Risk Factors for Future Cardiac Diseases in Childhood Cancer Survivors

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RISK FACTORS FOR FUTURE CARDIAC DISEASES IN CHILDHOOD CANCER SURVIVORS

By

David C. Landy

A DISSERTATION

Submitted to the Faculty of the University of Miami in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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RISK FACTORS FOR FUTURE CARDIAC DISEASES IN CHILDHOOD CANCER SURVIVORS

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**Background:** With 12,000 children diagnosed with cancer annually in the United States and survival rates approaching 80%, the long-term health of childhood cancer survivors is an increasingly important concern. This is especially true given that over 70% of survivors develop a chronic health condition by 30 years after their original diagnosis. Cardiovascular diseases (CVD) are the most common non-cancer related complications. Although some risk factors for therapy-induced cardiovascular damage have been identified, their influence on longitudinal CVD risk is not well described, and therefore, their clinical utility is limited. While guidelines exist for protecting the long-term cardiovascular health of survivors, they are generalized from general population recommendations, placing a strong reliance on healthy lifestyle habits such as diet. By failing to consider the clinical heterogeneity of survivors, these recommendations may miss those survivors with the greatest need for risk management and ignore the possibility that survivors require unique strategies for effective CVD prevention. It is also unclear how a history of childhood cancer affects diet, how diet in-turn affects the development of traditional CVD risk factors among survivors, and what the combined effects of these traditional CVD risk factors imply for the long-term health of survivors.
Methods: This dissertation presents results from 3 investigations related to the long-term cardiovascular health of survivors using data from the Cardiac Risk Factors in Pediatric Cancer Survivors Study. This study included 201 survivors, a median of 11 years from cancer diagnosis, and 76 of their siblings who were assessed during day-long study visits including echocardiography, patient histories, and laboratory tests conducted from 1999 to 2003. Cancer treatment records were reviewed and 3-day food records collected. First, the associations between cranial irradiation and cardiac abnormalities associated with anthracycline chemotherapy were examined. Associations with insulin-like growth factor 1 (IGF-1), a marker of growth hormone, were also examined. Second, diet records were used to estimate daily caloric intake relative to recommended levels and dietary quality using the Healthy Eating Index-2005 (HEI). The diets of survivors and siblings were compared and associations with cancer types and treatments investigated. The association between dietary quality and adiposity among survivors was also examined. Third, future CVD risk due to traditional CVD risk factors was examined using Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scores and the Framingham Risk Calculator (FRC), both expressed as ratios relative to an individual of similar age and sex without modifiable risk factors. The PDAY odds ratio represents the increased odds of currently having an advanced coronary artery lesion. The FRC risk ratio represents the increased risk of a myocardial infarction, stroke, or coronary death in the next 30 years. Survivor and sibling risk estimates were compared and associations with cancer diagnoses and treatments as well as physical inactivity examined.

Results: Survivors exposed to cranial radiation had an additional 12% decrease in LV mass compared to unexposed survivors (P<.01), and an additional 3.6% decrease in LV
Survivors exposed to cranial radiation also had a greater decrease in IGF-1 relative to normal levels than unexposed survivors (30.8% vs. 10.5% decrease, \( P < 0.01 \)). There were no differences between survivors and siblings in daily caloric intake (97 vs. 105% of recommended caloric intake) or the HEI total score (55.5 vs. 53.3), respectively. Survivors exposed to cranial radiation had lower total HEI scores (-6.4, \( P = 0.01 \)). Among survivors, increasing dietary quality was associated with decreasing percent body fat (\( \beta = -0.19, \ P = 0.04 \)). The median PDAY odds ratio for survivors was 2.2 (interquartile range, 1.3-3.3). The median FRC risk ratio was 1.7 (interquartile range, 1.0-2.0). Survivors and siblings had similar mean PDAY odds ratios (2.33 vs. 2.29, \( P = 0.86 \)) and FRC risk ratios (1.72 vs. 1.53, \( P = 0.24 \)). Cancer type and treatments were not associated with the CVD risk estimated from traditional metabolic CVD risk factors, cardiometabolic health. There was a suggested association of physical inactivity with PDAY odds ratios (\( r = 0.17, \ P = 0.10 \)) and FRC risk ratios (\( r = 0.19, \ P = 0.12 \)).

**Discussion:** Among anthracycline-treated survivors, those with cranial radiation exposure had significantly greater decreases in LV mass and dimension. Because cranial irradiation was also associated with decreased IGF-1, it is possible that GH deficiencies mediated this effect suggesting that GH replacement therapy may help prevent the development of cardiotoxicity. Survivors consumed diets similar in quality to their siblings though both groups were only moderately adherent to guidelines. Dietary quality was associated with increased body fat in survivors suggesting interventions focused on diet quality may help reduce their adiposity. Cardiometabolic health was poor in survivors but not different than that of their siblings, highlighting the importance of managing traditional CVD risk factors and considering novel exposures in survivors.
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Chapter 1. Introduction

1.1 Dissertation Overview

Every year, over 12,000 children in the United States are diagnosed with cancer\textsuperscript{1} and as many as 80\% of these children will survive for at least 5-years.\textsuperscript{2,3} It is hoped that survivors will go on to lead normal, healthy lives, though by 30 years after their original cancer diagnosis, over 70\% will have developed a chronic health condition.\textsuperscript{4} These complications often occur as a result of cancer therapies such as chemotherapy and radiation, though the specific pathways responsible for such changes and the factors influencing their progression are not fully elucidated.\textsuperscript{5,6} Chief among these complications are cardiovascular diseases (CVD) which are the leading causes of serious, non-cancer related morbidity and mortality in survivors and include cardiomyopathy and ischemic heart disease.\textsuperscript{7-11} By 30 years after cancer diagnosis, 7\% of survivors treated with moderate to high anthracycline doses will have developed heart failure and 6\% exposed to moderate levels of cardiac irradiation will have suffered a myocardial infarction.\textsuperscript{11}

It is recommended that survivors be screened for cardiac abnormalities and traditional CVD disease risk factors such as obesity, hyperlipidemia, and insulin resistance and that any cardiometabolic abnormalities be managed through lifestyle interventions and medications.\textsuperscript{12,13} These strategies are generalized from studies of the general population, are unfocused, and may not reduce the CVD burden of all survivors. By failing to consider the clinical heterogeneity of survivors, these recommendations may fail to identify those with the greatest need for risk management and ignore the possibility that some survivors require unique strategies for effective CVD prevention. Although some risk factors for having cardiac and vascular abnormalities and traditional CVD risk...
factors have been reported, many are not well documented, and therefore, their clinical utility is limited.\textsuperscript{5,14,15} In relation to the reliance of current strategies on dietary concepts generalized from the general population, it remains unclear how childhood cancer and treatment affect the diets of survivors and how diet quality may in turn affect the development of traditional CVD risk factors in survivors. Further, the combined effects of traditional CVD risk factors on the long-term health of survivors, aggregated risk, has not been considered.

To address these issues, data prospectively collected in the NCI-funded “Cardiac Risk Factors in Pediatric Cancer Survivors Study” (CRG, R01-CA-79060) was analyzed. The CRG, conducted from 1999 to 2003, includes 201 childhood cancer survivors and 76 of their siblings from the geographic catchment area treated at Golisano Children’s Hospital, Rochester, NY and, as such, represents a nearly population based sample of survivors. These survivors and siblings had comprehensive cardiometabolic assessments at a median of 11 years from cancer diagnosis, ranging from 3 to 32 years.\textsuperscript{16} Three-day food records were obtained and analyzed using NDSR dietary software. Echocardiography, patient histories and laboratory tests were also completed and cancer treatment records reviewed. This dataset allows for an investigation of CVD risk factors in survivors, while comparing their CVD risk to genetically and environmentally similar controls. Specifically, three questions will be addressed.

First, the association between cranial irradiation and anthracycline cardiotoxicity will be examined using models adjusting for other known risk factors (age at diagnosis, anthracycline dose, length of follow-up, cardiac irradiation, and sex). Further, the association between insulin-like growth factor 1 (IGF-1), a marker of growth hormone
function, and left ventricular structure and function will be examined in survivors exposed to cranial radiation for whom growth hormone deficiency may underlie cardiac abnormalities. Investigating the possible association between cranial irradiation and anthracycline cardiotoxicity may help improve the ability to predict which survivors will develop cardiotoxicity as well as help guide cardiac screening and the development of new treatments.

Second, the diet quality scores of survivors will be compared to those of sibling controls and possible associations between cancer types and treatments with dietary quality investigated. The association between dietary quality and adiposity in survivors will also be examined. Understanding how treatments are associated with dietary habits could identify survivor subgroups at risk of having poor diet quality and may suggest possible causes. Understanding how these habits are associated with adiposity will inform the appropriateness of current recommendations and the need to focus on novel pathophysiologic causes of CVD risk in survivors. Diets will be described by processing 3-day food records using Nutrition Data System for Research (NDSR) software to measure adherence to dietary guidelines. A method has been recently proposed for calculating Healthy Eating Index (HEI) scores using NDSR output to estimate diet quality through adherence to current guidelines. Daily caloric intake will be expressed relative to Institute of Medicine recommendations.

Third, the anticipated CVD burden of survivors due to traditional CVD risk factors will be examined. Two recently developed tools have made the aggregation of traditional CVD risk factors possible for younger patients. The Pathological Determinants of Atherosclerosis in Youth (PDAY) risk score predicts the presence of
an advanced atherosclerotic coronary artery lesion while the Framingham Risk Calculator\textsuperscript{21} (FRC) predicts the 30-year risk of CVD. Risk estimates of survivors will be compared to those of sibling controls and associations between these risk estimates and specific cancer diagnoses and treatments will be investigated. Producing estimates of CVD risk that aggregate traditional risk factors and comparing these estimates between survivors and sibling controls will provide insight into the expected importance of such factors as well as the degree to which they may explain the observed increased incidence of CVD in survivors.

This dissertation presents the results of using CRG data to examine the three specific research areas described above, all of which are related to better understanding the CVD burden of survivors (Figure 1.1). Specifically, Chapter 2 is focused on the association between cranial irradiation and anthracycline cardiotoxicity; Chapter 3 is focused on the diets of survivors; and Chapter 4 is focused on the aggregation of traditional CVD risk factors in survivors. The following sections of this chapter will describe in greater detail the general background related to CVD in survivors, the conduct and initial findings of the CRG, and a conceptual model of the increased CVD burden of survivors in order to prepare readers for the following chapters. Additionally, Chapter 5 will present conclusions related to how the results presented in this paper advance the current understanding of the CVD burden of survivors as well as how they can be used to help protect the long-term health of survivors.

The overarching purpose of the dissertation is to better understand why survivors face increased morbidity and mortality from CVD. Though some reasons have been previously described, as will be discussed in later sections of this chapter, there is still a
significant amount that is unknown with respect to the development of CVD in survivors. Specifically, whether there exists an association between cranial irradiation and the cardiac damage caused by anthracycline chemotherapy is not known. Further, whether survivors have altered diets and how diet is association with traditional CVD risk factors among survivors are not known. Even the relative importance of the contribution of traditional CVD risk factors to the increased CVD morbidity and mortality of survivors is not known. This dissertation seeks to answer these questions in order to improve current understanding of CVD in survivors.

1.2 General Background

Over 12,000 children are diagnosed with cancer in the United States annually.\(^1\) While less than half of these children would have been expected to survive in the 1960s, recent advances in cancer therapies have led to 5-year survival rates of roughly 80\% across the spectrum of pediatric cancers.\(^2,3\) In fact, it is estimated that over 325,000 survivors of childhood cancer are living in the United States today.\(^22\) Much of this improvement is due to therapies with known cardiotoxic effects that were initially limited by acute cardiac complications.\(^23\) While newer protocols that restrict chemotherapy dosing and reduce the radiation exposure of cardiovascular tissues have resulted in acute complication rates of less than 1\%, it is increasingly clear that the cardiotoxicity associated with these therapies can also manifest chronically.\(^24\) Exposed survivors appear to be at increased risk for CVD over the course of their lifetimes.\(^7-11,26\)

The leading non-cancer related cause of mortality and morbidity in survivors is CVD.\(^7-9\) Not only are survivors up to 8-times more likely than the general population to
This figure provides a conceptual overview of how the complications of childhood cancer contribute to the cardiac disease burden of survivors. Arrows indicate the paths between cancer complications, cardiac disease risk, cardiac disease, and cardiac disease burden. Specific paths addressed in this dissertation are labeled by the chapter number in which they are discussed.
die from CVD\textsuperscript{7}, but compared to siblings, they are 15-times more likely to suffer from heart failure (HF), more than 10-times as likely to have coronary artery disease, and more than 9-times as likely to have had a cerebrovascular accident during the first 30-years following cancer diagnosis.\textsuperscript{4,11} Cardiotoxicity from cancer treatments has even been identified as an increasingly appreciated cause for heart transplantation in young adults.\textsuperscript{27} Specific therapeutic regimens, most notably those containing anthracyclines or cardiac irradiation, have been associated with increased risk of CVD.\textsuperscript{10,11}

Subclinical cardiotoxicity is identifiable in over half of survivors exposed to these cardiotoxic treatments.\textsuperscript{28-32} This cardiotoxicity ranges from decreased left ventricular (LV) systolic and diastolic functions associated with anthracyclines\textsuperscript{28-30} to pericardial or valvular damage associated with cardiac and vascular radiation exposure.\textsuperscript{31} This subclinical cardiotoxicity appears to be progressive and may eventually lead to clinical CVD.\textsuperscript{30} Higher cumulative doses of anthracyclines and cardiac irradiation, higher dose rate of anthracyclines, use of concomitant cardiotoxic therapies such as vinca alkaloids, younger age at treatment, increasing time since treatment, female sex, elevations of serum cardiac troponin-T (cTnT) or N-terminal pro-brain natriuretic peptide (NT-proBNP) measured during anthracycline therapy, and congestive heart failure during anthracycline therapy are associated with the development of cardiovascular abnormalities.\textsuperscript{14,33,34} In addition to direct damage to cardiac and vascular tissues, many survivors have poor cardiometabolic health defined by increased prevalence rates of several traditional metabolic CVD risk factors such as obesity, dyslipidemia, and insulin resistance.\textsuperscript{35-38} The combined effects of cardiac damage and increased CVD risk factors
are ill-defined, but additional insights would aid the development of successful prevention strategies.39

The adverse effects of cancer treatment may be especially problematic in pediatric patients.40 These therapies may interfere with the potential for growth of normal tissue as is most clearly demonstrated in survivors who fail to attain normal height.41 Likewise, because of their physical immaturity, children may be less able to compensate for therapy related insults. This concern has been supported by several studies documenting higher rates of heart failure in children compared to adults treated at the same anthracycline dose adjusted for body size.23 Finally, the overall life expectancy of childhood cancer survivors is longer than their adult counterparts and long-term adverse effects of cancer treatments in these pediatric cancer patients will only be determined with long-term, or even lifelong, follow-up. Even subclinical changes, magnified over the course of a lifetime, may result in adverse cardiovascular outcomes for survivors of childhood cancer as compared to the cardiovascular risk in survivors of adult-onset cancer.

This section will review the cardiovascular complications associated with the treatment of childhood cancer to better prepare the reader for the subsequent chapters of this dissertation.

1.2.1 Cardiotoxic Cancer Therapies

The treatment of childhood cancers often involves the use of therapies that are known to be associated with cardiotoxicity including anthracyclines and radiation therapy with cardiac exposure.15 While heart failure in adults and children most often manifests as a dilated cardiomyopathy, in which the left ventricle (LV) has expanded and there is
reduced LV function, this is often not the case in survivors. For survivors, the cardiotoxic manifestations of anthracyclines as well as cardiac and vascular radiation exposure are often similar to a restrictive-like cardiomyopathy. Although the pathophysiology likely differs from a pure restrictive cardiomyopathy, it can be described most simply as a disease in which the LV fails to properly fill during diastole because of improper LV relaxation and compliance. Often due to myocardial stiffness, impaired stretching means the LV is unable to accommodate appropriate blood volumes at a normal filling pressure. For these survivors, LV dysfunction is often the result of both reduced LV systolic performance and altered diastolic LV filling. As will be discussed, reduced LV function is often the product of different underlying abnormalities including a reduction in the number of cardiomyocytes and damage to the remaining cardiomyocytes and stem cells capable of producing further cardiomyocytes.

** Anthracyclines**

For several decades, anthracyclines have been used to effectively treat a variety of hematological and solid tumors in children. The use of anthracyclines such as doxorubicin has been instrumental in improving the survival of pediatric cancer patients and is part of first-line therapy for many childhood cancer treatment protocols. Over half of survivors have received anthracyclines. These agents can also cause clinically significant cardiotoxicity which has led to the use of lower doses in children. The potential for cardiotoxicity in anthracycline-treated childhood cancer patients has made awareness of cardiac health important during treatment and follow-up.
Anthracycline cardiotoxicity can be categorized at the time of presentation as either acute or chronic, with chronic cases further categorized as early- or late-onset. Cardiac abnormalities presenting within hours or days of anthracycline treatment are acute and often present as conduction abnormalities and arrhythmias. Acute LV dysfunction can also occur at the time of treatment, especially at higher doses, which can even result in heart failure. Severe cardiotoxicity during or shortly after treatment is strongly associated with future heart failure despite an intervening asymptomatic interval. In a follow-up study of anthracycline-treated survivors who developed acute heart failure, all had a temporary recovery though nearly half later had recurrent heart failure.

In anthracycline-treated survivors with chronic cardiovascular complications, early-onset refers to cardiotoxicity manifesting in the first year following treatment while late-onset refers to manifestations that present years or even decades after therapy. Although estimates of the incidence of chronic heart failure in anthracycline-treated survivors have ranged from 1% to 16%, the true rate may be even greater with more extended follow-up. In addition to cases of symptomatic LV dysfunction, chronic anthracycline cardiotoxicity also frequently manifests as subclinical abnormalities in LV structure and function. These subclinical changes may in some cases progress to heart failure and cardiac death. Such effects may also leave survivors more vulnerable to future non-anthracycline related cardiovascular insults such as ischemic heart disease.

A series of detailed echocardiographic studies in 115 anthracycline-treated survivors of acute lymphoblastic leukemia was conducted to describe their long-term LV structure and function. Six years after cancer treatment, survivors had an average decreased LV wall thickness relative to body-surface area. This decrease in LV wall
thickness is important because such changes are inversely proportional to the amount of stress being placed on LV cardiomyocytes. Increased LV wall stress impairs cardiomyocyte systolic performance by limiting the ability of the LV to contract properly, which can ultimately reduce cardiac output. This LV wall stress is referred to as LV afterload and is directly proportional to LV dimension and blood pressure and inversely proportional to LV wall thickness. In this study, reduced LV wall thickness was related to increased LV afterload in over half of survivors, as LV dimension and LV pressure remained normal.

The intrinsic ability of the heart to contract, regardless of external measures of LV wall stress, such as LV afterload, is dependent on load-independent LV contractility which is measured as the LV stress-velocity index. In this study, LV load-independent contractility was below normal in nearly one-fifth of survivors indicating cardiomyocyte dysfunction was common. LV fractional shortening, a measure of how strongly the heart is able to pump blood during systole, is dependent on LV wall stress and LV contractility as well as heart rate and LV preload. Left ventricular fractional shortening was reduced in one-fourth of the survivors studied. Additionally, this reduced LV fractional shortening was related to elevated LV wall stress, measured as LV afterload, and to decreased health of the cardiomyocytes, measured as LV contractility. These findings provided clear evidence that at 6 years after anthracycline treatment, many survivors had significantly abnormal LV systolic function related to both increased LV afterload and decreased LV contractility.

A follow-up study of these survivors at 8 years after treatment which also included anthracycline-treated survivors of childhood osteogenic sarcoma was conducted
to identify factors associated with anthracycline-related cardiotoxicity. This study found that a younger age at diagnosis and an increasing length of follow-up were associated with decreased LV wall thickness. Increased individual anthracycline dosage was associated with an abnormally increased LV dimension which indicates LV dilation. Decreased LV wall thickness and increased LV dimensions contributed to increased LV afterload, which was elevated in relation to these risk factors in study subjects. Female gender and increased cumulative anthracycline dose were associated with reduced LV contractility indicating unhealthy heart muscle. Reduced LV contractility could ultimately result in reduced LV systolic performance and cardiac output.

A third follow-up study of these patients 12 years after treatment examined temporal trends in LV structure and function. These analyses found that previously described anthracycline-related abnormalities of LV structure and function progressed over time. LV mass continued to decline with subsequent elevations in LV afterload indicating a continually rising LV wall stress that would require increasing compensation by LV cardiomyocytes to maintain LV systolic performance. LV contractility also continued to decline indicating that the health of cardiac muscle cells within the LV worsened over time. Especially troubling were declines in LV systolic function measured as reduced LV fractional shortening and blood pressure values that may portend future premature CVD. This study also revealed that even survivors treated with low cumulative doses of anthracyclines were at risk for chronic cardiotoxicity.

In total, these studies documented a restrictive-like cardiomyopathy in anthracycline-treated survivors. At 12-years of follow-up these survivors continued to have declining LV systolic function while LV dimensions remained normal. The
restrictive-like nature of anthracycline cardiotoxicity may be of clinical significance in that it suggests theories and treatments derived from studies of dilated cardiomyopathy could be of limited value to understanding anthracycline cardiotoxicity. Abnormal LV structure and function as well as a restrictive-like cardiomyopathy pattern are consistent with other long-term follow-up studies of anthracycline-treated survivors.\textsuperscript{32,49,50}

Because not all children exposed to anthracyclines develop cardiac abnormalities and because the clinical severity of such abnormalities varies significantly, determining the factors associated with these cardiotoxic effects is of great importance. Previous research has shown that higher cumulative doses of anthracyclines, higher anthracycline dose rates, the use of concomitant cardiotoxic therapies such as mediastinal irradiation, younger age at treatment, increasing time since treatment, female sex, elevations of serum cardiac troponin-T or N-terminal pro-brain natriuretic peptide (NT-proBNP) measured during anthracycline therapy, and HF during anthracycline therapy are risk factors for anthracycline cardiotoxicity.\textsuperscript{14} Despite the identification of these risk factors, determining the individual risk for a specific patient is limited. Presently, all anthracycline-treated survivors should be followed closely after treatment for cardiotoxicity including long-term follow-up into adulthood. These risk factors are currently used to guide follow-up frequency and may also help increase our understanding of the underlying pathophysiologic mechanisms. Such insight will hopefully lead to novel strategies for prevention and treatment.
Cardiac and Vascular Irradiation

A wide range of cardiovascular abnormalities are found in survivors who received cardiac or vascular radiation exposure during their cancer treatment. Irradiation can damage the pericardium, myocardium, conduction system, valves, and coronary arteries. Microcirculatory damage in the heart is thought to be a common and initiating step in several forms of radiation-induced cardiac pathology resulting in diminished blood flow to areas of the myocardium and pericardium leading to ischemia and subsequent fibrosis.\textsuperscript{51} Radiation-induced endothelial injury is likely responsible for coronary artery damage.\textsuperscript{51} The mechanisms underlying damage to cardiac valves which are avascular are less clear, however chronic inflammation is a likely contributor.\textsuperscript{51} Radiation-induced pathology can have diverse clinical manifestations including coronary artery disease, pericarditis, cardiomyopathy, valvular disease, and conduction abnormalities. Cardiac irradiation can also potentiate anthracycline cardiotoxicity.\textsuperscript{6,31}

A systematic review of CVD and related mortality in survivors with cardiac radiation exposure identified 14 studies, 6 of which compared cardiac related mortality in survivors to the general population.\textsuperscript{52} All but 2 studies showed an increased risk of cardiac death with standardized mortality ratios ranging from 22 to 68. The reported frequency of symptomatic CVD varied widely likely due to differences in study design, quality, and study populations but some studies found CVD in over 20\% of survivors. A follow-up study of survivors with cardiac radiation exposure found that at 11-years after treatment, 10\% had developed coronary artery disease and another 6\% had clinically significant valvular abnormalities.\textsuperscript{39} Of those who developed coronary artery disease, all had at least one traditional CVD risk factor such as diabetes, hypertension, or high
cholesterol while increasing radiation exposure was also a risk factor. A separate report of over 8,000 survivors with cardiac and vascular radiation exposure found that increasing radiation exposure was associated with valvular disease, myocardial infarction, and heart failure. At thirty years following treatment, nearly 12% of survivors in the highest exposure group, defined by a cumulative dose greater than 3500 cGy, had developed heart failure and 6% had experienced a myocardial infarction. Even survivors in the lowest exposure group, defined by a cumulative dose less than 500 cGy, frequently developed CVD.

A more detailed clinical evaluation of 48 asymptomatic survivors who were 14 years from their original diagnosis of Hodgkin’s disease and who had been received cardiac radiation exposure found that in addition to the increased risk of symptomatic CVD, subclinical abnormalities in cardiac structure and function are even more common. Even though all of the survivors described their health as good or better, 98% were found to have at least one cardiac abnormality. Significant intracardiac valvular defects were identified in 43% of patients. These survivors also had significant reductions in LV mass, LV wall thickness, LV end-diastolic dimensions, and LV end-systolic wall stress, which suggest this population may suffer from a restrictive-like cardiomyopathy. Twenty of the 37 survivors had evidence of LV diastolic dysfunction consistent with a restrictive-like cardiomyopathy. Only 4 of the survivors had also received anthracyclines indicating that these changes likely reflect the effects of cardiac and vascular radiation exposure.
1.2.2 Traditional Cardiovascular Disease Risk Factors in Survivors

Previous research has identified several traditional risk factors for the development of atherosclerosis and CVD. Survivors, like the general population, may have one or more of these risk factors, which would likely place them at increased risk for CVD. In addition, some survivors may be at increased risk of having these risk factors, which could provide an additive risk of CVD beyond that related to the direct cardiac and vascular damage from cancer therapies such as anthracyclines. Several studies have reported associations between growth hormone deficiency and increased risk factors including adiposity, dyslipidemia, and insulin resistance.

The most commonly examined traditional risk factors in survivors, discussed below, are tobacco use, physical inactivity, poor diet, excess adiposity, dyslipidemia and insulin resistance. These risk factors are each commonly employed in risk stratification tools and can be modified by prevention efforts and treatment. An improved understanding of the lifetime CVD risk associated with these factors in survivors may help guide current treatment decisions and the potential additional cardiovascular risk of specific cancer therapies such as prophylactic cranial irradiation. For survivors already at increased risk for atherosclerotic disease or who are less able to compensate for ischemic cardiac damage, knowledge of the role these factors play in determining the overall CVD burden of survivors could inform the aggressiveness with which to pursue preventive interventions.
Physical Inactivity

Physical inactivity is associated with traditional atherosclerotic disease risk factors such as insulin resistance, dyslipidemia, and obesity as well as an increased risk of CVD. Increasing physical activity is not only recommended by several medical associations including the American Academy of Pediatrics, but guidelines have been created by organizations including the US Department of Health and Human Services.\textsuperscript{59,60} A recent report of 1000 children whose physical activity was measured using an accelerometer found that levels of physical activity decrease markedly from 9 to 15 years of age, and that by 15 years of age, nearly 70\% of children fail to exercise at least one hour a day which is noncompliant with current guidelines.\textsuperscript{61}

Though physical inactivity is common in the general population, it appears to be even more common in survivors. A questionnaire of nearly 10,000 survivors and 3,000 of their siblings revealed that survivors were 1.6 times more likely to report engaging in no leisure time physical activity in the past month and 1.2 times more likely to fail to meet recommended physical activity guidelines.\textsuperscript{62} In total, less than half of survivors met current guidelines for physical activity. This report and others have found that due to physical limitations from cancer-related surgery or treatment-related cardiac damage, some survivors may be unable to comply with these guidelines. Hopefully, interventions that lead to appropriate and safe increases in the physical activity levels of survivors will result in a decreased risk for future atherosclerotic disease and associated negative health outcomes.\textsuperscript{63}
Diet

In the general population diet is known to cause obesity and increased CVD risk and dietary interventions are aimed at reducing this risk.\textsuperscript{64-66} One prospective study in the general population found a strong association between the consumption of specific unhealthy foods such as potato chips and sugar-sweetened beverages and weight change over the course of four years.\textsuperscript{64} Due to this, current recommendations rely heavily on these findings being generalizable to survivors.\textsuperscript{12,13}

In the general population, several dietary guidelines have been proposed with most sharing the same traits.\textsuperscript{67} In the United States, the United States Department of Agriculture’s MyPyramid food guidance system is the most widely publicized.\textsuperscript{68} MyPyramid as well as most guidelines recommend minimal values for the consumption of several food groups including whole fruits, whole vegetables, and whole grains and maximal values for the consumption of several nutrients including salt, saturated fats, and refined sugars. With respect to cardiovascular health, the National Heart, Lung, and Blood Institute’s DASH diet is similar and designed to reduce blood pressure.\textsuperscript{69}

Unfortunately, not much is known about the diets of survivors. One of the few studies to address this reported that of 72 survivors, none met any of the three general population dietary guidelines used for evaluation.\textsuperscript{70} However, as with the results from this study and others, it is unknown if this finding simply reflects population trends or is a finding related to a history of childhood cancer. It is also unclear how dietary habits are related to traditional CVD risk factors in survivors.
Tobacco Use

Cigarette smoking is a major preventable risk factor for CVD and death as well as all-cause mortality. While the increased mortality associated with smoking is age- and sex-specific, a 50-year old male smoker is predicted to die more than 6 years earlier than a similar non-smoker and cardiovascular related deaths account for a majority of these premature deaths.\(^7\) Evidence for an increased rate of CVD in smokers has been evident since the 1960s.\(^7\) Despite these findings, over 20\% of the adult population in the United States currently smokes.\(^7\) A recent systematic review of the health behaviors of survivors found that most studies have reported lower rates of smoking in survivors relative to the general population though these rates are still high enough to produce significant health concerns and warrant intervention.\(^7\) Additionally, this review found the survivors are older at smoking initiation than the general population and less likely to attempt quitting smoking or to be successful at quitting. Up to 17\% of survivors in the United States are active smokers.\(^7\) Because smoking causes increased atherosclerotic disease risk, this risk poses concern regarding future CVD risk in survivors.

The increased CVD burden associated with smoking may be magnified in survivors who already have underlying cardiac abnormalities as a result of cancer therapies. While these effects may be mediated through separate pathways, they may ultimately have synergistic negative cardiac consequences. Further, smoking is associated with increased levels of systemic inflammation that may also contribute to the progression atherosclerotic CVD.\(^7\) Efforts aimed at preventing smoking in survivors and promoting smoking cessation in current smokers is likely an important step toward preventing CVD in this group.\(^7\) Understanding the association between smoking and
other treatment-specific risk factors for CVD would help better estimate the total CVD burden of survivors. Identification of factors, which lead to high-risk behaviors, such as tobacco use, in survivors, could inform more effective prevention strategies leading to a decrease in total long-term CVD in this already vulnerable population.

**Obesity**

Over the past 30 years childhood obesity has become an increasingly prevalent problem in the United States. Over 15% were overweight by the year 2000. This trend is consistent across gender, race, and ethnicity. Using the adult definition of obesity, a body-mass index greater than 30, over 11% of 12- to 19-year olds were obese in 2000. The most recent data available from the CDC indicates this problem is only worsening as over 17% of 12- to 19-year olds were overweight as of 2004. In another study almost 80% of obese 10- to 14-year olds who had an obese parent were obese as adults. This is especially troubling given that childhood overweight and obesity are associated with poor health outcomes such as coronary artery disease, hypertension, and diabetes and that childhood obesity is strongly associated with adult obesity which is associated with an increased risk of CVD and death. These study findings resulted in the following conclusion from the American Heart Association’s Childhood Obesity Research Summit: “Obesity contributes to a significant burden in terms of chronic diseases, rising healthcare costs, and, most importantly, disability and premature death. It appears that this burden will increase in the future.”
Studies of obesity in survivors have found similarly troubling trends suggesting that survivors may be at increased risk for obesity as a result of their cancer history. The largest report to date of nearly 8000 survivors found that nearly 13% were obese, with a body-mass index greater than 30, and that another 28% were overweight, with a body-mass index between 25 and 30.83 This study also found that despite a high prevalence of obesity, survivors were not more likely to be obese than the general population, though certain groups such as survivors of acute lymphoblastic leukemia were at increased risk of obesity. Similar findings were also reported from a Canadian study of more than 400 survivors which found one-third were either overweight or obese, but that this high prevalence was similar to that found in the general population except for survivors of acute lymphoblastic leukemia who were at increased risk of obesity.84 The idea that certain survivor subgroups are at increased risk of obesity is supported by studies of survivors exposed to cranial radiation.35-38 Treatment-related damage to the hypothalamic-pituitary axis, with subsequent growth hormone deficiency, can lead to eventual obesity. However, it should be noted that not all studies have found such a relationship and that other factors such as obesity prior to diagnosis may be more powerful predictors of obesity after treatment.85 It is clear that obesity is highly prevalent in survivors of all types of childhood cancer and may predispose this group to future health problems, especially atherosclerotic disease, which may be especially problematic for these patients who are less able to compensate for ischemic cardiac insults. Further, this situation may actually be worse as studies have found the body compositions of survivors differ and that even at similar body-mass index, survivors may have a higher
percentage of body fat.\textsuperscript{38} The high obesity prevalence seen in these survivors will hopefully be amenable to modification via prevention and treatment interventions.

**Dyslipidemia**

While specific therapies such as cranial irradiation have been linked to significantly abnormal cholesterol levels, it is unclear if all survivors are at-risk for dyslipidemia and the mechanisms that underlie these findings have not been determined. An investigation of abnormal cholesterol levels in 50 survivors an average of 13 years after cancer diagnosis found that, compared to age- and sex-matched controls, they had decreased high density lipoprotein (HDL) cholesterol, a protective factor associated with decreased cardiovascular risk.\textsuperscript{35} This study also suggested that dyslipidemia was associated with endocrine dysfunction and possibly growth hormone deficiency. Another study of 23 patients who had undergone bone marrow transplantation as children, 17 of whom were survivors, found that at a median follow-up of 20 years, the survivors were more likely to have abnormally low levels of HDL cholesterol and abnormally high low density lipoprotein (LDL) cholesterol.\textsuperscript{86} Other studies have reported similar results and suggest that survivors exposed to cranial radiation or those who have abnormal growth hormone levels may be at markedly increased risk of abnormally low HDL-cholesterol and abnormally high LDL cholesterol, which are risk factors for future CVD.\textsuperscript{87,88} And though still understudied, as in the general population, it is possible that survivors may also have abnormalities in specific lipid subfractions such as lipoprotein a.\textsuperscript{89,90} Whether these changes will simply mirror those of broader measures is also unknown.
The significance of these cholesterol abnormalities is based on studies in adults, which have shown that increased levels of LDL cholesterol and decreased levels of HDL cholesterol are strongly associated with atherosclerosis and future cardiovascular complications. A re-analysis of 300,000 individuals from multiple studies found that a 15 mg/dL increase in HDL cholesterol and an 80 mg/dL decrease in LDL cholesterol would reduce CVD incidence by two-thirds in otherwise normal individuals.91 This finding is particularly relevant as both lifestyle modifications and pharmacological interventions have been proven to positively affect both LDL cholesterol and HDL cholesterol levels.57 While these lifestyle and pharmacological interventions and medications have yet to be tested in survivors, they have greatly reduced the risk of CVD and death in the general population. Hopefully, the application of these interventions to survivors, who are already at increased risk for elevated LDL cholesterol and reduced HDL cholesterol, will result in improved outcomes.

**Insulin Resistance**

As levels of obesity have risen and physical activity has declined, the prevalence of insulin resistance and overt diabetes has steadily risen. Currently, over 6% of the United States population has diabetes and the prevalence increases as the population ages.92 Diabetes is a major risk factor for cardiovascular disease. Current recommendations for adults state that the added cardiovascular disease risk associated with diabetes is equivalent to that of a previous myocardial infarction.57 Even conditions considered as pre-diabetes, such as impaired fasting glucose and impaired glucose transport, are recommended to be treated as a part of CVD prevention.93
A recent report of over 8000 survivors found that they were nearly twice as likely to have diabetes as sibling controls.\textsuperscript{94} This report also found that total body, abdominal, and cranial irradiation were all associated with increased risk of having diabetes, even after adjusting for body-mass index and physical activity. Traditional prevention methods may be only partially effective and novel approaches may be necessary to prevent CVD and the other health related complications of insulin resistance and diabetes in survivors. Another longitudinal study of over 200 survivors found that 4\% had diabetes, another 7\% had impaired glucose tolerance, and another 4\% had hyperinsulinemia.\textsuperscript{95} These findings are especially worrisome given that the average age of adult survivors in the study was 25 years and all were less than 40 years old, which otherwise would be considered a low-risk group for impaired glucose metabolism. Complicating matters further for many survivors is that prior cancer treatment-related cardiotoxicity may have left them more vulnerable to CVD.

\subsection*{1.2.3 Risk Aggregation Measures}

The ability to aggregate traditional CVD risk factors into a single measure of CVD risk in survivors had been limited by a lack of any measure designed and validated for patients under 30 years old which represents most of the CRG survivors. This is due to the relatively young age of the survivor population. As modern treatments only recently emerged, survivors are still relatively young. For instance, a survivor diagnosed at 5 years old in 1990 would only be 27 years old as of 2012. Recently, two new tools were created that help address this issue.

The PDAY scoring system estimates the probability of having an advanced
atherosclerotic disease coronary artery lesion in individuals 15- to 34-years old using a weighted combination of age, sex, total cholesterol, HDL cholesterol, smoking, systolic BP, hyperglycemia, and BMI. 

Additionally, the PDAY scoring system estimates the odds ratio of having such a lesion relative to an ideal individual without any modifiable risk factors. The scoring system is based on autopsy data from over 1000 patients in which traditional CVD risk factors and coronary artery lesions were assessed and the relationship described using logistic regression.

The FRC provides an estimate of the 30-year risk of myocardial infarction, stroke, or coronary death in individuals 20 years old or older by using a weighted combination of age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, diabetes, and hypertensive treatment. The FRC also produces ideal risk estimates based on age and sex. These estimates can be used to generate a ratio that expresses the increased risk of these events associated with a risk factor profile relative to that of an ideal individual without any modifiable risk factors. The FRC is based on data from over 4000 young men and women who had traditional CVD risk factors measured at baseline and who were followed for 30 years to track the development of CVD outcomes. The association between these risk factors and CVD was described using a competing risks analysis.

1.3 The Cardiac Risk Factors in Childhood Cancer Survivors Study

The CRG was conducted from 1999 to 2004 in Rochester, NY at the University of Rochester Medical Center (URMC). The URMC was the sole provider of health care for children diagnosed with cancer in a geographically isolated Finger Lakes region of upstate New York and Pennsylvania. Thus, this follow-up study of children treated for
cancer at the University of Rochester provides a representative sample of the survivors in this region, an assumption confirmed empirically by comparing the cancer diagnoses and therapy exposures of CRG participants and non-participants.

Fundamental to the CRG’s success was the recruitment of a large regional based sample of survivors who were representative of the region’s survivor population with respect to cancer types and therapy exposures. The CRG is the first and only study to show that such a group can be located and studied in a truly rigorous way. Eligible survivors were identified from patient records at the Long-Term Survivors Clinic where most survivors originally treated at the URMC receive follow-up care. To identify survivors not receiving follow-up care at this clinic, oncology patient charts were reviewed. For each survivor, a sibling was invited to participate in the study to serve as a control. Siblings could not have a history of serious medical illness and the closest in age was preferred.

The CRG was able to study 201 survivors and 76 sibling controls for nearly an entire day in a hospital setting. In total, these 201 survivors represented 45% of the 450 eligible survivors and there were no differences in diagnosis or therapy exposures between participants and non-participants. And while the socioeconomic status of participants and non-participants were unable to be compared, this was controlled for in many comparative analyses using a matched sibling control group. This allowed for the performance of advanced clinical studies in addition to patient histories. Obtaining such a representative group of survivors was attributed to both the geographic region selected for study and the strong relationship between the cancer clinic and survivors in the area. The CRG was conducted in the Finger Lakes Region where there is a single center at
which almost all childhood cancer cases are treated, and geographic mobility in this area is low. Nearly half of the study population was female; 6 subjects were of Hispanic ethnicity, 13 subjects were of African-American race, and 1 subject was of Asian race.

Detailed assessments of cardiometabolic health and clinical status were performed during day-long study visits consisting of several measurement activities. Survivors and siblings, or an accompanying parent, completed detailed questionnaires concerning any current and prior health issues as well as lifestyle habits of survivors and siblings. Survivors and siblings underwent detailed physical exams including anthropomorphic measurements. They also had heparinized plasma samples collected after an overnight fast, which were available for subsequent laboratory testing. Echocardiographic studies of survivors and siblings were performed and blood pressure measured digitally. Echocardiograms were read by a cardiologist unaware of cancer status or therapy exposures. In addition, original treatment records were reviewed for all survivors to obtain information on their original cancer diagnosis and therapy exposures. After the completion of all study forms, personnel visually checked the form for completeness and clarified responses if necessary. Construction of the database and data entry were overseen by the study’s principal investigator (Dr. Steven Lipshultz) and senior statistician (Dr. Stuart Lipsitz). Finally, 3-day food records were prospectively collected from survivors and siblings. Measures are described in greater detail, where relevant, in subsequent chapters.

Initial descriptive echocardiographic and cardiovascular results for CRG survivors and siblings have been recently published to provide an assessment of the overall global cardiac status of childhood cancer survivors. This initial report serves in many respects
as the starting point for the more specific correlative hypotheses investigated and results presented in this dissertation. In the initial report, survivors were divided into two groups based on exposure to either anthracyclines or cardiac radiation, cardiotoxic therapies. Survivors with such exposure created a cardiotoxic therapy exposed group and the other survivors created a cardiotoxic therapy unexposed group.

Survivors in the exposed group showed abnormalities in both LV structure and function compared to sibling controls. These survivors had decreased LV mass and LV wall thickness, increased LV afterload, and decreased LV fractional shortening as well as markedly increased levels of NT-proBNP. Additionally and somewhat surprisingly, even the unexposed survivors showed changes in LV structure and function compared to the sibling controls. These survivors had decreased LV mass and increased NT-proBNP, a serum biomarker of increased LV wall stress. Both exposed and unexposed survivors had increased levels of systemic inflammation, assessed using serum high-sensitivity C-reactive protein. Finally, both exposed and unexposed survivors had increased levels of traditional CVD risk factors including non-HDL cholesterol. Taken together, these findings indicate that increased risk of CVD is not limited to only those survivors exposed to traditional cardiotoxic therapies and that survivors are at increased risk of CVD due to alterations in several different domains related to cardiovascular health. These findings are summarized in Figure 1.2.
Serum levels of cardiac biomarkers by cancer treatment history and sex. Box plots show the minimum, maximum, interquartile range (box), and median values for survivors of childhood cancer exposed or unexposed to known cardiotoxic treatments and for sibling controls, by sex. HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide. *J Clin Oncol* 2012;30:1050-7.32
1.4 Conceptual Model

While the link between childhood cancer and an increased CVD burden is well established, the path between this heterogeneous exposure and constellation of disease outcomes is less clear.5,15 Prior studies reveal that survivors are at markedly increased risk of developing and dying from CVD in the decades following their cancer diagnosis and treatment.4,7-11 Further, a history of childhood cancer can be associated with alterations of lifestyle habits, endocrine and metabolic abnormalities, and cardiac and vascular damage.5,74,99 However, the extent to which these changes contribute to the increased CVD burden of survivors is unknown.

Both alterations in lifestyle habits and endocrine and metabolic abnormalities may contribute to the development of increased levels of traditional atherosclerotic disease risk factors among survivors. Certainly for subpopulations, such as survivors of brain cancer with high levels of cranial irradiation exposure, endocrine issues have significant effects.35,36 The potential influence of more subtle, sub-clinical endocrine and metabolic abnormalities are unclear. These endocrine and metabolic abnormalities may also lead directly to increased cardiac and vascular damage, though this topic has received little attention. That direct cardiac and vascular damage occurs following treatment with anthracycline and chest irradiation is well known, although the degree to which this damage increases the risk of atherosclerotic disease is not.28-32 It is possible that radiation-induced vessel damage predisposes to the development and worsening of atherosclerotic disease.

In addition to the potentially increased risk of atherosclerotic disease among survivors, cardiac and vascular damage may also increase their susceptibility to this
Survivors with reduced LV mass may be less able to compensate for the effects of atherosclerosis-induced ischemic damage, although this has not been studied. In addition to the CVD of atherosclerosis, survivors are also at increased risk of non-atherosclerotic CVD such as that resulting from anthracycline cardiotoxicity. The progression of such cardiac damage to clinical disease, such as heart failure, and the factors affecting this progression are incompletely understood. Together, both atherosclerotic and non-atherosclerotic diseases contribute to the total CVD burden of survivors.

Understanding these pathways is complicated by different paths likely contributing differentially to the CVD burden of survivor subpopulations. For instance, the paths from cardiac damage to non-atherosclerotic disease are probably most important following anthracycline exposure though they may be less important for survivors not exposed to anthracycline or cardiac radiation. Further complicating the interpretation of these paths is that even within exposure-specific subgroups, these pathways may contribute differentially over time. For instance, the CVD burden associated with cardiac and vascular damage may be largely mediated through non-atherosclerotic CVD earlier in life and through increased susceptibility to atherosclerotic CVD later in life. Finally, it is important to consider that these paths describe the increased CVD burden of survivors. However, certain factors such as traditional atherosclerotic disease risk factors are likely significantly associated with CVD among survivors even if they are not responsible for much of the increase in this burden due high prevalence rates in the general population. While the initial conceptual model is presented in Figure 1.1, additional considerations are presented in Figure 1.3.
Potential CVD burden of childhood cancer survivors, both early and late in life, by simplified exposure examples. All component magnitudes are hypothetical, although theory based and survivor subgroups are assumed to have a single uncomplicated therapy.
Chapter 2. Cranial Irradiation and Anthracycline Cardiotoxicity

2.1. Background

Anthracyclines, used to treat more than half of childhood cancer patients, are currently indispensible, given their oncologic efficacy. However, anthracycline cardiotoxicity is a serious complication that can result in heart failure, heart transplantation, and cardiac death. Chronic cardiotoxicity, defined as a presentation at least 1 year after cancer treatment, is common and can occur even after treatment with a low anthracycline cumulative dose. Within 10 years after cancer diagnosis, more than half of survivors treated with anthracyclines have echocardiographic evidence of abnormal cardiac structure and function.

Anthracycline cardiotoxicity characteristically results from myocardial cell death that leads to decreased left ventricular (LV) mass and LV wall thickness. This reduced thickness can increase the stress on the remaining LV wall as it tries to generate sufficient cardiac output, and these changes can be progressive, even a decade after treatment. Over time, if compensation becomes inadequate, the stress can result in LV dysfunction. Risk factors for cardiotoxicity include younger age at diagnosis, longer time from diagnosis, anthracycline dose rate and cumulative dose, concomitant cardiac irradiation, and female sex. There are currently no long-term effective treatments though identifying additional risk factors may lead to new treatment strategies and assist in risk prediction.

Cranial irradiation, used to treat childhood leukemia and brain cancers and to prevent brain metastases, is another common treatment for childhood cancers. Cranial radiation exposure damages the hypothalamic-pituitary axis. One of the first
complications of such damage is growth hormone (GH) deficiency which can occur after relatively low radiation exposures. Children with GH deficiency from other causes have decreased LV mass that improves with GH replacement therapy. GH has marked cardiac effects and has even been tested as a cardiac treatment in children and adults without GH deficiency.

The cardiac effects of cranial irradiation-induced GH deficiency in patients treated with anthracyclines are not well understood. Prior studies have often lacked a control group of anthracycline-treated survivors who were not exposed to cranial radiation. It is possible that GH deficiency exacerbates LV dysfunction in anthracycline-treated survivors. The potential for a continued effect of cranial irradiation on cardiotoxicity through GH deficiency is consistent with the progressive nature of the cardiac damage from anthracyclines and further supports examining this relationship.

We sought to determine whether cranial irradiation was associated with anthracycline cardiotoxicity by examining anthracycline-treated childhood cancer survivors from the National Cancer Institute-funded Cardiac Risk Factors in Pediatric Cancer Survivors Study (CRG). We hypothesized that anthracycline-treated survivors exposed to cranial radiation would show greater cardiotoxicity than unexposed survivors and that insulin-like growth factor 1 (IGF-1), a marker of GH functioning, would be more strongly associated with cardiac abnormalities in exposed than in unexposed survivors.

### 2.2 Methods

Information on cancer diagnosis and treatment was abstracted from the medical records. All other information, including echocardiograms, phlebotomy,
anthropomorphic measurements, and demographics, was collected during a single, daylong study visit. A cardiologist and sonographer blinded to subject characteristics read 2-dimensional and Doppler echocardiograms and measured LV parameters. IGF-1 was measured from fasting serum samples. For survivors younger or older than 20 years, BMI was classified using CDC growth charts or standard definitions, respectively, as underweight (<5% or <18.5 kg/m²), normal (5 to 85% or 18.5 to 24.9 kg/m²), overweight (85 to 95% or 25 to 29.9 kg/m²), or obese (>95% or ≥30 kg/m²) using CDC growth charts for survivors younger than 20 years. All survivors from the CRG treated with anthracyclines were grouped by exposure to cranial irradiation. Two survivors, both in the cranial radiation exposure group, having received GH replacement therapy were excluded.

Demographic characteristics were compared using Fisher’s exact test for categorically measured variables and the Wilcoxon rank-sum test for continuously measured variables.

Because normal values for LV parameters vary with aging and somatic growth, echocardiographic data from a sibling control group (n = 76) was used to assess how the values of survivors differed from development-specific normal values. For each echocardiographic parameter, a series of power regression models were fit to the sibling control data with the adjusted R² statistic used to select the best fitting model, similar to the methodology used by Colan et al. to obtain equations to generate Z scores. For models of structural parameters (LV mass, LV end-systolic wall thickness, and LV end-diastolic dimension), the dependent variables included sex and body-surface area. For models of the functional parameters (LV end-systolic wall stress and LV fractional
shortening), the dependent variables included sex and age. Selected models were used to
generate normal predicted echocardiographic parameter values for each survivor based on
sex and either body-surface area or age. The actual echocardiographic parameter values
of the survivors were compared to the normal predicted values and expressed as the
percent difference from normal, and these values were used for subsequent analyses.

Because normal values for IGF-1 also vary during aging, IGF-1 values from the
sibling control group were used to assess how the values of survivors differed from age-
specific normal values. The IGF-1 values of the sibling control group were first graphed
over age by sex. This relationship appeared to most closely resemble a quartic function
with IGF-1 increasing in the age range associated with puberty and then decreasing,
leveling off, and remaining somewhat constant throughout the age range of subjects in
the CRG. This was supported empirically by the quartic regression having the largest
adjusted $R^2$ statistic when compared with quadratic and cubic regression models. This
model was then used to generate normal predicted IGF-1 values for each survivor based
on sex and age. The actual IGF-1 values of the survivors were compared to the normal
predicted values and expressed as the percent difference from normal and these values
were used for subsequent analyses. This same process was repeated to determine the
percent difference in height from age- and sex-specific normal predicted values, based on
the sibling control data and assuming a cubic relationship with age.

LV parameter values were compared between cranial irradiation exposure groups
using the Wilcoxon rank-sum test. Because other factors are known to affect LV
parameters, linear regression models were used to estimate the mean difference in LV
parameters for anthracycline-treated survivors exposed and unexposed to cranial
radiation adjusted for gender, cardiac irradiation, cumulative anthracycline dose, age at
diagnosis, and time from diagnosis. Because the distribution of BMI classifications
differed between exposure groups, additional analyses adjusting for BMI were conducted
to assess its impact on the results above and were consistent with other analyses.

IGF-1 and height were compared between groups using the Wilcoxon rank-sum
test. The association between LV parameters and IGF-1 in anthracycline-treated
survivors exposed to cranial radiation was assessed using Spearman’s Rho.

Finally, all analyses involving LV parameters were repeated with the LV
parameter values expressed as age- or body surface area-adjusted Z scores, calculated
relative to a standard population.111,112 The Z scores were calculated by dividing the
difference between a survivor’s observed value and the normal predicted value, based on
the standard population, by the standard deviation of the normal predicted values. The
standard population consisted of 285 subjects from Children’s Hospital Boston whose
ages were similar to those of the survivors included in the present study. These results
were consistent with those resulting from analyses in which LV parameters were
expressed as the percent difference from normal, relative to the sibling controls. All
analyses presented in the text of this dissertation refer to those involving LV parameters
expressed as the percent difference from normal relative to sibling controls.

Data were analyzed using Stata 11.2 (StataCorp LP; College Station, TX). When
necessary, transformations were made to meet normality assumptions, and estimates
back-transformed for reporting. Alpha was set at .05, all P values are two-sided and no
adjustments were made for multiple hypothesis testing.
2.3 Results

The CRG cohort consisted of 130 childhood cancer survivors treated with anthracyclines, and who had not received GH replacement therapy. Of these, 59 had received exposure to cranial radiation and 71 were unexposed (Table 2.1). Cranial irradiation dose ranged from 6 Gy to 100 Gy with the median dose being 18 Gy, and only 3 survivors receiving more than 30 Gy.

Exposed and unexposed survivors had similar mean ages at cancer diagnosis (7.0 vs. 7.6 years, P=.73) and similar mean times since diagnosis (10.3 vs. 10.5 years, P=.95). The exposed group contained a lower proportion of females (42% vs. 62%, P=.03) and a lower proportion of survivors receiving cardiac irradiation (22% vs. 32%, P=.24) but had received a higher mean cumulative dose of anthracyclines (296 vs. 244 mg/m², P<.01). The exposed group also contained a higher proportion of survivors diagnosed with leukemia (80% vs. 20%, P<.01).

Compared to unexposed survivors, exposed survivors had significantly decreased LV mass and LV end-diastolic dimension and non-statistically significantly decreased LV end-systolic wall thickness and increased LV wall stress (Figures 2.1 and 2.2). Both cranial radiation exposure groups had similar LV fractional shortening.
Table 2.1: Characteristics of 130 Anthracycline-treated Survivors Exposed or Unexposed to Cranial Radiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cranial radiation</th>
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<tbody>
<tr>
<td></td>
<td>Exposed (n = 59)</td>
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<tr>
<td></td>
<td>n (%)</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>34 (58)</td>
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<tr>
<td>Female</td>
<td>25 (42)</td>
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<tr>
<td>Age at time of study (years)</td>
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<tr>
<td>6 to 12</td>
<td>15 (25)</td>
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<td>13 to 19</td>
<td>29 (49)</td>
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<tr>
<td>20 to 37</td>
<td>15 (25)</td>
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<td>BMI classification at time of study (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Normal</td>
<td>32 (54)</td>
</tr>
<tr>
<td>Overweight</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Obese</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>47 (80)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Brain</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
</tr>
<tr>
<td>0 to 5</td>
<td>34 (58)</td>
</tr>
<tr>
<td>6 to 12</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Older than 12</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Time from diagnosis (years)</td>
<td></td>
</tr>
<tr>
<td>3 to 9</td>
<td>32 (54)</td>
</tr>
<tr>
<td>10 to 16</td>
<td>20 (34)</td>
</tr>
<tr>
<td>17 to 31</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Cumulative anthracycline dose (mg/m²)</td>
<td></td>
</tr>
<tr>
<td>45 to 240</td>
<td>18 (31)</td>
</tr>
<tr>
<td>241 to 360</td>
<td>13 (22)</td>
</tr>
<tr>
<td>≥360</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Cardiac irradiation treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (22)</td>
</tr>
<tr>
<td>No</td>
<td>46 (78)</td>
</tr>
<tr>
<td>Cranial irradiation dose (gy)</td>
<td></td>
</tr>
<tr>
<td>0 to 18</td>
<td>39 (66)</td>
</tr>
<tr>
<td>&gt;18 to 30</td>
<td>9 (15)</td>
</tr>
<tr>
<td>&gt;30 to 59.9</td>
<td>2 (3)</td>
</tr>
<tr>
<td>≥60</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>8 (14)</td>
</tr>
</tbody>
</table>
Figure 2.1: Left Ventricular Parameters of 130 Anthracycline-treated Survivors by Exposure to Cranial Radiation

Box plots of the distribution of left ventricular (LV) parameters of 130 childhood cancer survivors treated with anthracyclines by exposure to cranial radiation (CR). LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters are expressed as % change relative to normal. The Wilcoxon rank-sum test was used to compare the LV parameters across CR exposure groups with the resulting P values reported.
Figure 2.2: Left Ventricular Parameters of 130 Anthracycline-treated Survivors by Exposure to Cranial Radiation, Expressed using Z Scores

Box plots of the distribution of left ventricular (LV) parameters of 130 childhood cancer survivors treated with anthracyclines by exposure to cranial radiation (CR). LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters are expressed as Z scores relative to normal. The Wilcoxon rank-sum test was used to compare the LV parameters across CR exposure groups with the resulting P values reported.
After adjusting the difference in LV parameters for age at diagnosis, length of time since diagnosis, sex, cardiac irradiation, and cumulative anthracycline dose, LV mass was still decreased by an additional 12% relative to normal and LV dimension by 3.6% relative to normal in the cranial radiation-exposed survivors compared to the unexposed survivors (Tables 2.2 and 2.3). Cranial radiation-exposed survivors also had additional decreases relative to normal in LV wall thickness of 2.5% and increases in LV afterload of 1.8% compared to the unexposed survivors, but these differences were not statistically significant.

Table 2.2: Adjusted Difference in Left Ventricular Parameters of 130 Anthracycline-treated Survivors by Exposure to Cranial Radiation

<table>
<thead>
<tr>
<th>LV parameter</th>
<th>Adjusted* difference in percent change from normal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>-12.0%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>-2.5%</td>
<td>.39</td>
</tr>
<tr>
<td>Dimension</td>
<td>-3.6%</td>
<td>.03</td>
</tr>
<tr>
<td>Afterload</td>
<td>+1.8%</td>
<td>.77</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>-0.7%</td>
<td>.74</td>
</tr>
</tbody>
</table>

* A separate linear regression model was fit for each left ventricular (LV) parameter [mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening], with the parameter as the dependent variable and included the following independent variables: cranial irradiation, gender, cardiac irradiation, cumulative anthracycline dose, age at diagnosis, and time from diagnosis. LV parameters measured as % change relative to normal.
Table 2.3: Adjusted Difference in Left Ventricular Parameters of 130 Anthracycline-treated Survivors by Exposure to Cranial Radiation, Expressed using Z Scores

<table>
<thead>
<tr>
<th>LV Parameter</th>
<th>Adjusted* difference in Z score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>-0.60</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>-0.30</td>
<td>.17</td>
</tr>
<tr>
<td>Dimension</td>
<td>-0.36</td>
<td>.05</td>
</tr>
<tr>
<td>Afterload</td>
<td>0.28</td>
<td>.50</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>0.01</td>
<td>.97</td>
</tr>
</tbody>
</table>

* A separate linear regression model was fit for each left ventricular (LV) parameter [mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening] with the parameter as the dependent variable and included the following independent variables: cranial irradiation, gender, cardiac irradiation, cumulative anthracycline dose, age at diagnosis, and time from diagnosis. LV parameters measured as Z scores relative to normal.

Compared to survivors unexposed to cranial radiation, those exposed to cranial radiation also had a statistically significantly decreased IGF-1 relative to normal (median, -30.8% vs. -10.5% ng/mL, P<.001) and also had statistically-significantly decreased height relative to normal (median, -5.0% vs. -1.3%, P<.001) (Figure 2.3). In survivors exposed to cranial radiation, IGF-1 was associated, although not significantly, with LV mass (Rho=.11), LV wall thickness (Rho=.17) and LV afterload (Rho=-.12) (Figures 2.4 and 2.5).
Figure 2.3: IGF-1 and Height in 130 Anthracycline-treated Survivors by Exposure to Cranial Radiation

Box plots of the distributions of IGF-1 and height of 130 childhood cancer survivors treated with anthracyclines by exposure to cranial radiation (CR). IGF-1 and height expressed as the % change relative to normal. P values reported based on Wilcoxon rank-sum test.
Figure 2.4: Association of Left Ventricular Parameters and IGF-1 in 59 Anthracycline-treated Survivors Exposed to Cranial Radiation

Scatter plots depicting the association between IGF-1 and left ventricular (LV) parameters in 59 childhood cancer survivors treated with anthracyclines and exposed to cranial radiation. LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters and IGF-1 are expressed as % change relative to normal. Spearman’s Rho was used to assess the association between LV parameters and IGF-1, with P values reported, and a linear trend line has been added.
Figure 2.5: Association of Left Ventricular Parameters and IGF-1 in 59 Anthracycline-treated Survivors Exposed to Cranial Radiation, Expressed using Z Scores

Scatter plots depicting the association between IGF-1 and left ventricular (LV) parameters. LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters are expressed as Z scores relative to normal. Spearman’s Rho was used to assess the association between LV parameters and IGF-1, with P values reported, and a linear trend line has been added.
2.4 Discussion

In anthracycline-treated childhood cancer survivors from the CRG, cranial radiation exposure was significantly associated with decreased LV mass and LV end-diastolic dimension and a non-statistically significantly decreased LV end-systolic wall thickness and increased LV end-systolic wall stress. These same cranial radiation-exposed survivors had decreased IGF-1, a marker of GH deficiency. Though not statistically significant, cardiac abnormalities trended toward an association with decreased IGF-1 in survivors exposed to cranial radiation.

Cranial irradiation was associated with an additional decrease in LV mass relative to normal of 12% in anthracycline-treated survivors and reductions in LV mass trended towards an association with decreased IGF-1 in exposed survivors. This decreased LV mass appears to be the result of GH abnormalities which is consistent with the decrease in LV mass seen in patients with GH deficiency not related to cranial irradiation. Further, the association between IGF-1 and LV mass is consistent with the increases in LV wall thickness and mass reported in studies of anthracycline-treated survivors given GH replacement therapy.

Cranial irradiation was also associated with an additional decrease relative to normal of roughly 3% in LV wall thickness and 4% in LV dimension, which underlie the relationship with decreased LV mass. LV wall thickness was moderately associated with IGF-1 and this may be reflected in the additional increase relative to normal of 2% in LV afterload. This provides some evidence that the structural abnormalities associated with cranial irradiation may have functional consequences consistent with the known pathway of anthracycline cardiotoxicity. While decreased LV dimension is not usually viewed
as problematic, this may not be true for patients with the restrictive-like pattern of anthracycline cardiotoxicity.\textsuperscript{97,98} For these patients, in which the LV may have difficulty relaxing during diastole, a smaller chamber size may serve as an additional limitation to LV filling and further impair cardiac output.

Cranial irradiation was not associated with LV fractional shortening, and there was no association between IGF-1 and LV fractional shortening among those exposed to cranial radiation. This finding may reflect that the changes in LV structure associated with cranial radiation exposure are not related to cardiac functioning. Two prior studies examining the impact of GH replacement therapy in anthracycline-treated survivors found no effect on LV fractional shortening, though therapy was initiated several years after cranial irradiation exposure in both studies.\textsuperscript{108,109} The lack of an association in this study could also be due to limited follow-up and the chronic nature of anthracycline cardiotoxicity. At less than 10 years from treatment, the heart may still be capable of compensating for structural abnormalities. This possibility is consistent with reports that LV fractional shortening begins to decline markedly after 10 years,\textsuperscript{30} the same time at which the incidence of heart failure continues to increase.\textsuperscript{11}

The strength of the association between IGF-1 and LV parameters in the anthracycline-treated survivors exposed to cranial radiation was only weak to moderate. However, this is expected given that other factors such as anthracycline dose, age at diagnosis, cardiac irradiation, and sex explain substantial portions of the variation in anthracycline cardiotoxicity.\textsuperscript{14,34} It is important to note that even after adjusting for these other factors, survivors with cranial irradiation exposure still had statistically significantly worse abnormalities in LV structure. Having a more complete
understanding of the risk factors underlying anthracycline damage might help produce clinically useful risk prediction models.\textsuperscript{15}

Although LV parameters and IGF-1 were standardized relative to a sibling control group to adjust for the effects of aging and growth on the normal values of these variables, measurements of abnormalities may still contain some error. For LV parameters, analyses were repeated with abnormalities determined relative to a standard population and yielded consistent results.\textsuperscript{111} In addition to helping confirm the relationship between cranial irradiation and LV structure, the similarity of these results also cross-validates the use of this standard population to measure development-specific abnormalities which is needed when a control group is unavailable. Because these measures were created to describe the LV parameters of both survivors exposed and unexposed to cranial radiation, measurement error is less likely to have introduced bias.

Error in measuring abnormalities in IGF-1 may have reduced the ability to determine if variation in hypothalamic-pituitary axis damage is associated with cardiac abnormalities in anthracycline-treated survivors. It is possible that the reported associations are actually underestimates of the true association between IGF-1 and LV structure and function in this population. Also relevant to interpreting these results are the limited sample size and low power to detect statistically significant relationships. Given the relative rarity of childhood cancer, identifying large numbers of anthracycline-treated survivors both exposed and unexposed to cranial radiation and obtaining detailed clinical measurements, such as echocardiograms, is often not feasible. Finally, variation in the cancer diagnoses of exposed and unexposed survivor groups was present but has
not been previously found to have an independent association with cardiotoxicity and was not a focus of this study looking at the effect of a particular cancer therapy.

Although not examined in these analyses, cranial irradiation has been associated, in this study population and others, with having traditional risk factors for cardiovascular disease,\textsuperscript{35,37} such as obesity and dyslipidemia, and may be one mechanism by which survivors are at increased risk of cardiovascular disease.\textsuperscript{10,38} Taken together, it is possible that GH replacement therapy could reduce the burden of cardiovascular disease in survivors by improving both cardiac structure and cardiometabolic health. Although concerns over cancer recurrence and second malignancies have limited the use of GH replacement therapy, recent evidence indicates that this risk is low or possibly non-existent.\textsuperscript{113-115} And while prior studies in survivors with anthracycline cardiotoxicity have not shown sustained improvements in cardiac function with GH replacement therapy, these studies started therapy years after cranial radiation exposure and after irreversible GH-related cardiac damage may have already occurred. Additionally, these studies have shown temporary improvements in LV wall thickness, mass, and systolic blood pressure.\textsuperscript{30}
Chapter 3. Caloric Intake, Dietary Quality, and Adiposity in Childhood Cancer Survivors and Their Siblings

3.1 Background

Childhood cancer survivors are at increased risk of cardiovascular disease (CVD) years after their original cancer diagnosis and possibly for life.\(^7,11,26\) Although much of this increased risk is the result of therapy-related cardiac and vascular damage, traditional CVD risk factors likely exacerbate this increased risk.\(^5,32,39\) Survivors are more likely to have excess adiposity, dyslipidemia, and insulin resistance.\(^35,37,38\) Their poor cardiometabolic health may be a consequence of cancer therapies such as chemotherapy and radiation but it may also be caused by unhealthy lifestyle habits, which themselves could be associated with a history of childhood cancer.\(^30,116\)

Although chemotherapy- and radiation-induced cardiovascular damage cannot yet be treated in evidence-based ways, managing traditional CVD risk factors, such as excess adiposity, hypertension, dyslipidemia, and insulin resistance, reduces CVD risk in the general population.\(^56,57\) Current guidelines for the follow-up care of survivors recommend screening for these risk factors and promoting healthy lifestyle habits including physical activity and diet.\(^12,13\) This recommendation is justified, in part, by the pathophysiologic association of diet and sedentary behaviors with adiposity and other CVD risk factors in the general population.\(^64,66\)

Studies describing the dietary habits of survivors suggest they fail to meet dietary guidelines for fresh fruit and vegetable consumption, though it is unclear whether this simply reflects trends in the general population or is related to specific factors associated with childhood cancer.\(^116-119\) Although endocrine dysfunction is associated with adiposity in cancer survivors,\(^70,120,121\) it is unknown how dietary patterns further
contribute to these changes in body composition. Dietary studies of survivors have been limited by small sample sizes, poorly detailed diet descriptions, a lack of appropriate controls, and the lack of data on adiposity and traditional CVD risk factors.

Here, we describe the diets of pediatric cancer survivors and compare them to those of a group of their siblings without a history of childhood cancer. We also examine whether specific cancer diagnoses or therapies are associated with diet and how diet is related to adiposity and traditional CVD risk factors among survivors.

3.2 Methods

3.2.1 Data Collection

During daylong study visits, survivors and siblings had weight and standing height measured by the recommended techniques and body composition measured using GE Lunar Prodigy DF 10370 (Madison, WI) dual-energy X-ray absorptiometry, a relatively non-invasive method that quantifies fat-free and fat masses. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m²) and classified as underweight, normal, overweight, and obese, using definitions appropriate for age and sex. Percent total body fat was determined with Lunar software (Version 6.10). Fasting blood samples were tested for traditional CVD risk factors including levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glucose, and insulin. All tests, except glucose, were performed at the Strong Memorial Hospital Clinical Laboratory, Rochester, NY, which is in full compliance with the Clinical Laboratory Improvement Amendments. Blood pressure was recorded by a Dinamap oscillometric monitor (GE Healthcare Critikon,
Chalfont St. Giles, United Kingdom). Physical inactivity was measured as self-reported hours of television watching per week and activity as the number of hours of moderate to intense activity per week. Original treatment records were reviewed for cancer diagnoses and therapies. Survivors and siblings were also instructed on how to keep a food record by the project coordinator and given a booklet in which to complete a 3-day diet record with 2 days being week days and 1 day being a weekend day. The instructions (both written and verbal) included a discussion of how to estimate portion sizes. Survivors and siblings were given an addressed envelope to return the record.

3.2.2 Data Processing and Diet Measures

Diet records were processed using Nutrition Data System for Research software (University of Minnesota Nutrition Coordinating Center, Minneapolis, MN). Total daily caloric intakes were expressed as a percentage relative to age-, sex-, activity-, height-, and weight-specific recommendations from the Institute of Medicine (IOM).\textsuperscript{19} Recommended intake values were determined using ideal weight-for-height which was calculated as the weight needed for a child to have the median age-specific BMI\textsuperscript{122} or for an adult to have a BMI of 22.5, the median BMI of the normal range.\textsuperscript{123} Percentages above 100% represent excessive energy intake and those below 100% indicate inadequate energy intake. Macronutrient intakes were expressed as a proportion of total daily caloric intake.

Diet quality was assessed using the Healthy Eating Index-2005 (HEI), a measure developed by the USDA, which measures adherence to USDA guidelines.\textsuperscript{17,124} The HEI consists of 12 food-group and nutrient component scores that range from 0 to a maximum
of either 5, 10, or 20 depending on the component. The maximum score represents full adherence to a specific USDA recommendation and 0 represents no adherence. While the grading of specific component scores is not recommend, scores between 0 and the maximum represent increasing adherence to specific recommendations. The component scores sum to range from 0 (no adherence) to 100 (full adherence). Standard methods have been proposed to convert Nutrition Data System for Research output into HEI scores. The HEI scores reported and analyzed were calculated by averaging the scores for each individual, each day. HEI scores were also calculated using the average intake per individual and analyses re-run producing similar results (data not shown).

Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as the product of insulin and glucose over a constant. Traditional risk factors for atherosclerotic disease were aggregated, according to methods appropriate for age, with odds ratios interpolated from modified Pathobiological Determinants of Atherosclerosis in Youth risk scores and by calculating the ratio of predicted-to-ideal risks estimated by the Framingham 30-Year Calculator. The PDAY odds ratio represents the increased odds of currently having an advanced coronary artery lesion, and the FRC risk ratio represents the increased risk of having a myocardial infarction, stroke, or coronary death in the next 30 years. Ratios are relative to an individual of similar age and sex without CVD risk factors.

3.2.3 Statistical Methods

Characteristics of survivors and siblings were compared using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables.
The mean total daily caloric intake relative to recommended of survivors and siblings were compared using a linear mixed model to account for the dependencies within pairs due to survivor-sibling matching. Age and sex were added to the model to compare adjusted means. Survivors and siblings were categorized by having a diet greater than 110% of recommended and the proportions with a diet in excess of this mark compared using a generalized linear mixed model. Age and sex were added to the model to compare adjusted proportions. The mean HEI component scores and total scores of survivors were compared using a linear mixed model adjusting for age and sex. Values and their comparisons were similar when unadjusted (data not shown).

Associations between cancer diagnoses and dietary characteristics, total caloric intake relative to recommended and total HEI score, were age and sex adjusted using analysis of covariance. Adjusted means and the F test for the type III sum of squares are reported. Associations between cancer therapies and dietary characteristics were assessed using a linear regression model including age, sex, and all therapies. The resulting mean differences, adjusted for age, sex, and other therapies, and the associated confidence intervals associated with each therapy are reported. For cancer diagnoses and therapies found to be associated with total HEI scores, analyses were repeated to determine their associations with individual HEI component scores.

The associations between dietary characteristics and BMI were assessed using analysis of covariance to compare the age- and sex-adjusted means of normal weight, overweight, and obese survivors (mixed models were not needed since this analysis only included survivors and not matched siblings). Comparisons of individual groups were conducted using two sample t-tests. The associations between dietary characteristics and
percent body fat were assessed using linear regression to adjust for age and sex, with the standardized regression coefficients and associated P values reported. A standardized regression coefficient can be interpreted as the standard deviation change in the mean of the outcome for a one-standard deviation increase in the predictor. For significant associations, analyses were also repeated after stratifying for any cancer diagnoses or therapies found to be associated with the specific dietary characteristic. Associations between dietary characteristics and traditional CVD risk factors among survivors were age- and sex-adjusted using risk factor-specific linear regression models. Standardized regression coefficients and P values are reported. All P values are two-sided. No adjustments were made for multiple comparisons. All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC) and figures were prepared using Stata 11.0 (StataCorp LP, College Station, TX).

3.3 Results

Of 201 survivors and 76 siblings enrolled in the parent study, dietary records were completed by 93 survivors (46%), 2 of whom were the only underweight subjects, had extremes of diet, and were excluded from these results, and 30 siblings. Of survivors, those completing a dietary record were of similar mean age (18.7 vs. 20.7 years, P=.09), sex (47% vs. 52% male, P=.52), and BMI (40% vs. 38% overweight, P=.79) and had similar treatment exposures compared to those not completing a dietary record. Compared to siblings, survivors tended to be older, more physically inactive, and with increased percent body fat (Table 3.1). Survivors had a variety of original cancer diagnoses and had received a heterogeneous collection of therapies (Table 3.2).
Table 3.1: Characteristics of Survivors and Siblings with Diet Measures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors (n = 91)</th>
<th>Siblings (n = 30)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%*)</td>
<td>n (%*)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49 (54)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (46)</td>
<td>18 (60)</td>
<td>.19</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 12 years</td>
<td>21 (23)</td>
<td>13 (43)</td>
<td></td>
</tr>
<tr>
<td>13 to 18 years</td>
<td>20 (22)</td>
<td>7 (23)</td>
<td></td>
</tr>
<tr>
<td>19 to 29 years</td>
<td>34 (38)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>30 years or older</td>
<td>16 (18)</td>
<td>2 (7)</td>
<td>.03</td>
</tr>
<tr>
<td><em><em>Inactivity</em>, TV watching</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 9 hours per week</td>
<td>35 (45)</td>
<td>18 (64)</td>
<td></td>
</tr>
<tr>
<td>10 to 19 hours per week</td>
<td>22 (29)</td>
<td>8 (29)</td>
<td></td>
</tr>
<tr>
<td>20 to 29 hours per week</td>
<td>10 (13)</td>
<td>1 (4)</td>
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</tr>
<tr>
<td>30 hours per week or more</td>
<td>10 (13)</td>
<td>1 (4)</td>
<td>.02</td>
</tr>
<tr>
<td><em><em>Physical activity</em>, exercise</em>*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 to 2 hours per week</td>
<td>32 (44)</td>
<td>6 (22)</td>
<td></td>
</tr>
<tr>
<td>3 to 6 hours per week</td>
<td>31 (42)</td>
<td>17 (63)</td>
<td></td>
</tr>
<tr>
<td>7 hours per week or more</td>
<td>10 (14)</td>
<td>4 (15)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>BMI, CDC classification</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>54 (59)</td>
<td>16 (53)</td>
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</tr>
<tr>
<td>Overweight</td>
<td>16 (18)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>21 (23)</td>
<td>6 (20)</td>
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<td><strong>Body fat</strong>*</td>
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<td>30 to 39%</td>
<td>31 (37)</td>
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<tr>
<td>40% or greater</td>
<td>23 (28)</td>
<td>3 (13)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

* Due to missing data, some frequencies do not sum to the total; percentages are of respondents.
† Though variables were categorized for reporting, P values were calculated using the chi-squared test for sex and BMI and the Wilcoxon rank-sum test for all other variables.
### Table 3.2: Characteristics of Survivors with Diet Measures

<table>
<thead>
<tr>
<th>Cancer characteristic</th>
<th>Survivors (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>24 (26)</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>15 (16)</td>
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<tr>
<td>Sarcoma</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13 (14)</td>
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<tr>
<td>Other</td>
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<td><strong>Age at diagnosis</strong></td>
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</tr>
<tr>
<td>0 to 5 years</td>
<td>42 (46)</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>29 (32)</td>
</tr>
<tr>
<td>13 years or older</td>
<td>20 (22)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
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</tr>
<tr>
<td>Alkylating agents</td>
<td>56 (62)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>49 (54)</td>
</tr>
<tr>
<td>Cranial irradiation</td>
<td>39 (43)</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>38 (42)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>33 (36)</td>
</tr>
<tr>
<td><strong>Time from diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>3 to 10 years</td>
<td>39 (43)</td>
</tr>
<tr>
<td>11 to 19 years</td>
<td>38 (42)</td>
</tr>
<tr>
<td>20 years or more</td>
<td>14 (15)</td>
</tr>
</tbody>
</table>
The mean daily caloric intake relative to IOM recommendations of survivors was not statistically significantly different than that of siblings (97% vs. 102%, P=.34) and there was no difference in the macronutrient distribution of total caloric intake between groups (Figure 3.1). After adjusting for age and sex, the difference in mean total daily caloric intake relative to IOM recommendations was not statistically significant (98% vs. 100%, P=.59). The proportion of survivors with a total daily caloric intake above 110% of the IOM recommendations was not statistically significantly different than that of siblings (30% vs. 29%, P=0.99) nor was there a difference after adjusting for age and sex (29% vs. 23%, P=.55).

Neither the unadjusted (Figure 3.2 and Table 3.3) nor the age- and sex-adjusted HEI component scores and total scores (Table 3.4) of survivors were different than those of siblings. Both survivors and siblings had diets moderately adherent to current guidelines as assessed by the HEI. Survivors and siblings scored highest for the consumption of total grains and worst for the consumption of dark green leafy vegetables, whole fruits, and whole grains.

Among survivors, there was little difference in diet based on cancer diagnosis (Table 3.5). Among survivors, there was also little difference in diet based on treatment exposures except for cranial irradiation which was associated with decreased total HEI scores (Table 3.5). There was significant variation in the meat and bean component scores by cancer type (F(4)=2.5, P<.05) with brain cancer survivors having the lowest scores (6.3/10). Cranial irradiation was associated with lower scores for both the whole fruits (1.3 vs. 2.4, P<.01) and saturated fat (5.2 vs. 6.6, P=.02) component scores.
Distributions, in survivors and siblings, of daily caloric intakes expressed as a percentage relative to age-, sex-, activity-, height-, and weight-specific recommended daily caloric intakes from the Institute of Medicine (IOM).\textsuperscript{19} Recommended intakes were determined using ideal weight-for-height which was calculated as the weight needed for a child to have the median age-specific BMI\textsuperscript{119} or for an adult to have a BMI of 22.5, the median BMI of the normal range.\textsuperscript{123} Percentages above 100% represent excessive energy intake and those below 100% indicate inadequate energy intake. For example, the average survivor daily caloric intake of 97% means that on average survivors eat 97% of the IOM recommended number of calories. For a low active 22 year old female, 163 cm tall (≈5 foot, 4 inches), with an ideal weight-for-height of 59.8 kg, this translates into consuming 2089 of the recommended 2154 calories (A). Mean macronutrient distribution of total daily caloric intake in survivors and siblings (B).
Figure 3.2: Healthy Eating Index Total Scores of Survivors and Siblings

Distributions, in survivors and siblings, of Healthy Eating Index total scores. A score of 100, the maximum, represents full adherence to a specific USDA recommendation and 0, the minimum, represents no adherence. While grading the score is not recommend, scores between 0 and the maximum represent increasing adherence to specific recommendations.
Table 3.3: Unadjusted Healthy Eating Index Scores for Survivors and Siblings

<table>
<thead>
<tr>
<th>HEI component (maximum score)*</th>
<th>Survivors (n = 91)</th>
<th>Siblings (n = 30)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fruit (5)</td>
<td>2.0 (0.2)</td>
<td>2.0 (0.3)</td>
<td>.99</td>
</tr>
<tr>
<td>Whole fruit (5)</td>
<td>1.8 (0.2)</td>
<td>2.1 (0.3)</td>
<td>.33</td>
</tr>
<tr>
<td>Total vegetable (5)</td>
<td>2.3 (0.1)</td>
<td>2.2 (0.2)</td>
<td>.46</td>
</tr>
<tr>
<td>Dark green vegetables (5)</td>
<td>1.0 (0.1)</td>
<td>0.9 (0.2)</td>
<td>.66</td>
</tr>
<tr>
<td>Total grains (5)</td>
<td>4.4 (0.1)</td>
<td>4.4 (0.1)</td>
<td>.99</td>
</tr>
<tr>
<td>Whole grains (5)</td>
<td>1.5 (0.2)</td>
<td>1.3 (0.3)</td>
<td>.33</td>
</tr>
<tr>
<td>Milk (10)</td>
<td>6.5 (0.3)</td>
<td>6.0 (0.4)</td>
<td>.30</td>
</tr>
<tr>
<td>Meat and beans (10)</td>
<td>7.4 (0.2)</td>
<td>7.4 (0.4)</td>
<td>.94</td>
</tr>
<tr>
<td>Oils (10)</td>
<td>7.7 (0.2)</td>
<td>7.7 (0.3)</td>
<td>.95</td>
</tr>
<tr>
<td>Sodium (10)</td>
<td>3.3 (0.2)</td>
<td>3.4 (0.4)</td>
<td>.82</td>
</tr>
<tr>
<td>Saturated fat (10)</td>
<td>5.8 (0.3)</td>
<td>5.4 (0.4)</td>
<td>.32</td>
</tr>
<tr>
<td>Solid fat and added sugars (20)</td>
<td>11.5 (0.5)</td>
<td>10.2 (0.7)</td>
<td>.09</td>
</tr>
<tr>
<td>Total HEI score</td>
<td>55.3 (1.0)</td>
<td>53.3 (1.6)</td>
<td>.19</td>
</tr>
</tbody>
</table>

* HEI component scores range from 0 to a maximum of 5, 10, or 20. The maximum score represents full adherence to a specific USDA recommendation and 0 represents no adherence.17

While the grading of specific component scores is not recommended,124 scores between 0 and the maximum represent increasing adherence to specific recommendations. For example, the average survivor total fruit score of 2.1 means that, on average, survivors consume 42% (2.1/5) of the recommended amount of whole fruits.

† Survivors and sibling means were estimated using a mixed linear regression model that accounted for survivor-sibling matching.
Table 3.4: Adjusted Healthy Eating Index Scores for Survivors and Siblings

<table>
<thead>
<tr>
<th>HEI component (maximum score)*</th>
<th>Survivors (n = 91)</th>
<th>Siblings (n = 30)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fruit (5)</td>
<td>2.1 (0.2)</td>
<td>2.0 (0.3)</td>
<td>.84</td>
</tr>
<tr>
<td>Whole fruit (5)</td>
<td>1.8 (0.2)</td>
<td>2.1 (0.2)</td>
<td>.33</td>
</tr>
<tr>
<td>Total vegetable (5)</td>
<td>2.3 (0.1)</td>
<td>2.2 (0.2)</td>
<td>.58</td>
</tr>
<tr>
<td>Dark green vegetables (5)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.2)</td>
<td>.79</td>
</tr>
<tr>
<td>Total grains (5)</td>
<td>4.5 (0.1)</td>
<td>4.4 (0.1)</td>
<td>.45</td>
</tr>
<tr>
<td>Whole grains (5)</td>
<td>1.6 (0.2)</td>
<td>1.3 (0.3)</td>
<td>.26</td>
</tr>
<tr>
<td>Milk (10)</td>
<td>6.5 (0.3)</td>
<td>6.0 (0.4)</td>
<td>.18</td>
</tr>
<tr>
<td>Meat and beans (10)</td>
<td>7.3 (0.2)</td>
<td>7.5 (0.4)</td>
<td>.68</td>
</tr>
<tr>
<td>Oils (10)</td>
<td>7.7 (0.2)</td>
<td>7.7 (0.3)</td>
<td>.97</td>
</tr>
<tr>
<td>Sodium (10)</td>
<td>3.3 (0.2)</td>
<td>3.4 (0.4)</td>
<td>.91</td>
</tr>
<tr>
<td>Saturated fat (10)</td>
<td>5.8 (0.3)</td>
<td>5.3 (0.4)</td>
<td>.27</td>
</tr>
<tr>
<td>Solid fat and added sugars (20)</td>
<td>11.5 (0.5)</td>
<td>10.2 (0.7)</td>
<td>.09</td>
</tr>
<tr>
<td>Total HEI score</td>
<td>55.5 (1.0)</td>
<td>53.3 (1.5)</td>
<td>.16</td>
</tr>
</tbody>
</table>

* HEI component scores range from 0 to a maximum of 5, 10, or 20. The maximum score represents full adherence to a specific USDA recommendation and 0 represents no adherence.¹⁷

While the grading of specific component scores is not recommended,¹²⁴ scores between 0 and the maximum represent increasing adherence to specific recommendations. For example, the average survivor total fruit score of 2.1 means that, on average, survivors consume 42% (2.1/5) of the recommended amount of whole fruits.

† Survivors and sibling means were adjusted for age and sex using a mixed linear regression model that accounted for survivor-sibling matching.
Table 3.5: Daily Caloric Intake and Healthy Eating Index Scores by Cancer Diagnosis and by Cancer Therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Daily caloric intake*</th>
<th>HEI total score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer diagnosis, adjusted† mean by diagnosis, (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>95 (83 to 108)</td>
<td>54.8 (50.9 to 58.7)</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>88 (73 to 104)</td>
<td>53.5 (48.5 to 58.4)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>101 (84 to 117)</td>
<td>52.3 (47.2 to 57.4)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>89 (72 to 106)</td>
<td>60.5 (55.1 to 65.8)</td>
</tr>
<tr>
<td>Other</td>
<td>105 (92 to 118)</td>
<td>56.2 (52.2 to 60.2)</td>
</tr>
</tbody>
</table>

| **Cancer therapy, adjusted‡ mean difference by therapy (P value)** |                      |                  |
| Alkylating agents                | 0 (.96)               | -1.0 (.65)       |
| Anthracyclines                   | 1 (.92)               | 1.6 (.48)        |
| Cranial irradiation              | 0 (.95)               | -6.4 (.01)       |
| Antimetabolites                  | 6 (.57)               | -2.8 (.35)       |
| Corticosteroids                  | -9 (.39)              | 6.0 (.06)        |

* Daily caloric intake is expressed as a percentage relative to age-, sex-, activity-, height-, and weight-specific recommended daily caloric intakes from the Institute of Medicine (IOM).¹⁹

Percentages above 100% represent excessive energy intake and those below 100% indicate inadequate energy intake.

† Group means are age and sex adjusted using analysis of covariance. The F test for cancer diagnosis, using type III sum of squares, nearly reached statistical significance for daily caloric intake (F(4)=1.00, P=.41) but not the HEI total score (F(4)=1.51, P=.21) with P values representing the probability of finding the observed differences between cancer diagnoses groups were there no differences.

‡ Mean differences are adjusted for age, sex, and other therapies using linear regression with the mean difference representing the expected change associated with having the therapy compared to not having the therapy. P values represent the probability of finding a difference among means as extreme as the observed differences were assuming there were no differences.
Among survivors, there was no association between daily caloric intake relative to IOM recommendations and either BMI classification (F(2)=0.52, P=.60) or percent body fat (β=-0.05, P=.59). There was a difference between the total HEI scores of survivors based on BMI classification, with obese survivors having lower HEI scores compared to overweight survivors (Figure 3.3). Among survivors, decreasing total HEI scores were associated with increasing percent body fat (β=-0.19, P=.04). When stratified by cranial radiation exposure, the same trends existed in both groups.

Among survivors, there were no significant associations between total daily caloric intake relative to IOM recommendations or HEI scores and individual CVD risk factors including LDL and HDL cholesterol, systolic and diastolic blood pressure, glucose, insulin, HOMA-IR or aggregated measures including the PDAY OR and FRC RR (Table 3.6).

3.4 Discussion

This study of dietary intakes in childhood cancer survivors, a mean 13 years from their original cancer diagnosis, and siblings showed that survivors have similar total daily caloric intake and macronutrient distributions to their siblings. The dietary quality of survivors and siblings were also similar across 12 different dietary domains with both groups having diets lower in dark green and leafy vegetables, whole fruits, and whole grains. Among survivors, there was a trend towards those exposed to cranial radiation having lower quality diets. There was also an association between decreased dietary quality and increased adiposity in survivors though there was no association between dietary characteristics and other traditional CVD risk factors.
Distributions of HEI total scores for survivors by BMI classification, normal weight, overweight, or obese. F test for BMI classification, using type III sum of squares and adjusted for age and sex using ANCOVA, tests the probability of observing a difference between groups as large as or larger than that observed. The P value associated with the marker is for the comparison of the groups marked (A). The HEI total scores are plotted over percent body fat. $\beta$ is the age- and sex-adjusted standardized regression coefficient, presented with its associated P value, and it is represented by the graphed line (B).
Table 3.6: The Association of Daily Caloric Intake and Healthy Eating Index with Traditional CVD Risk Factors among Survivors

<table>
<thead>
<tr>
<th>CVD risk factors</th>
<th>Standardized regression coefficient* (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily caloric intake†</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.08 (.46)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.08 (.47)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.18 (.09)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.09 (.41)</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.05 (.63)</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.18 (.11)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.19 (.10)</td>
</tr>
<tr>
<td>PDAY OR‡</td>
<td>0.02 (.88)</td>
</tr>
<tr>
<td>FRC RR‡</td>
<td>0.00 (.98)</td>
</tr>
</tbody>
</table>

* Standardized regression coefficients are age and sex adjusted using linear regression.

† Daily caloric intake is expressed as a percentage relative to age-, sex-, activity-, height-, and weight-specific recommended daily caloric intakes from the Institute of Medicine (IOM).\(^19\)

Percentages above 100% represent excessive energy intake and those below 100% indicate inadequate energy intake.

‡ Due to age limitations imposed by the risk aggregation methodologies, analyses contained 50 survivors for the PDAY OR and 42 survivors for the FRC RR.

CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment-insulin resistance; PDAY OR: Pathobiological Determinants of Atherosclerosis in Youth odds ratio; FRC RR: Framingham Risk Calculator risk ratio.
The total daily caloric intake of survivors is consistent with age-, sex-, and activity level-specific recommendations and not different from that of their siblings. The diets of survivors contain a mean 33% of their calories from fat which is above 27%, a recommendation from the National Heart Lung and Blood Institute in their Dietary Approaches to Stop Hypertension diet, but similar to that of their siblings. This finding confirms a recent study which also reported survivors obtain 33% of their calories from fat though this study measured fat intake using a 17-item screener. The average survivor diet also contained 52% of calories from carbohydrates and 15% from protein. While these values are consistent with those of the general population, it is possible that decreased carbohydrate intake could result in favorable changes in adiposity.

The average HEI total score of survivors was 55.5 suggesting their diets are moderately adherent to recommendations and that their dietary quality was not dissimilar from that of their siblings. This estimate is similar to that from another study of survivors that calculated HEI scores based on food frequency questionnaires and reported a mean HEI score of 56.9 for survivors over 18 years of age. These estimates are also similar to those of the general US population, which is 58. Both survivors and siblings scored worst for the consumption of dark green and leafy vegetables, whole fruits, and whole grains. This finding is consistent with other studies that have reported survivors do a poor job of meeting recommendations with respect to the consumption of fruits and vegetables. Thus, there exists potential for significant improvements in the dietary quality of survivors.

We found little association between original cancer diagnosis or therapies and diet, with the exception of survivors with cranial radiation exposure. These survivors had
significantly poorer quality diets than did other survivors. It is possible that these survivors, who are at increased risk of having growth hormone abnormalities and reduced stature, may have difficulty consuming high quality diets in relation to their more limited caloric intake needs. Endocrine and non-endocrine complications may also result in these survivors having altered diets through complex mechanisms involving diminished cognitive capacity or an altered psychosocial environment.\textsuperscript{130,131}

Dietary quality was associated with adiposity in survivors. Survivors who were obese had significantly lower quality diets than did overweight survivors. Lower dietary quality was also associated with increasing percent body fat. This association further underscores the potential benefits that may be associated with dietary interventions that seek to improve the diet quality of survivors and are consistent with diet quality being associated with adiposity and CVD.\textsuperscript{132} This finding could also reflect that dietary quality, which may be less dependent on the correct estimation of portion sizes than other measures such as total caloric intake, is less subject to respondent error.

Though diet quality was associated with adiposity, no dietary characteristics, including diet quality, were associated with other traditional CVD risk factors including cholesterol and blood pressure. This could be explained by survivors with higher levels of these factors having already modified their diets to reduce CVD risk. It is also possible, given the young age of the survivors studied, that poor diets and adiposity had yet to result in increased levels of CVD risk factors though such changes may ultimately emerge. However, the lack of association may suggest that the reliance of current recommendations to prevent CVD in survivors on the promotion of healthy lifestyle habits may be insufficient. It is possible that novel mechanisms, unrelated to diet,
underlie the increased CVD risk observed in survivors and where prevention efforts should be focussed.\textsuperscript{35}

There was no association between total caloric intake and adiposity despite energy imbalance being important to its etiology.\textsuperscript{133,134} However, overweight survivors may still have developed increased body fat due to having previously consumed diets with excess calories even if their current diets did not contain excess calories. It is also possible that overweight survivors underreported their caloric intakes, a finding consistent with another study of survivor diets.\textsuperscript{120} As with any study of diet utilizing self-report, our findings are limited by the ability and willingness of respondents to accurately record their diets. Not all survivors and siblings from the Cardiac Risk Factors in Childhood Cancer Survivors Study completed dietary records. While this could have resulted in bias, respondents and non-respondents were similar with respect to basic demographic and clinical characteristics including BMI.

Diet records were recorded in conjunction with a study of the long-term health of survivors. It is possible that this health focus could have altered the diets of survivors. The results of the current study are strengthened by the inclusion of a sibling control group. While our findings are largely consistent with prior work indicating that the diets of survivors are of relatively poor quality\textsuperscript{116,118,121}, it is important to note that this does not appear to be because of their history of childhood cancer, with the possible exception of brain cancer survivors and those exposed to cranial radiation. As with children at increased risk of CVD for other reasons such as those with chronic diseases, it is important to understand how lifestyle factors can be modified to reduce their CVD burden.\textsuperscript{13,135}
Chapter 4. Aggregating Traditional Cardiovascular Disease Risk Factors to Assess the Cardiometabolic Health of Childhood Cancer Survivors

4.1 Background

Among childhood cancer survivors, radiation and chemotherapy-induced vascular damage account for much of the increased risk of CVD in the first decades after cancer treatment, although endocrine and metabolic abnormalities may be responsible for a larger portion of this increased risk with longer survival.\textsuperscript{5,136,137} The importance of considering both treatment-induced vascular damage and traditional CVD risk factors was made clear in a study of 450 survivors treated with cardiac irradiation.\textsuperscript{39} Of 42 survivors who developed coronary artery disease, at just a median of 9 years after diagnosis, all had at least 1 traditional CVD risk factor, and survivors with either high cholesterol or hypertension were 3 times more likely to develop coronary artery disease.

In the 1980s, reports began documenting an increased prevalence of obesity in survivors relative to healthy populations,\textsuperscript{138} a result still found in contemporary cohorts.\textsuperscript{38,83} In 1996, Talvensaari and colleagues found that survivors had lower fasting serum levels of high-density lipoprotein cholesterol and higher levels of glucose relative to healthy populations.\textsuperscript{35} Additional studies confirmed these findings and found abnormalities are associated with cranial irradiation and decreased growth hormone.\textsuperscript{36,87,88,94,95}

Recently, studies have found increased clustering of traditional CVD risk factors in survivors of acute lymphoblastic leukemia treated with cranial or total body irradiation; however, this association was not seen in survivors of other cancer types and these studies did not include non-cancer controls.\textsuperscript{139,140} Another study, with sibling controls, found no difference between survivors and siblings but did find total body
irradiation was associated with risk factor clustering. Several studies have also reported an independent association between physical inactivity and risk-factor clustering in survivors.

The fact that obesity, dyslipidemia, and insulin resistance are modifiable risk factors for CVD has led to the creation of screening guidelines for survivors. The early identification and aggressive management of traditional risk factors will hopefully reduce the overall CVD burden of survivors. Combining traditional CVD risk factors into a single measure might help identify survivors needing more aggressive interventions and increase survivors’ understanding of the importance of risk-factor management. Traditionally, risk-aggregation instruments have only been available for older populations. Recently however, two such instruments have been developed and validated for younger patients.

We used these new risk-aggregation instruments to describe the cardiometabolic health of survivors who were part of a National Cancer Institute-funded cohort study and who had been evaluated for traditional CVD risk factors. Further, we compared estimates of their cardiometabolic health to those of sibling controls and determined whether cancer type, cancer treatments, or physical inactivity were associated with their cardiometabolic health.

4.2 Methods

Information on cancer diagnosis and treatment was abstracted from the medical records. All other information was collected during a single, daylong study visit. Fasting blood samples were tested for traditional CVD risk factors including levels of total
cholesterol, high-density lipoprotein (HDL) cholesterol, and insulin. All tests were performed at the Strong Memorial Hospital Clinical Laboratory, Rochester, New York, which is in full compliance with the Clinical Laboratory Improvement Amendments.

Blood pressure was recorded by Dinamap. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Physical inactivity was measured as self-reported hours of TV watching per week.

Traditional risk factors for atherosclerotic disease—age, sex, non-HDL cholesterol, HDL-cholesterol, current smoking status, hypertension, obesity, and hyperglycemia—were aggregated with Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scores. Each patient receives a score based on their risk factor profile which estimates the probability of currently having an advanced coronary artery lesion in either the left anterior descending artery (an American Heart Associate grade 4 or 5 lesion) or right coronary artery (any raised lesion covering at least 9% of the intimal surface). The PDAY scoring system uses a glycosylated hemoglobin level above 8% to define hyperglycemia. Because this measure was not recorded in the Cardiac Risk Factors in Childhood Cancer Survivors Study, a fasting serum insulin level greater than 18 μU/mL was used; 12% of eligible survivors and 3% of siblings met this criteria.

The modified PDAY score is calculated by subtracting the points associated with age and sex from the above PDAY score. By the design of the PDAY scoring system, this modified PDAY score estimates the odds ratio of currently having an advanced coronary artery lesion in either the left anterior descending coronary artery or right coronary artery compared to an individual of similar age and sex without CVD risk.
factors. The odds for the individual without any modifiable CVD risk factors is estimated by the model. PDAY probabilities and odds ratios were calculated for each subject between 15 and 34 years old, the age range for which the instrument was developed.

The Framingham Risk Calculator (FRC) uses a weighted combination of age, sex, total cholesterol, HDL-cholesterol, smoking status, systolic blood pressure, diabetes, and hypertensive treatment. The FRC estimates expressed the 30-year risk, as a percentage, of experiencing a myocardial infarction, stroke, or coronary death. Because diabetes was not clinically diagnosed in the Cardiac Risk Factors in Childhood Cancer Survivors Study, a fasting serum insulin level greater than 30 μU/mL was used; 6% of eligible survivors and no siblings met this criteria.146,148

The FRC also estimates an ideal 30-year risk of these events based on having no modifiable CVD risk factors. The risk for the individual without any modifiable CVD risk factors is estimated by the model. An FRC risk ratio was created for each person by dividing the FRC risk by the ideal risk estimated by the FRC. This FRC risk ratio represents the increased risk of having a myocardial infarction, stroke, or coronary death in the next 30 years relative to an individual of similar age and sex without CVD risk factors. An FRC risk and risk ratio were calculated for all subjects between 20 and 39 years old, the lowest end of the age range for which the instrument was developed.

To confirm that the PDAY odds ratio and FRC risk ratio were less age-dependent than the PDAY probability and FRC risk, as would be expected from their origin and methods of calculation, we assessed the correlations between age and these measures using Spearman’s rho (Figures 4.1 and 4.2). Because the ratio measures depended less
on age, they were deemed more appropriate for describing impaired cardiometabolic health and analyzed further.

Because some survivors lacked a sibling control, mixed-models were used to compare survivors and siblings. To assess the association of cancer type and the PDAY odds ratios and FRC risk ratios, analysis of covariance was used to adjust for age and sex. To assess the association of cancer treatments and the PDAY odds ratios and FRC risk ratios, a single linear regression model was used with all treatments of interest simultaneously included and adjusted for age and sex. To assess the association of physical inactivity and the PDAY odds ratios and FRC risk ratios in survivors, correlation coefficients were used, as well as linear regression, to adjust for age and sex with standardized regression coefficients (Betas) reported.

PDAY and FRC measures are reported as medians to describe the raw values and as means when from a statistical model. Because the PDAY odds ratio and FRC risk ratio were positively skewed (Figures 4.1 and 4.2), they were log-transformed. Transformed variables were used in procedures assuming normality and estimates back-transformed for reporting, unless the Betas are reported. Alpha was set at 0.05, and all tests were two-tailed. Analyses were performed using SAS, Version 9.2 (SAS Institute Inc., Cary, NC) and figures made using Stata, Version 9.2 (StataCorp LP, College Station, TX).
Relationship between age and PDAY score measures in 101 survivors of childhood cancers and 31 siblings. PDAY probabilities represent the probability of currently having an advanced coronary artery lesion while the ratio is the odds ratio of having an advanced coronary artery lesion relative to an individual of similar age and sex without CVD risk factors. (■ = male survivors; □ = male siblings; ● = female survivors; ○ = female siblings).

Relationship between age and FRC measures in 73 survivors of childhood cancers and 16 siblings. FRC risks represent the 30-year risk of myocardial infarction, stroke, or coronary death while the ratio is that risk relative to an individual of similar age and sex without CVD risk factors. (■ = male survivors; □ = male siblings; ● = female survivors; ○ = female siblings).
4.3 Results

Of 201 survivors and 76 siblings enrolled in the Cardiac Risk Factors in Childhood Cancer Survivors Study, PDAY estimates could be calculated for 101 survivors and 31 siblings, and FRC estimates for 73 survivors and 16 siblings (Table 4.1). Of the 129 subjects without an estimate, 101 were below 15 or above 40 years of age and 28 were missing data for a specific risk factor. Other than age, there were no systematic differences between the survivors eligible and ineligible for this analysis. Roughly half the survivors had an original cancer diagnosis of leukemia or lymphoma, and most were at least 10 years from cancer diagnosis (Table 4.2).

Survivors had a median PDAY odds ratio of 2.2 (IQR, 1.25 to 3.30), and 17% of survivors had ratios greater than 4 (Figure 4.3). Survivors had a median FRC risk ratio of 1.67 (IQR, 1.00 to 2.00), and 12% of survivors had ratios greater than 4 (Figure 4.3). Siblings had a median PDAY odds ratio of 2.2 (IQR, 1.70 to 3.30), with 6% having ratios greater than 4, and a median FRC risk ratio of 1.50 (IQR, 1.00 to 2.00); none had ratios greater than 4 (Figure 1). The difference in the proportion of survivors and siblings with ratios greater than 4 was not statistically significant for the PDAY odds ratio (P=.24) or FRC risk ratio (P=.35).

Compared to siblings, survivors had similar mean PDAY odds ratios (2.32 vs. 2.25, P=.80) and FRC risk ratios (1.70 vs. 1.63, P=.73). After adjusting for age and sex, neither PDAY odds ratios (2.33 vs. 2.29, P=.86) nor FRC risk ratios (1.72 vs. 1.53, P=.24) differed significantly between survivors and siblings. These results were consistent with analyses including only the survivor-sibling pairs (Figure 4.4).
### Table 4.1: Characteristics of Survivors of Childhood Cancer and Siblings with Cardiometabolic Aggregated Risk Measures, by Instrument

<table>
<thead>
<tr>
<th>Cardiometabolic risk-aggregation instrument</th>
<th>PDAY Survivors</th>
<th>Siblings</th>
<th>FRC Survivors</th>
<th>Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=101)</td>
<td>(n=31)</td>
<td>(n=73)</td>
<td>(n=16)</td>
</tr>
<tr>
<td><strong>Characteristic</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (45)</td>
<td>15 (48)</td>
<td>31 (42)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (54)</td>
<td>16 (52)</td>
<td>42 (58)</td>
<td>7 (44)</td>
</tr>
<tr>
<td><strong>Age at risk factor assessment, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 to 19</td>
<td>36 (36)</td>
<td>15 (48)</td>
<td>...*</td>
<td>...*</td>
</tr>
<tr>
<td>20 to 29</td>
<td>50 (50)</td>
<td>13 (42)</td>
<td>49 (67)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>30 to 39</td>
<td>15 (15)</td>
<td>3 (10)</td>
<td>24 (33)</td>
<td>3 (19)</td>
</tr>
<tr>
<td><strong>Inactivity, TV hours per week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 9</td>
<td>46 (50)</td>
<td>18 (60)</td>
<td>36 (51)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>10 to 19</td>
<td>25 (27)</td>
<td>9 (30)</td>
<td>19 (27)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>6 (6)</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>30 to 39</td>
<td>16 (17)</td>
<td>2 (7)</td>
<td>11 (16)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

**PDAY**: Pathological Determinants of Atherosclerosis in Youth

**FRC**: Framingham Risk Calculator

* PDAY measures were calculated only for subjects between 15 and 34 years old and FRC measures only for subjects between 20 and 39 years old, the age ranges for which these instruments were developed.
Table 4.2: Characteristics of Survivors of Childhood Cancer with Cardiometabolic Aggregated Risk Measures, by Instrument

<table>
<thead>
<tr>
<th>Cardiometabolic risk-aggregation instrument</th>
<th>PDAY (n=101)</th>
<th>FRC (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer characteristic</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>32 (32)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>23 (23)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>15 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>14 (14)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (17)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Treatment exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>60 (59)</td>
<td>48 (66)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>58 (57)</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Cranial irradiation*</td>
<td>51 (51)</td>
<td>29 (40)</td>
</tr>
<tr>
<td>Antimetabolite</td>
<td>47 (47)</td>
<td>28 (39)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>46 (46)</td>
<td>31 (43)</td>
</tr>
<tr>
<td>Years from diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to 10</td>
<td>34 (34)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>11 to 20</td>
<td>55 (54)</td>
<td>38 (52)</td>
</tr>
<tr>
<td>21 to 31</td>
<td>12 (12)</td>
<td>19 (26)</td>
</tr>
</tbody>
</table>

PDAY: Pathological Determinants of Atherosclerosis in Youth
FRC: Framingham risk calculator
*51% of those with PDAY estimates and 41% of those with FRC estimates received less than 18 Gy with 22% and 28% receiving over 60 Gy, respectively.
The PDAY odds ratios and FRC risk ratios of survivors of different types of childhood cancer did not appear to differ markedly (Table 4.3) nor was the variance in either ratio explained by cancer type statistically significant. The PDAY odds ratios and FRC risk ratios of survivors were not strongly associated with specific cancer treatments (Table 4.4).

There was a suggested association for physical inactivity with the PDAY odds ratios and the FRC risk ratios ($r=.17$; $P=.10$ and $r=.19$; $P=.12$, respectively), even after adjusting for age and sex ($\beta=0.16$; $P=.12$ and $\beta=0.19$; $P=.10$).
Figure 4.4: Comparison of PDAY Odds Ratios and FRC Risk Ratios among Survivor-sibling Pairs

The natural log (Ln) of PDAY odds ratios and FRC risk ratios for survivor-sibling pairs. Pairs are connected with sex-labeled lines (male pair, blue; female pair, pink; and mixed sex pair, black). Not all survivor-sibling pairs contained subjects of similar age, which in some cases prevented obtaining scores for both members of the pair. Specifically, FRC risk ratios could not be obtained for persons between 15 and 19 years old and PDAY odds ratios could not be obtained for persons between 35 and 39 years old. In these cases neither subject was included.
Table 4.3: Association of Cancer Diagnosis with Cardiovascular Disease Risk in Survivors of Childhood Cancer, by Risk-Aggregation Instrument

<table>
<thead>
<tr>
<th>Cancer Diagnosis†</th>
<th>PDAY Odds Ratio (95% CI)</th>
<th>FRC Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>2.37 (1.87 to 3.00)</td>
<td>1.91 (1.44 to 2.53)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2.25 (1.71 to 2.96)</td>
<td>1.65 (1.30 to 2.10)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2.16 (1.53 to 3.04)</td>
<td>1.24 (0.90 to 1.71)</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>2.71 (1.89 to 3.89)</td>
<td>2.00 (1.42 to 2.82)</td>
</tr>
<tr>
<td>Other</td>
<td>2.26 (1.64 to 3.12)</td>
<td>2.10 (1.49 to 2.96)</td>
</tr>
</tbody>
</table>

* Group means are age- and sex-adjusted using analysis of covariance.
† The F-test for cancer diagnosis was not statistically significant for either the PDAY odds ratio (P=0.91) or for the FRC risk ratio (P=0.17), with P-values representing the probability of finding the observed differences between cancer diagnoses groups were there no differences.

Table 4.4: Association of Cancer Treatments with Cardiovascular Disease Risk in Survivors of Childhood Cancer, by Risk-Aggregation Instrument

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PDAY Odds Ratio (P-value)</th>
<th>FRC Risk Ratio (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial Irradiation</td>
<td>0.48 (.22)</td>
<td>0.15 (.66)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>-0.25 (.54)</td>
<td>-0.38 (.22)</td>
</tr>
<tr>
<td>Alkylating Agent</td>
<td>-0.03 (.93)</td>
<td>-0.11 (.73)</td>
</tr>
<tr>
<td>Antimetabolite</td>
<td>0.36 (.44)</td>
<td>-0.19 (.58)</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>-0.22 (.71)</td>
<td>0.50 (.42)</td>
</tr>
</tbody>
</table>

* Mean differences between survivors with and without the treatment exposures are adjusted for age, sex, and the other treatments using linear regression. P-values represent the probability of finding a difference as extreme as the observed difference was there no difference.
4.4 Discussion

Our results show that PDAY scores and the FRC can be applied in survivors of childhood cancer to combine the results of recommended CVD risk factor screening. These estimates, based on traditional risk factors, suggest that many survivors have impaired cardiometabolic health and are at increased long-term risk of CVD, although for most survivors this risk may not differ largely from that of their siblings. And, while this risk was not strongly associated with a specific cancer type or treatment, there was a trend towards an association with physical inactivity.

In this study, a significant proportion of survivors had either a PDAY odds ratio or a FRC risk ratio greater than 4, meaning that they were at least four-times more likely to currently have a coronary artery lesion or to suffer from CVD in the next 30 years than individuals of similar sex and age without CVD risk factors. This finding supports the current emphasis on promoting cardiometabolic health in survivors and identifying at-risk survivors through screening,13 and is consistent with other studies showing increased risk factor clustering in some survivors.139-141

Additionally, finding that physical inactivity trended towards an association with poor cardiometabolic health suggests that lifestyle interventions for survivors may reduce CVD risk in high-risk survivors and maintain a low risk profile in those not yet at high-risk.13 This finding is consistent with other studies139,141 and may partially explain the lack of a strong association between cancer and treatment characteristics with cardiometabolic health.

The similar estimates of cardiometabolic health, which were based on traditional CVD risk factors alone, between survivors and siblings suggests that much of the
increase in early CVD incidence in survivors may result from the direct effects of cancer treatment, such as treatment-induced vascular damage. The similarities in cardiometabolic health between survivors and siblings may also reflect a diluting of the difference in the prevalence of individual CVD risk factors by those similarly prevalent in survivors and siblings, such as smoking and hypertension.37,75

The lack of a strong relationship between estimates of cardiometabolic health and cancer type or specific treatments likely reflects the pathophysiologic heterogeneity of the individual risk factors aggregated in these measures. Individual CVD risk factors are unlikely to be affected by the same cancer treatments or associated with the same pathophysiologic changes. Thus, specific treatment-to-risk-factor associations are likely to be obscured by other, unaffected, risk factors in the aggregated measures. This finding underscores the need for a broad-based screening approach because poor cardiometabolic health does not appear to be limited to a specific survivor subgroup. As mentioned, this finding may reflect the importance of lifestyle habits, such as diet and physical inactivity, on the development of traditional CVD risk factors in survivors.

These aggregated measures are clinically attractive, in part because of their ability to provide information beyond the sum of their parts. Unlike counting the number of risk factors present, which requires ignoring variation above and below a specific point, risk-aggregation instruments provide an objective and evidenced-based method of considering more subtle variations in risk. Further, these measures provide a single estimate of cardiometabolic health. These measures make possible a baseline assessment of cardiometabolic health that can be followed over time to detect the development of elevated CVD risk.
Unlike the case for adults, where the absolute risks estimated by risk-aggregation instruments represent outcomes of sufficient probability, immediacy, and importance to guide treatment decision-making, the absolute risks in adolescents and young adults are often very low and most strongly influenced by age, as opposed to cardiometabolic abnormalities. In these patients, ratios in which the absolute risk is expressed relative to the absolute risk if the patient had no cardiometabolic abnormalities may hold greater clinical value.

In addition to abnormalities in cardiometabolic health, the CVD burden of survivors is driven by novel mechanisms related to cancer treatment. Although radiation and certain chemotherapeutics cause vascular damage and are risk factors for CVD, they were not considered in the aggregation instruments used in this report. Survivors exposed to anthracyclines and cardiac radiation have subclinical cardiotoxicity, including reduced left ventricular wall thickness and increased left ventricular afterload. These changes may leave survivors less able to compensate for ischemic cardiac damage and more susceptible to CVD. However, effective treatments are lacking for these novel factors, limiting their value as screening targets.

The risk-aggregation instruments used in this study were developed in a non-survivor population. It is possible that CVD risk factors affect survivors differently. However, it seems unlikely that a history of childhood cancer would be protective, meaning any bias would likely under-estimate cardiometabolic impairments. These risk-aggregation instruments do not account for novel risk factors, which may further contribute to underestimation. The Cardiac Risk Factors in Childhood Cancer Survivors
Study did not collect data on CVD endpoints, such as myocardial infarction, stroke, or coronary death, which are rare in younger populations, even those at relatively high-risk. For associations between cardiometabolic health and survivor characteristics, there was likely insufficient power to detect statistically significant differences. It is therefore not possible to exclude an association such as that between cranial irradiation and decreased cardiometabolic health due to a lack of statistical significance. However, the small size and heterogeneous nature of this population and the difficulty inherent in obtaining detailed clinical measurements decades after treatment mean larger samples are rare.
Chapter 5. Conclusions

Population based death certificate studies have demonstrated that childhood cancer survivors have increased cardiovascular disease (CVD) mortality compared to the general population.\textsuperscript{7,9,10} Survey studies of survivors and siblings have revealed that survivors are also more likely to report developing CVD than siblings.\textsuperscript{4,8,11} However, these studies have failed to fully describe the pathophysiologic processes underlying this increased CVD burden or the clinical and lifestyle factors affecting it. Of studies attempting to address this issue, most have focused on anthracycline- and radiation-induced cardiotoxicity\textsuperscript{6,30} and on describing the development of traditional CVD risk factors.\textsuperscript{37,38} In this dissertation, we set out to more closely examine three specific areas related to the CVD burden of survivors. First we sought to assess whether cranial irradiation is associated with increased cardiotoxicity among survivors who received anthracyclines. Second, we sought to determine whether the diets of survivors are different than those of sibling controls as well as whether cancer diagnoses or therapies are associated with diet and, in turn, whether diet was associated with adiposity among survivors. Finally, we sought to assess the combined CVD risk from several traditional metabolic CVD risk factors, cardiometabolic health, of survivors using recently developed risk factor aggregation instruments, to compare their cardiometabolic health to that of their siblings, and to see if their cardiometabolic health is associated with cancer diagnoses and therapies or physical inactivity.

Among anthracycline-treated survivors, those with cranial radiation exposure had statistically significantly greater decreases in left ventricular (LV) mass and LV dimension. There were also trends towards cranial irradiation being associated with
decreased LV wall thickness and increased LV afterload. These LV changes may predispose survivors exposed to cranial radiation to have worsening anthracycline cardiotoxicity over time, especially considering that decreased LV mass and LV wall thickness underlie this cardiotoxic pathway. These LV changes are also consistent with reduced growth and may be a product of decreased growth hormone (GH) due to radiation-induced brain damage. This hypothesis is supported by the decreased levels of insulin-like growth factor 1 (IGF-1) and height that were observed in the survivors exposed to cranial radiation. Further, among these survivors there was a trend towards decreased levels of IGF-1 being associated with increased anthracycline cardiotoxicity.

Survivors consume diets that are consistent with recommendations for daily caloric intake but which are only moderately adherent to recommendations for diet quality. Specifically, survivors consume too few whole fruits and dark green vegetables and on average consume diets with an excess of calories from fat. However, these dietary characteristics were similar to those of the diets of siblings. As might be expected given the similar dietary characteristics of survivors and siblings, there were no associations between cancer diagnoses or therapies and diet with one notable exception. Cranial irradiation was associated with a statistically significantly lower quality diet, a finding which may reflect therapy-induced brain damage that could negatively impact diet through metabolic and psychosocial pathways. Among childhood cancer survivors, decreased diet quality was associated with increased adiposity, assessed using BMI classification and percent body-fat.

We found that survivors have less than ideal cardiometabolic health on average with some survivors having extremely poor cardiometabolic health, consistent with a
four-fold or greater increased risk of currently having an advanced atherosclerotic lesion in their coronary artery or suffering a heart attack, stroke, or coronary artery disease related death in the next 30 years. However, for most survivors their cardiometabolic health was not largely different than that of sibling controls. Specific cancer diagnoses and therapies were also not associated with cardiometabolic health though there was insufficient power to rule out an association between either brain cancer or cranial irradiation with decreased cardiometabolic health, both of which trended towards a weak association in that direction. Among survivors, there was a trend towards an association between physical inactivity and decreased cardiometabolic health.

Currently, it is not possible to predict with any clinical value which anthracycline-treated survivors will go on to display significant chronic cardiotoxicity and there are no effective treatments for this chronic cardiotoxicity when it is identified.\textsuperscript{5,15} Cranial irradiation appears to be an additional risk factor for the development of cardiotoxicity and GH replacement therapy may even prove to be a treatment for anthracycline cardiotoxicity. This is consistent with the progressive nature of anthracycline cardiotoxicity.\textsuperscript{5,30,49} Prior studies have shown that anthracycline related abnormalities in LV wall thickness and afterload appear to worsen over time which would fit with the progressive effects that may occur from a continued absence of appropriate GH signaling.\textsuperscript{5,30,49} This work also provides further support for the important role that GH functioning plays in the development of cardiac structure and function.\textsuperscript{102-107} As in these other studies, a wide range of distinct health conditions, all of which have GH deficiency involved, result in decreased cardiac size, likely reflecting decreased growth.\textsuperscript{102,105}
though mixed, some studies have shown favorable cardiac benefits from GH replacement therapies.\textsuperscript{102-104,106,107}

Prior studies have found that the diets of survivors are not consistent with current recommendations for the consumption of fresh fruits and vegetables and that their diets appear to be high in the proportion of calories from fat.\textsuperscript{70,116-121} However, these studies have been largely based on the results of food frequency questions incorporated into larger surveys of lifestyle habits. Additionally, this prior work has not been able to elucidate whether dietary quality is associated with a history of childhood cancer due to a lack of appropriate controls or whether it is associated with adiposity. Our results suggest that the failure of survivors to adhere to fruit and vegetable recommendations as well as those for calories from fat is true when assessed using prospectively collected food records and appears to be a reflection of general population trends as opposed to the result of childhood cancer. However, we found that for survivors exposed to cranial radiation, there is an association with decreased diet quality. Further we found that that decreased diet quality is associated with increased levels of adiposity among survivors.

The Cardiac Risk Factors in Childhood Cancer Survivors Study (CRG) as well as other studies have found that survivors are more likely to develop traditional CVD risk factors than are similar individuals without a history of childhood cancer.\textsuperscript{32,35} However, when considered in the aggregate, these traditional CVD risk factors do not predict a much greater risk of CVD for most survivors than that of their siblings. Thus, while certain specific therapies may be associated the development of specific CVD risk factors,\textsuperscript{36-38} this contribution appears to be minor with respect to the total risk from all traditional CVD risk factors. This suggests that much of the excess CVD burden
observed in survivors is related to non-traditional risks such as those from anthracycline-
and radiation-induced cardiac and vascular damage. Fully preventing excess CVD in
survivors will likely require preventing cardiac and vascular damage from occurring or
developing effective treatments for this damage once it has occurred.

With respect to the initial conceptual model in Figure 1.1, the results presented in
this dissertation help clarify the contributions of several important paths. First, finding
that cranial irradiation is associated with LV abnormalities in anthracycline-treated
survivors not only suggests a novel factor affecting the path to cardiac and vascular
damage among survivors, but also provides support for the cross-path from endocrine and
metabolic abnormalities to cardiac and vascular damage. Second, finding that for most
survivors, their diets are not different than those of their siblings reveals this is likely one
lifestyle habit not altered as a result of having childhood cancer. However, survivors
exposed to cranial radiation do appear to have reduced diet quality. This provides
additional evidence for the importance of alterations in lifestyle habits as mediators of
increased CVD in survivors. The potential importance of this path is further supported by
the association between decreased diet quality and increased adiposity among survivors.
Finally, the finding that predictions of early atherosclerotic disease among survivors are
similar to those of siblings provides evidence for this pathway being less important to
increased CVD burden of survivors, at least in the first few decades following cancer
diagnosis and treatment.

With respect to the considerations of the conceptual model in Figure 1.3, the
results presented in this dissertation provide substantial confirmation for the need to
consider the CVD risks of survivors across a number of different pathways and in the
context of their therapy exposures and duration from exposure. Specifically, even among anthracycline-treated survivors there are additional therapy related exposures and pathways that affect the magnitude of cardiac and vascular damage suffered and which may lead to an increased CVD burden. Alterations in lifestyle habits do not appear to be consistent across all survivors, though among survivors, diet and physical activity are associated with profiles consistent with increased CVD. With respect to the duration from therapy exposure, the results presented show that early in the survivor course atherosclerotic disease mediated through traditional CVD risk factors does not likely explain much of the increased burden of survivors. However, given their overall poor cardiometabolic health relative to ideal, it is still likely that this pathway will contribute to a significant CVD burden in survivors with increasing age, even if this burden is not purely in excess of that which would otherwise have occurred in the absence of a history of childhood cancer.

**Strengths and Limitations**

Across these individual investigations, the use of CRG data provided several strengths. First, having a sibling control group allowed for the investigation of whether a history of childhood cancer was associated with clinically important outcomes such as cardiometabolic health and dietary characteristics. Without this control, it would have been unclear whether the poor adherence to current dietary recommendations and relatively poor cardiometabolic health of survivors was a result of their cancer history or simply reflective of general population trends. In comparison to most other studies of survivors, the CRG did not focus on a group of survivors who shared a single specific
cancer diagnosis or therapy. This allowed for the investigation of whether specific therapies or diagnoses were associated with CVD risk factors. Without having anthracycline-treated survivors exposed and unexposed to cranial radiation, it would not have been possible to determine whether the observed abnormalities in LV structure and function were associated with cranial irradiation or simply that expected from anthracycline therapy. Likewise, without this variation among survivors, it would not have been possible to learn that cranial irradiation appears to be associated with decreased diet quality.

Like most clinically detailed studies of survivors, the CRG had a limited power to assess certain specific associations and this limitation was present across the individual investigations. Specifically, the ability to assess weaker associations such as those between a brain cancer diagnosis and cardiometabolic health or between IGF-1 levels and anthracycline cardiotoxicity in cranial radiation exposed survivors were limited. Were the CRG to have included a larger number of survivors, it would have been possible to determine whether the trends observed were reflective of real associations or simply a chance finding. However, given the relative rarity of childhood cancer and the difficulty of recruiting survivors many years after their original diagnosis, the CRG offers one of the largest detailed descriptions of the cardiac health of survivors. Survivors in the CRG were recruited from a single region of the United States, the Fingers Lake region of upstate New York and Pennsylvania which is largely Caucasian, as reflected by CRG study population. This homogeneity may impact the ability to generalize these findings to other populations.
However, using a single well defined region is also credited with the ability of the CRG to have recruited a survivor sample that was representative of the underlying survivor population with respect to cancer diagnoses and therapies. Most detailed survivor studies to date have been limited to only studying survivors of a single cancer and often survivors with the same therapy exposures. Conducting this in a region with limited geographic mobility was also responsible, in part, for the ability to bring these survivors in for assessments over a decade after their original cancer treatment, for detailed studies in a clinical environment. This was critical in allowing for a more complete assessment of cardiac health such as through echocardiography.

**Future Research Directions**

In the future, studies should determine the relative contributions of different exposures and pathways to the future CVD burden of survivors to help guide efforts to prevent disease. This will require follow-up studies of survivor sub-groups to understand how therapy-induced cardiac damage and other abnormalities predict the development of clinically significant disease. Such information is currently lacking as reflected in the currently vague follow-up screening and treatment guidelines.\textsuperscript{12,13} For instance, if possible, following-up the CRG cohort of survivors could provide this type of data. The results presented in this dissertation reveal clearly that, as expected, the survivors in this sample have abnormalities across a range of factors expected to impair future cardiovascular health. Additionally, many of these factors such as echocardiographic parameters and traditional CVD risk factors are those recommended by current screening guidelines.\textsuperscript{12,13} There was also variation among the survivors followed with respect to
their cardiac risk profiles. Obtaining follow-up data on these survivors would allow for an assessment of how variation across these markers of cardiac damage and CVD risk factors predict future CVD. And finally, as childhood cancer therapies change over time, continuing to monitor new survivor cohorts is necessary in order to understand how the increased CVD burden of survivors is altered by variation in these exposures.

It is also possible to use lessons learned from the analyses presented in this dissertation to inform the conduct of future survivor studies. For specific exposures of interest, such as cranial radiation, it would likely be worth the added expense to over-recruit these survivor sub-groups in order to ensure sufficient numbers are included to generate the statistical power needed to detect moderately sized effects. While obtaining a diverse cohort of survivors is ideal for determining how different therapy-exposures differentially affect survivor health, including only adults or only adolescents may be more ideal for certain study questions. With a mixed population, it can be difficult to separate out age-related differences in normal from therapy-related differences. This would be simpler for studies of only adults. For studies of only adolescents, it would become practical to devote the added resources necessary to more specifically measure markers of development other than age such as pubertal status.

Finally, conducting a study with a cohort already previously studied using measures reasonable to be recommended for screening would be ideal. First, such a study could produce the knowledge needed to guide screening recommendations. Studying a new cohort on a single follow-up occasion would not allow for the separation of whether the screening results provide additional information beyond that of knowing the associated therapy exposures. However, having follow-up data on those previously
studied would allow for a determination of the value of these prior measures. Second, following a previously studied survivor cohort should entail following survivors at lengthy duration from their original cancer diagnosis and treatment. While such a study may not have previously been possible due to the relative novelty of modern treatments and the younger age of the survivor population, in the coming decades a large number of survivors will enter their fifties and sixties with significant disease rates manifesting.

**Future Clinical Directions**

Based on the results presented in this dissertation, we would suggest that the incorporation of cranial radiation exposure into risk prediction models of anthracycline cardiotoxicity may help increase their accuracy. With further work in this area, it may be possible to obtain clinically useful predictions. This information could help guide screening recommendations to ensure the most efficient use of resources. Further, it might be possible to make more informed decisions during original cancer treatment. There may be some patients who would benefit from reduced anthracycline doses, alternative therapies, or the addition of cardioprotective agents even if such strategies reduced oncologic efficacy. It is possible that GH replacement therapy could reduce the burden of cardiovascular disease in survivors by improving both cardiac structure and cardiometabolic health. Although concerns over cancer recurrence and second malignancies have limited the use of GH replacement therapy, recent evidence indicates that this risk is low or possibly non-existent.\(^{113-115}\)

The association of increased diet quality with reduced levels of adiposity among survivors provides support for current guidelines that rely heavily on the promotion of a
healthy diet and physical activity to reduce the CVD burden of survivors.\textsuperscript{12,13} Future research is needed to determine what interventions are most effective at promoting increased diet quality in survivors and confirming that such changes result in decreased adiposity and reduced levels of other traditional CVD risk factors in this population. It may also necessary to develop specific dietary interventions for survivors exposed to cranial radiation, as this group may have unique factors underlying their decreased dietary quality.

When considered in the aggregate, a subset of survivors are at markedly increased risk of CVD, based on traditional CVD risk factors alone. For this purpose, we propose that inexpensive risk-aggregation instruments—the Pathobiological Determinants of Atherosclerosis in Youth odds ratio and Framingham 30-year Risk Calculator risk ratio—be used as an additional method for identifying survivors at elevated risk of CVD. These instruments may also facilitate patient understanding of the possible benefits of risk-factor modification, which could increase adherence to risk-reduction strategies. Although there was no evidence that most survivors are at greater risk of cardiometabolic impairment than their siblings, their increased risk relative to an ideal person underscores the importance of promoting cardiometabolic health in survivors, whom are also at risk of CVD from treatment-induced vascular and cardiac damage.

**Concluding Remarks**

Anthracycline-treated survivors exposed to cranial radiation have significantly greater decreases in LV mass and dimension. It is possible that GH deficiency mediates this effect and that GH replacement therapy may help prevent the development of
cardiotoxicity in this high risk group. Survivors consume diets similar to their siblings though only moderately adherent to guidelines with dietary quality being associated with increased body fat among survivors. Interventions focused on diet quality may help reduce the adiposity and CVD risk of survivors. Cardiometabolic health is poor in survivors but not largely different than that of their siblings. This highlights the importance of managing traditional CVD risk factors and considering novel exposures like cardiac irradiation and anthracycline chemotherapy among survivors.

The overarching message from this dissertation is that the increased CVD morbidity and mortality observed in survivors is not solely the product of widely appreciated cardiotoxic therapies such as radiation- and chemotherapy-induced vascular and cardiac damage, though these factors do likely explain much of the increased CVD burden early in the survival period. Rather, the increased CVD burden of survivors is exacerbated by other factors. Specifically, we found evidence that cranial irradiation, a factor not previously associated with cardiac damage, is associated with increased anthracycline cardiotoxicity. And further, while we found no evidence that the diets or CVD risk profiles of survivors are significantly worse than that of their siblings, both are far from ideal. This suggests that while diet and traditional CVD risk factors may not contribute to the increased CVD burden of survivors, they may provide one route by which to reduce it. By more fully understanding the pathways to CVD in survivors, it will hopefully be possible to develop and test strategies to reduce it.
References


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