aged 20-49 years, the incidence rate of thyroid cancer was 27.8 per 100,000, of breast cancer was 73.1 per 100,000, of cervix uteri cancer was 10.1 per 100,000, of ovarian cancer was 6.0 per 100,000, and of leukemia was 4.7 per 100,000 (14).

According to the National Cancer Institute, “an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life” (15). Five percent of cancer survivors are younger than 40 years of age (11). The 5-year relative survival rate from 2008-2014 for women aged 20 to 49 years diagnosed with any cancer is 83.6 percent (14). From 2007 to 2013, 89.6 percent of women aged 20 to 49 years who were diagnosed with breast cancer survived at least 5 years (14). By January 1, 2022, there is expected to be 9.2 million women cancer survivors (11). The large and expanding pool of cancer survivors in the world signals a need to conduct more research related to the long-term health of cancer survivors. Identifying known cardiometabolic risk factors early among cancer survivors can lead to prevention efforts that can help to reduce the risk of chronic disease morbidity and mortality.

Cardiometabolic Health

Chronic diseases are the leading causes of mortality in the world (16). In 2008, the National Center for Health Statistics reported that 25% of deaths in the U.S. were caused by heart disease alone (17). Cardiovascular disease is the leading cause of death among women and is the third leading cause of death among women aged 18-44 years (18). A U.S.-based study found the prevalence of diabetes to be 2.9% in 2009 in U.S. women aged 18-44 years (19). Not only are chronic diseases a leading cause of death in the U.S., they also have high costs associated with treatment and care (10). In 2007, the U.S. spent over $2.2 trillion on healthcare, and three-quarters of this sum was allocated for the treatment of patients with one or more chronic diseases (20).

Of particular interest to researchers are risk factors that are associated with major cardiometabolic diseases. Identifying risk factors early can lead to prevention efforts that might decrease the likelihood of developing diabetes, stroke, and heart disease. These risk factors are often grouped together under a term called “metabolic syndrome.” Many medical and healthcare organizations have different criteria for determining whether a person should be characterized as having metabolic syndrome (Table 1.1). These definitions typically include raised triglycerides, reduced HDL cholesterol, raised blood pressure, central obesity, and raised fasting blood glucose (21) (Table 1.1). The heterogeneous definitions make it difficult to compare results across multiple studies. However, information on the prevalence of individual conditions contributing to the definition are more readily available. For example, in a study of U.S. adults, the prevalence of high blood pressure in women aged 18-44 years was 10.1% in 2009, and in

2008, the proportion of women aged 20-49 years with HDL cholesterol less than 40 mg/dl was 13% (19, 22).

Obesity is a risk factor for metabolic syndrome and recently, the obesity epidemic has received greater attention worldwide. In 2015-2016, the prevalence of obesity in U.S. women aged 20-39 years was 36.5% (23). Technological change, through agricultural innovation and sedentary home-and market production, coupled with larger portion sizes are factors that are helping to drive the obesity epidemic (24, 25). A study of Australian adults revealed that women who watched television for more than 14 hours per week were at an increased risk of obesity (26). While characteristics of the general population, such as a sedentary lifestyle, make the population more prone to developing cardiometabolic risk factors, prior publications reveal that therapeutic regimens for cancer can further increase the risk of developing these risk factors among cancer survivors (27).

Cancer and Cardiometabolic Health

Cancer survivors may be at greater risk of developing cardiometabolic diseases, including diabetes and heart disease (5, 28). In an analysis of the data from the Childhood Cancer Survivor Study (CCSS), cancer survivors were 3.3 times (95% CI:3.0, 3.5) more likely than their siblings to have been diagnosed with a chronic health condition (28). In a cohort study of childhood cancer survivors in Nordic countries, childhood cancer survivors had a standardized hospitalization rate ratio (SHRR) of 1.6 (95% CI:1.5, 1.8) for hospital contact for diabetes mellitus, compared to people who were never diagnosed

with cancer (5). Further, survivors of childhood leukemia having a premature mortality ratio of 9.5 (95% CI:8.8, 10.2) with non-cancer-related mortality usually attributed to a cardiovascular cause (29, 30). Thus, the increased risks of mortality and morbidity among these populations of children diagnosed with cancer give reason to suspect that mortality and morbidity risk might also be higher among young adult cancer survivors compared to those who were never diagnosed with cancer. The increased risks of mortality and morbidity could be related to the cancer itself or the treatment that cancer survivors receive.

Effects of Chemotherapy on Cardiometabolic Health

The type of treatment cancer patients receive depends on a number of factors, such as age, in addition to the site and stage of the cancer (11). Among females who are diagnosed with early stage breast cancer, about 50% undergo radiation alone and nearly 33% receive both chemotherapy and radiation (11). Women diagnosed with late stage breast cancer undergo chemotherapy in addition to surgery and other treatments (11).

Studies have indicated that some types of chemotherapy put cancer patients at greater risk of developing cardiovascular diseases (1). Anthracyclines are a class of chemotherapeutic drugs most commonly implicated in causing cardiomyopathy, which could lead to heart failure (3, 31, 32). However, the pathophysiology of anthracycline cardiotoxicity is not completely understood (7). Childhood cancer survivors who received doses larger than 360 mg/m^2 were 4.4 times (RR=4.4, 95% CI:1.3, 15.3) more likely to die of cardiac disease, compared to those who did not receive anthracyclines (33). Even

those who received doses of anthracyclines between 240-359 mg/m^2 had an increased risk (RR=1.3, 95% CI:0.3, 6.3) (33). Some young adult cancer survivors are treated with anthracyclines, but the cardiotoxicity of other chemotherapies is less well studied.

Effects of Radiation on Cardiometabolic Health

Radiation is a common treatment for cancer patients. In addition to chemotherapy, radiation therapy is associated with an increased risk of cardiometabolic risk factors among childhood cancer survivors (4, 8, 21). The effect of radiation on the development of cardiometabolic risk factors has been reported to vary according to the part of the body that receives radiation (4). Sites of radiation treatment that are associated with adverse cardiometabolic health include the entire body, chest, and brain (4, 8, 21, 28, 34). The effect of radiation on development of cardiometabolic risk factors also varies by the dose received (4).

Meacham et al. used the Childhood Cancer Survivor Study (CCSS) cohort to assess whether factors associated with the development of a Cardiovascular Risk Factor Cluster (CVRFC) were more common in cancer survivors compared to those who had never been diagnosed with cancer (21). The researchers considered certain factors related to cardiometabolic health and the presence of three or more of these factors as a surrogate for metabolic syndrome. One of the treatments that was associated with an increased risk of CVRFC was total body irradiation (OR=5.5, 95% CI:1.5, 15.8) or abdominal plus chest radiation (OR=2.3, 95% CI:1.2, 2.4). Radiation vs. no radiation had a stronger association with the development of CVRFC, compared to chemotherapy vs. no

chemotherapy. In a study by Oeffinger et al., the authors reported that in cancer survivors who were exposed to one of five different combinations of treatment, the risk of cardiovascular disease was approximately 10 times higher (highest RR=13.6, 95% CI: (9.8, 18.7), lowest RR=10.0, 95% CI:(8.2, 12.1)) than their siblings (28). Four out of the five treatment combinations involved a form of radiation (28).

In other studies, researchers have identified a link between cranial irradiation and factors associated with cardiometabolic diseases (4, 8, 34). Acute lymphoblastic leukemia (ALL) survivors treated with cranial irradiation had an increased risk of developing metabolic syndrome, compared to acute lymphoblastic leukemia survivors not treated with cranial irradiation (23% vs. 7%) (8). While the exact biological mechanisms that may explain how cranial irradiation affects cardiometabolic health are unknown at this time, one idea that has been posited is that cranial irradiation might induce metabolic syndrome by affecting the hypothalamic-pituitary axis, which may induce pituitary hormone deficiencies (4). Growth hormone, thyroid hormones, and sex hormones are associated with factors that fall under metabolic syndrome (4). Growth hormone deficiency can change the body's composition, leading to insulin resistance and obesity (4).

Total Body Irradiation and Stem Cell Transplantation

Factors associated with metabolic syndrome are more common in pediatric leukemia survivors who underwent total body irradiation-based hematopoietic cell transplantation, compared to those who did not receive hematopoietic cell transplantation

(23.1% vs. 4.2%) (2). The premature mortality rate is 2.3 times higher among hematopoietic transplant survivors compared to the general population, and it has been hypothesized that the higher rate of premature mortality in transplant survivors is due to the development of adverse cardiovascular risk factors in these individuals (35). The incidence of hypertension was 17% among 689 long-term survivors of hematopoietic transplant survivors during a median follow-up period of 16 (5-36) years (36).

Other Factors that Influence Cardiometabolic Health and Intervention Efforts

Other factors that could potentially affect the relationship between cancer survivorship and development of risk factors associated with cardiometabolic health include a sedentary lifestyle, genetic traits, and diet (2, 37). Because diet and physical activity are two factors that an individual can actively modify on their own, cancer survivors could focus on these two factors when attempting to improve their health. Thus, early interventions, such as a tailored diet and exercise plan, might help decrease the risk of developing cardiometabolic risk factors (30, 38).

Summary and Research Question

There appears to be a gap in the relevant literature about young adult women cancer survivors and their cardiometabolic health. Most studies examine the cardiometabolic health of childhood cancer survivors and not cancer survivors who were diagnosed in young adulthood (2, 4, 5, 8, 36). Young adults have some of the same

cancers, treatments, and may also have the same side effects that lead to a sedentary lifestyle. Therefore, young adult women may also be at risk of adverse cardiometabolic health. There are more people diagnosed with cancer as young adults than as children so if cancer treatment affects cardiometabolic health in this population, the potential impact is greater (13). In this study, we evaluate whether young adult women cancer survivors have a higher risk of developing cardiometabolic risk factors, such as obesity, chronic hypertension or high blood pressure, diabetes, congestive heart failure or cardiomyopathy, and heart attack or myocardial infarction, than women who were never diagnosed with cancer.

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Table 1.1: Metabolic syndrome definitions.

	WHO 1999	**NCEP/ATPIII 2001**	**IDF 2005**
Obesity	BMI >30 kg/m^2 or waist to hip ratio of: Males>0.9 Females>0.85	Waist circumference: Males>102 cm. Females>88 cm.	Central obesity based on ethnic group definition of obesity
Hypertension	≥140/90 mm Hg or treatment for hypertension	≥130/85 mm Hg or treatment for hypertension	≥130/85 mm Hg or treatment for hypertension
Dyslipidemia	TG≥150 mg/dl or HDL-C: Males <35 mg/dl Females <39 mg/dl	TG≥150 mg/dl HDL-C: Males<40 mg/dl Females<50 mg/dl or treatment	TG≥150 mg/dl HDL-C: Males<40 mg/dl Females<50 mg/dl or treatment
Glucose	Diabetes or IGT or IR	Fasting plasma glucose ≥110 mg/dl or treatment	Fasting plasma glucose ≥100 mg/dl or Type 2 Diabetes Mellitus
Other	Microalbuminuria: overnight albumin>20 µg/min or albumin: Creatinine≥30 mg/g		
Required for diagnosis	Diabetes, IGT or IR plus two or more of the above factors. If normal glucose levels, then they must have at least three of the above factors	Three or more of the above criteria	Row one plus two of the other factors

Abbreviations: WHO, World Health Organization; NCEP/ATPIII, National Cholesterol Education Program/Adult Treatment Panel 3; BMI, body mass index; IDF, International Diabetes Federation; HDL-C, high-density lipoprotein cholesterol; mm, millimeter; Hg, mercury; TG, triglycerides; IGT, impaired glucose tolerance; IR, insulin resistance; mg, milligram; g, gram; dg, decigram; cm, centimeter; min, minute; µg, microgram

Female, Young Adult Cancer Survivors and Cardiometabolic Health

Seth Mitchell Penley, Penelope P. Howards

Introduction

The development of cancer treatment regimens and new technologies in the late 20th century and early 21st century have helped increase the likelihood of survival among cancer patients (1-10). The increasing population of cancer survivors has led to a growing research interest in cancer survivorship (2-8, 10). Some types of cancer and their treatments have deleterious effects on the health of cancer survivors long after treatment has ended (3). Further, several cancer treatments and lifestyle changes that accompany cancer treatment can lead to the development of risk factors associated with cardiometabolic diseases in childhood cancer survivors (1). However, few studies have focused on female survivors of young adult cancers, despite the fact that they are diagnosed with some of the same cancers and receive some of the same treatments as childhood cancer survivors.

Currently, one in three women will develop cancer in their lifetime (11). The incidence and prevalence of cancer varies among races, ethnicities, and age groups (12). As of January 1, 2012, an estimated 4 percent of women diagnosed with cancer were 20 to 39 years of age at the time of diagnosis (11). For the same year, the age-standardized incidence rate for cancer in women worldwide aged 20-39 years was 57.0 per 100,000 (13). The 5-year relative survival rate from 2008-2014 for women aged 20 to 49 years diagnosed with any cancer is 83.6 percent (14). From 2007 to 2013, 89.6 percent of women aged 20 to 49 years who were diagnosed with breast cancer survived at least 5

years (14). At the beginning of 2012, an estimated 3 million women living in the U.S. had a history of breast cancer diagnosis and about 20% of breast cancers occur in women aged younger than 50 years (11). By January 1, 2022, there is expected to be 9.2 million women cancer survivors (11). The large and expanding pool of cancer survivors in the world signals a need to conduct more research related to the long-term health of cancer survivors.

Specifically, cancer survivors may be at greater risk of developing chronic diseases, including diabetes and heart disease (5, 15). Identifying risk factors associated with cardiometabolic diseases early among cancer survivors might lead to prevention efforts that could decrease the likelihood of developing diabetes, stroke, and heart disease.

Studies of childhood cancer survivors have indicated that some types of chemotherapy put cancer survivors at greater risk of developing cardiometabolic illnesses (1). Specifically, anthracyclines have been associated with cardiomyopathy, which could lead to heart failure (3, 16, 17). Radiation to the entire body, chest, and brain has also been associated with an increased risk of developing cardiometabolic risk factors (4, 8, 15, 18, 19). Other factors that could potentially affect the relationship between cancer survivorship and development of risk factors associated with poor cardiometabolic health include a sedentary lifestyle, genetic traits, and diet (2, 20). Unlike cancer treatment, lifestyle and diet are modifiable factors. Thus, early interventions, such as a tailored diet and exercise plan, might help decrease the risk of developing cardiometabolic risk factors among cancer survivors (21, 22).

In this study, we address the gap in scientific information related to whether female survivors diagnosed with cancer as young adults (20-35 years old) are at greater risk of poor cardiometabolic health than young adult women who were never diagnosed with cancer. We also assess whether certain treatments for cancer increase the risk of developing cardiometabolic risk factors, compared to other forms of treatment among these cancer survivors.

Methods

Study Population

We used data from the Furthering Understanding of Cancer Health and Survivorship in Adult (FUCHSIA) Women's Study. The FUCHSIA Women's Study is a population-based study that was originally designed to evaluate the effect of cancer treatment during a woman's reproductive years on fertility, menopause, menstrual cycles, and other women's health outcomes. Eligible cancer survivors were identified in collaboration with the Georgia Cancer Registry (GCR) and had to have been diagnosed with a reportable malignant cancer or ductal carcinoma in situ (DCIS) between the ages of 20 and 35 years during the time period 1990-2009 and at least 2 years prior to recruitment (23). Eligible cancer survivors had to be between 22 to 45 years of age at enrollment, able to speak English, and have a working telephone to take part in the study. Women without a history of cancer were identified for comparison using a purchased marketing list that was matched on 5-year age groups and Georgia region of residence to cancer survivors. They were eligible to participate if they were between 22 to 45 years of

age, spoke English, and had a working telephone to use for the interview. Women who agreed to be contacted by members of the study team gave consent to participate in the study at the time of interview. The Emory University and the Georgia Department of Public Health Institutional Review Boards approved this study.

The exposure of interest is whether or not a woman was diagnosed with cancer. Information on cancer type was obtained from the GCR. The interview asked participants whether they had ever been treated with chemotherapy and whether they had ever been treated with radiation therapy. We defined radiation to the chest as breast and lung cancer survivors treated with radiation.

Study participants were asked about several items related to their cardiometabolic health. Women were asked whether they had ever been diagnosed with chronic hypertension or high blood pressure when not pregnant, whether they have ever been diagnosed with congestive heart failure or cardiomyopathy when not pregnant, and whether they had a heart attack or myocardial infarction. Study participants were also asked whether a doctor had ever diagnosed them with diabetes when not pregnant. Women were also asked if they were currently taking medication for high blood pressure and whether they were using insulin or taking another medication to control their diabetes.

The three main outcomes of interest were 1) any cardiovascular outcome (includes chronic hypertension or high blood pressure, and/or congestive heart failure or cardiomyopathy, and/or heart attack or myocardial infarction), 2) diabetes, and 3) any cardiometabolic outcome (includes any cardiovascular outcome and diabetes).

Demographic information, such as sex, race/ethnicity, income, relationship history, current health insurance, smoking, marijuana use, and parity, were collected during the interview.

Statistical Analyses

To determine which variables to include as potential confounders, we examined the existing literature and created a directed acyclic graph (DAG) which provided us with a graphic representation of the interrelationships between variables considered in this study. The DAG helped us to identify potential confounders that needed to be considered further. We identified the final set of confounders by the change in estimate for the exposure when including versus excluding each covariate.

The final covariates in the analyses included: race (reference=white; Black/African American, all other races), parity (reference=2; 0; 1; 3+), income (reference=more than $50,000; less than or equal to $50,000), smoking cigarettes (reference=no; yes), and age at interview (reference=22-25; 26-30; 31-35; 36-40; 41-45).

SAS 9.4 was used for all statistical analyses (Cary, N.C.). We performed logistic regression to examine the unadjusted association between cancer diagnosis and development of the three outcomes separately.

We performed adjusted logistic regression to examine the relationship between cancer diagnosis and development of the three main outcomes controlling for: race, education, income, cigarette smoking, and age at interview. We repeated these analyses restricted to 1) breast cancer survivors, 2) survivors who had radiation to the chest, 3)

survivors who were treated with chemotherapy, and 4) survivors who had both radiation to the chest and chemotherapy treatment.

Results

Our study population consists of 1282 cancer survivors and 1073 women who have never been diagnosed with cancer. The most common type of cancers in this study include breast (32.4%), thyroid (9.6%), Hodgkin (nodal) (9.5%), and cervix uteri (8.03%) (Supplemental Table).

Cancer survivors were similar to women who had never had cancer with respect to race, health insurance, smoking, marijuana use, age at interview, and body mass index (BMI) (Table 2.1). However, the comparison women were slightly more educated than cancer survivors (some graduate education: cancer survivors 29.6% vs comparison women 34.2%). A higher proportion of cancer survivors had an annual income of less than or equal to $50,000, compared to women who were not diagnosed with cancer (35.2% vs. 28.2%). A slightly greater proportion of people who had never been diagnosed with cancer had married or lived with someone as a couple within the past year compared to cancer survivors (73.0% vs. 60.7%). Cancer survivors were also less likely to have children. Although the proportion of cancer survivors and comparison women reporting high blood pressure was similar, cancer survivors were more likely to report congestive heart failure (1.6% vs. 0.5%). Cancer survivors were more likely to report heart attacks, compared to women who had not been diagnosed with cancer (1.4% vs. 0.1%). Cancer survivors were slightly more likely to report being diagnosed with diabetes

and they were more likely to report treatment with insulin (34.3% vs. 28.6%) or no medications (23.9% vs. 16.7%).

A smaller proportion of white women reported any of the three outcomes, compared to the proportion of white women who had none of the outcomes (Table 2.2). A higher proportion of women who developed any of the three outcomes had an income less than or equal to $50,000, compared to the women who had none of the outcomes. A higher proportion of women with diabetes had smoked on a regular basis (38.1%), compared to the proportion of women with no adverse outcome (26.3%). Women who had diabetes were more likely to be childless (38.1%), compared to those with no cardiometabolic outcomes (25.7%). A higher proportion of women with any of the three outcomes were aged 41-45, compared to women who did not have any outcome.

In the unadjusted model for all cancer survivors compared with those who were never diagnosed with cancer, the odds ratio (OR) for diabetes was 1.26 (95% CI:0.83, 1.90), the OR for any cardiovascular outcome was 1.24 (95% CI:0.98, 1.57), and the OR for any cardiometabolic outcome was 1.22 (95% CI:0.97, 1.52) (Table 2.3). After controlling for education, race, smoking, income, and age, the OR for each outcome shifted toward the null.

In the unadjusted and adjusted models restricted to breast cancer survivors and those who were never diagnosed with cancer, the results were null for all three outcomes.

Among those treated with chemotherapy, in the unadjusted model, the odds of all outcomes was slightly greater among cancer survivors, compared to those who were

never diagnosed with cancer. However, after adjusting for confounders, the OR for all outcomes were null.

For those who received radiation to the chest, the odds of any cardiometabolic outcome and any cardiovascular outcome were slightly higher for cancer survivors, compared to those who were never diagnosed with cancer. However, after adjusting for confounding, the results were null. The adjusted OR for diabetes was less than the null for cancer survivors vs. those never diagnosed with cancer (OR=0.71, 95% CI:0.33, 1.54). However, the results were imprecise.

Among those who received chemotherapy and radiation to the chest, the odds of having any cardiometabolic outcome or any cardiovascular outcome was slightly greater compared to those who were never diagnosed with cancer. However, after adjusting for confounders, the OR for any cardiometabolic outcome and any cardiovascular outcome were null. For diabetes, the unadjusted OR was null and the adjusted estimate moved below the null.

Discussion

Our results do not support our hypothesis that cancer treatment is associated with poor cardiometabolic health. Even though our unadjusted results were suggestive, the OR moved to the null after adjusting for confounders. However, cancer survivors were substantially more likely than those who were not diagnosed with cancer to report cardiomyopathy and heart attacks, but the total number of these events was small.

We restricted cancer survivors based on treatment type in an attempt to assess whether the cancer itself or its treatments affected the development of the outcomes of interest. We conducted an analyses on those who received both chemotherapy and radiation to the chest to see if the combination of both treatments led to a greater effect on cardiometabolic health. Our results reveal that the combination of both forms of treatment compared to women without cancer did not produce a substantial difference in whether or not a woman reported cardiometabolic health issues. The results were similar when evaluating chemotherapy or radiation to the chest alone. The unadjusted ORs were stronger when we restricted to women treated with chemotherapy, radiation to the chest, or both than for all survivors or breast cancer survivors. However, when we adjusted for potential confounders, the results were null.

While there is limited literature on the cardiometabolic health of young adult cancer survivors, the existing research suggests that survivors of childhood cancer are at higher risk of being diagnosed with adverse cardiometabolic health than those who were never diagnosed with cancer. We did see that cancer survivors were at higher risk for cardiomyopathy and heart attacks, but the numbers were small and the results for our broader outcomes were null, which could be due to the inability to restrict to specific treatments, such as anthracyclines. Anthracyclines have been associated with an increased risk of cardiometabolic risk factors in adult survivors of childhood cancers. Because we grouped all forms of chemotherapy treatment together, we were unable to determine whether different chemotherapy treatments had an effect on the development of the three main outcomes of interest. Another possible explanation for the null results could be due to the women being in different developmental stages of their lives at

treatment from survivors of childhood cancer. Another explanation could be that our follow-up period is too short. Cancer survivors might not have had enough time to develop cardiometabolic diseases and be diagnosed by their healthcare providers. As a result, our study may suggest that cancer survivors are not at increased risk of developing cardiometabolic diseases in the short term, but that risk may increase as the women age.

Another finding from our study is that there is a lower odds of diabetes among cancer survivors. Perhaps after cancer treatment, these women are more health conscious, so they alter their lifestyles and have better behaviors, such as healthy diets and high physical activity levels, that decrease their risk of diabetes. However, a limitation is that the sample size for those diagnosed with diabetes is small. Another limitation is that outcomes and cancer treatments were self-reported, meaning that these variables could be misclassified.

Our study may have suffered from survival bias. Some women who had some of the factors mentioned in this study, such as high blood pressure or diabetes, might have passed away due to these health issues and have not been included in this study. As a result, if cancer survivors are more likely to have high blood pressure or diabetes, there could possibly have been a stronger association between cancer survivorship and the development of these outcomes that our study did not reveal because the women who died were not included in the study. However, this population is relatively young, so mortality due to cardiometabolic factors is likely low.

The present study has several strengths. A strength of our study is that it is population-based and uses a large population of cancer survivors. Cancer cases were

identified by the Georgia Cancer Registry, which records all types of cancer in the state, making this a reliable data source for this study.

Our results are null and should be interpreted with caution. These results provide modest reassurance that cancer and its treatments broadly may not increase the risk of cardiometabolic outcomes in reproductive-aged women. However, the relatively high proportion, though small number, of survivors experiencing cardiomyopathy and heart attacks does suggest that a subset of survivors may be at an increased risk of adverse cardiovascular disease outcomes, which my increase over time. Further studies should try to attain data from medical records. We were unable to examine specific treatments in our present study, so future studies should measure the strength of this relationship among female cancer survivors of reproductive age.

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Table 2.1: Number and percent of cancer survivors and women who were never diagnosed with cancer by sociodemographic factors.

	Cancer Survivors (N=1282)		Non-cancer (N=1073)	
	N	**%**	**N**	**%**
Race				
White	889	69.9	712	66.8
Black/African American	325	25.6	309	29.0
Other	58	4.6	45	4.2
Missing	10		7	
Education				
High school graduate or less	98	7.7	52	4.9
Some college	343	26.8	257	24.0
College graduate	461	36.0	396	36.9
Some graduate school or a graduate degree	379	29.6	367	34.2
Missing	1		1	
Income				
Less than or equal to $50K	447	35.2	299	28.2
More than $50K	822	64.8	760	71.8
Missing	13		14	
Have you ever married or lived with anyone as a couple for at least a year?				
Yes	502	39.3	289	27.0
No	776	60.7	783	73.0
Missing	4		1	
Health insurance				
Yes	1150	89.7	961	89.6
No	132	10.3	112	10.4
Missing	0		0	
Have you ever smoked cigarettes on a regular basis?				
Yes	363	28.4	265	24.7
No	917	71.6	808	75.3
Missing	2		0	
Have you ever used marijuana on a regular basis?				
Yes	233	18.2	169	15.8

No	1049	81.8	904	84.2
Missing	0		0	
Age at Interview				
22-25	13	1.0	29	2.7
26-30	98	7.6	65	6.1
31-35	282	22.0	187	17.4
36-40	489	38.1	450	41.9
41-45	400	31.2	342	31.9
BMI				
Underweight	16	1.3	20	1.9
Normal	565	44.3	434	40.7
Overweight	322	25.2	308	28.9
Obese	373	29.2	305	28.6
Missing	6		6	
Number of children given birth to (parity)				
0	392	30.6	216	20.1
1	291	22.7	192	17.9
2	397	31.0	406	37.8
3+	202	15.8	259	24.1
Diabetes Diagnosis				
Yes	58	4.5	39	3.6
No	1223	95.5	1034	96.4
Missing	1		0	
Medication used to treat Diabetes				
Insulin	23	34.3	12	28.6
Other medication besides insulin	28	41.8	23	54.8
No medication	16	23.9	7	16.7
Missing	0		1	
High Blood Pressure				
Yes	168	13.1	129	12.0
No	1113	86.9	944	88.0
Missing	1		0	
Currently taking medication for high blood pressure				
Yes	115	68.5	97	75.2
No	53	31.5	32	24.8
Missing	1114		944	

Congestive Heart Failure or Cardiomyopathy				
Yes	20	1.6	5	0.5
No	1259	98.4	1068	99.5
Missing	3		0	
Heart Attack or Myocardial Infarction				
Yes	18	1.4	1	0.1
No	1262	98.6	1072	99.9
Missing	2		0	

Abbreviations: N, sample size; BMI, Body Mass Index.
Notes: There are a greater number of women taking diabetes medication than those diagnosed with diabetes because women might have reported taking both insulin and other medications besides insulin.

Table 2.2: Number of cancer survivors and women who were never diagnosed with cancer with each outcome, stratified by potential confounders.

	None of these outcomes		Any cardiometabolic outcome		Any cardiovascular outcome		Diabetes	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Potential Confounders								
Race								
White	1395	71.0	202	55.0	170	53.3	59	62.1
Black/African American	482	24.5	149	40.6	134	42.0	33	34.7
All other races	87	4.4	16	4.4	15	4.7	3	3.2
Missing	14		3		2		2	
Education								
High school graduate or less	110	5.6	40	10.8	37	11.5	14	14.6
Some college	478	24.2	119	32.2	102	31.8	34	35.4
College graduate	740	37.4	116	31.4	99	30.8	30	31.3
Some graduate school or a graduate degree	649	32.8	94	25.5	83	25.9	18	18.8
Missing	1		1		0		1	
Income								
Less than or equal to $50K	574	29.4	171	46.7	144	45.4	59	60.8
More than $50K	1381	70.6	195	53.3	173	54.6	38	39.2
Missing	23		4		4		0	
Have you ever married or lived with anyone as a couple for at least a year?								
Yes	631	32.0	158	42.7	134	41.7	47	48.5
No	1342	68.0	212	57.3	187	58.3	50	51.5
Missing	5		0		0		0	
Health insurance								
Yes	1787	90.3	317	85.7	276	86.0	80	82.5
No	191	9.7	53	14.3	45	14.0	17	17.5
Missing	0		0		0		0	
Have you ever smoked cigarettes on a regular basis?								
Yes	520	26.3	107	28.9	85	26.5	37	38.1
No	1456	73.7	263	71.1	236	73.5	60	61.9
Missing	2		0		0		0	
Have you ever used marijuana on a regular basis?								
Yes	328	16.6	73	19.7	61	19.0	18	18.6

No	1650	83.4	297	80.3	260	81.0	79	81.4
Missing	0		0		0		0	
Age at Interview								
22-30	192	9.7	13	3.5	12	3.7	2	2.1
31-35	414	20.9	55	14.9	47	14.6	14	14.4
36-40	786	39.7	150	40.5	132	41.1	35	36.1
41-45	586	29.6	152	41.1	130	40.5	46	47.4
Missing	0		0		0		0	
BMI								
Underweight	36	1.8	0	0.0	0	0.0	0	0.0
Normal	925	47.0	72	19.6	63	19.7	12	12.4
Overweight	534	27.1	94	25.5	83	26.0	16	16.5
Obese	473	24.0	202	54.9	173	54.2	69	71.1
Missing	10		2		2		0	
Number of children given birth to (parity)								
0	508	25.7	99	26.8	81	25.2	37	38.1
1	397	20.1	85	23.0	79	24.6	12	12.4
2	675	34.1	125	33.8	105	32.7	36	37.1
3+	398	20.1	61	16.5	56	17.4	12	12.4

Abbreviations: N, sample size; Any cardiometabolic outcome includes any cardiovascular outcome and diabetes; Any cardiovascular outcome includes high blood pressure, and/or cardiomyopathy, and/or heart attack

Table 2.3: Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals, comparing cancer survivors to those who were never diagnosed with cancer.

	Outcome	No Outcome	Unadjusted Model		Adjusted Model	
	N	N	OR	95% CI	OR	95% CI
All cancer survivors						
Any cardiometabolic outcome						
Cancer Survivor	216	1059	1.22	(0.97, 1.52)	1.14	(0.90, 1.43)
Non-Cancer	154	919	1.00		1.00	
Any cardiovascular outcome						
Cancer Survivor	189	1087	1.24	(0.98, 1.57)	1.16	(0.91, 1.49)
Non-Cancer	132	941	1.00		1.00	
Diabetes						
Cancer Survivor	58	1223	1.26	(0.83, 1.90)	1.08	(0.70, 1.66)
Non-Cancer	39	1034	1.00		1.00	
Breast cancer survivors						
Any cardiometabolic outcome						
Cancer Survivor	66	346	1.14	(0.83, 1.56)	0.96	(0.69, 1.33)
Non-Cancer	154	919	1.00		1.00	
Any cardiovascular outcome						
Cancer Survivor	58	354	1.17	(0.84, 1.63)	1.00	(0.71, 1.42)
Non-Cancer	132	941	1.00		1.00	
Diabetes						
Cancer Survivor	14	401	0.93	(0.50, 1.72)	0.71	(0.37, 1.37)
Non-Cancer	39	1034	1.00		1.00	
Treatment with chemotherapy						
Any cardiometabolic outcome						
Cancer Survivor	130	577	1.35	(1.04, 1.74)	1.19	(0.91, 1.55)
Non-Cancer	154	919	1.00		1.00	
Any cardiovascular outcome						
Cancer Survivor	112	595	1.34	(1.02, 1.76)	1.19	(0.90, 1.58)
Non-Cancer	132	941	1.00		1.00	
Diabetes						
Cancer Survivor	34	679	1.33	(0.83, 2.12)	1.07	(0.66, 1.75)
Non-Cancer	39	1034	1.00		1.00	
Radiation to the chest						
Any cardiometabolic outcome						
Cancer Survivor	43	208	1.23	(0.85, 1.79)	0.95	(0.64, 1.40)
Non-Cancer	154	919	1.00		1.00	

Any cardiovascular outcome						
Cancer Survivor	39	212	1.31	(0.89, 1.93)	1.01	(0.67, 1.52)
Non-Cancer	132	941	1.00		1.00	
Diabetes						
Cancer Survivor	9	245	0.97	(0.47, 2.04)	0.71	(0.33, 1.54)
Non-Cancer	39	1034	1.00		1.00	
Chemotherapy and Radiation to the chest						
Any cardiometabolic outcome						
Cancer Survivor	40	186	1.28	(0.88, 1.88)	0.97	(0.65, 1.45)
Non-Cancer	154	919	1.00		1.00	
Any cardiovascular outcome						
Cancer Survivor	36	190	1.35	(0.91, 2.02)	1.03	(0.68, 1.57)
Non-Cancer	132	941	1.00		1.00	
Diabetes						
Cancer Survivor	9	220	1.09	(0.52, 2.27)	0.79	(0.36, 1.70)
Non-Cancer	39	1034	1.00		1.00	

Abbreviations: N, sample size; CI, confidence interval; Any cardiovascular outcome includes high blood pressure, and/or cardiomyopathy, and/or heart attack; Any cardiometabolic outcome includes any cardiovascular outcome and diabetes; Adjusted model adjusts for education, race, smoking, income, and age

Appendix

Supplemental Table: Number and percent of female cancer survivors by cancer type.

	Cancer Survivors (N=1282)	
	N	**%**
Breast	415	32.4
Cervix Uteri	103	8.0
Hodgkin (Nodal)	122	9.5
Ovary	38	3.0
Brain	31	2.4
Colon	47	3.7
Corpus Uteri	32	2.5
NHL (Nodal)	39	3.0
Soft Tissue	50	3.9
NHL (Extranodal)	20	1.6
Melanoma	102	8.0
Thyroid	123	9.6
Other	38	3.0
Kidney	26	2.0
Leukemia	45	3.5
Lung	9	0.7
Placenta	10	0.8
Head and Neck	26	2.0
Vaginal	6	0.5

Abbreviations: N, sample size; NHL, Non-Hodgkin's Lymphoma