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Determinants and Early Detection of Late Cardiotoxic Effects of Anthracyclines in Childhood Cancer Survivors

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An abstract of a dissertation submitted to the Faculty of the
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ABSTRACT

Anthracyclines are used extensively in cancer treatment protocols and more than half of all childhood cancer survivors in the U.S. have been exposed. An important adverse effect of anthracyclines is cardiotoxicity, which requires continued monitoring of cardiac function to avoid further injury and ensure timely treatment. Childhood cancer survivors may also be at increased risk for cardiovascular disease because of their propensity for sedentary lifestyles. This dissertation explores the use of different screening techniques to assess cardiac and morbidity-related late effects of anthracyclines in childhood cancer survivors, and estimates the proportion of cardiac events preventable through exercise intervention.

We conducted resting and exercise echocardiography on 80 asymptomatic childhood cancer survivors at least 5 years post-treatment and asked participants to completed a Pediatric Quality of Life Inventory (PedsQL). We also analyzed data from the Childhood Cancer Survivor Study (CCSS) to assess the late effects following treatment. Using CCSS data and a new methodology we decomposed the influence anthracyclines have on cardiac outcomes into direct (treatment-related) and indirect (through physical inactivity) effects.

We found no clinical benefit of adding exercise echocardiography to screen for anthracycline cardiotoxicity. However, the results confirmed that cancer survivors at highest risk for cardiotoxicity had some evidence of diastolic filling abnormalities at rest despite normal systolic function, and addition of Tissue Doppler Imaging to resting echocardiography may be useful. With exercise, participants augmented their systolic and diastolic function to achieve relatively normal maximal aerobic capacity despite impaired stroke volume. In the PedsQL study, we observed a dose-response effect of exposure to anthracyclines on overall and physical health-related quality of life underscoring the importance of ongoing psychosocial assessments during survivorship. In the decomposition analysis we found very little, if any, evidence that cardiac outcomes among anthracycline-treated long-term childhood cancer survivors can be attributed to physical inactivity.

This dissertation research extends the literature on our understanding of the effects of anthracycline exposure in childhood cancer survivors. Continued research on the late effects and ways to detect them early is needed to support consensus-based clinical recommendations.

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CHAPTER 1 – INTRODUCTION

Over the past few decades there have been significant improvements in overall 5-year survival rates among children with cancer, largely due to the introduction of new therapeutic strategies.[1,2] However, because of these improvements, an increasing number of childhood cancer survivors are at increased risk for health problems related to their treatment.[3] Numerous studies have reported on the late effects of chemotherapy and radiation in childhood cancer survivors.[4,5] Recent data from 20,227 participants in the Childhood Cancer Survivor Study demonstrated a 10.8-fold excess in all-cause mortality and 8.2-fold excess risk of death related to cardiac events in this population compared to their siblings.[4]

Radiation and certain chemotherapeutic agents can cause irreversible cardiac damage.[6] Although anthracyclines are some of the most effective chemotherapeutic agents in use, they are the most common class of agents associated with cardiotoxicity.[7] The most commonly used drugs in this class are doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone. Mortality rates as high as 20% have been attributed to anthracycline-induced cardiac failure.[8] The cardiotoxicity related to anthracyclines can be acute (within a week of infusion), early onset (progressive and occurring within 1 year after treatment), or late onset (occurring after the first year).[6] Late onset cardiotoxicity is attributed to myocyte damage and loss that leads to progressive left ventricular dilation, left ventricular wall thinning, and a decrease in contractility.[9] The ventricle must compensate for the diminishing ventricular contractility, producing a chronic elevation in left ventricular wall stress that promotes further damage. Although many survivors appear asymptomatic, those with anthracycline cardiotoxicity may experience acute cardiac failure during times of increased metabolic demands, such as acute viral infections, pregnancy, surgery, or heavy isometric exercise (e.g., weight lifting).[10-12] Thus, prevention as well as early recognition and treatment of cardiac abnormalities will allow patients to live longer, more symptom free lives, and minimize additional damage to the cardiovascular system.[6]

This dissertation utilizes different screening techniques to explore the cardiac and morbidity-related late effects of anthracycline exposure in childhood cancer survivors, and seeks to estimate the proportion of early cardiac events that may be preventable through exercise intervention. Specifically, this dissertation will focus on three separate analyses:

1. **Research Question:** How does the heart muscle function, as detected by exercise echocardiography, differ in pediatric cancer survivors treated with different doses of anthracyclines compared to cancer survivors not treated with anthracyclines? **Study Design:** A cross-sectional clinical study of childhood cancer survivors at least five years off therapy. **Outcome:** Cardiac function (continuous) measured through various exercise echocardiography techniques. **Exposure:** Cumulative lifetime anthracycline dose (ordinal: none, low, moderate, high).
2. **Research Question:** How do the Pediatric Quality of Life Inventory (PedsQL) scores of long-term childhood cancer survivors differ with varying anthracycline exposure? Is this association modified by physical activity level? **Study Design:** A cross-sectional clinical study of childhood cancer survivors at least five years off therapy. **Outcome:** PedsQL Generic Core scale scores in physical, emotional, social, school, and total domains (continuous). **Exposure:** Cumulative lifetime anthracycline dose (ordinal: none, low, moderate, high).
3. **Research Question:** What, if any, indirect effect does exercise deconditioning have on the relationship between treatment with anthracyclines and late cardiac outcomes in pediatric cancer survivors? **Study Design:** A cohort study of cancer survivors free from cardiac abnormalities in 2003 that are followed through 2007. **Outcome:** Self-reported cardiac outcome occurring after the 2003 survey through 2007. **Exposure(s):** Anthracycline exposure (dichotomous) and exercise deconditioning (dichotomous) as measured in 2003.

Better understanding the late effects that these commonly-used chemotherapy drugs have on cardiac function and quality of life may open opportunities for more effective screening and intervention programs. By identifying new screening and prevention techniques, it may be possible to reduce the morbidity and mortality associated with anthracycline cardiotoxicity.

CHAPTER 2 – LITERATURE REVIEW

CHILDHOOD CANCER

In 2009, 14,023 children and adolescents younger than 20 years of age were diagnosed with cancer in the United States.[13] Over the past several decades, there have been significant improvements in overall 5-year survival rates among children with cancer, largely due to the introduction of new therapeutic strategies.[14] The 5-year survival rate for childhood malignancies is 79%, resulting in more than 300,000 long-term survivors of childhood cancers currently alive in the United States and this number is increasing.[15-17]

However, because of these improvements in survival, an increasing number of childhood cancer survivors are at increased risk for health problems related to their treatment.[3] Numerous studies have reported on the late effects of chemotherapy and radiation in childhood cancer survivors.[4,16,18,19] Mertens, *et al*. (2001) demonstrated an 18.8-fold excess in all-cause mortality and an 8.2-fold excess risk of death related to cardiac events in a cohort of 20,227 participants in the Childhood Cancer Survivor Study.[4] Additional analysis of these data showed that 73% of long-term survivors had a chronic illness and 42% had a severely disabling, life threatening, or fatal condition such as cardiovascular disease, stroke, kidney failure, or a second malignancy.[16] Compared with sibling controls, the long-term cancer survivors had a 10-fold higher rate of cardiovascular disease and a 15-fold higher rate of heart failure. Similar findings have been noted in studies of long-term survivors of childhood cancer from the Nordic countries.[18]

ANTHRACYCLINES

Anthracyclines are well-established, highly efficacious, and common antineoplastic agents used for various hematological cancers and solid tumors.[20-22] They have been used extensively in cancer treatment protocols since the late 1960s and are currently used in many

pediatric treatment protocols.[23] More than 50% of childhood cancer survivors in the United States have likely been treated with anthracyclines in the past.[24,25]

The main anthracyclines approved by the Food and Drug Administration for clinical uses are doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone.[20,26] Doxorubicin and daunorubicin are natural compounds isolated from the actinobacterium *Streptomyces peucetius* var. *caesius*.[27,28] Epirubicin (4'-epidoxorubicin)[29,30] and idarubicin (4-demethoxy-daunorubicin)[31,32] are synthetic analogues of doxorubicin and daunorubicin, respectively. Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics rather than anthracyclines; however, it is typically included with the anthracycline family because of its structural and cardiotoxic similarities.[33]

Anthracyclines belong to the class of antineoplastic antibiotics that act on DNA at every phase of the cell cycle, thus interfering with cell replication.[34] They are administered only intravenously and result in a range of toxicity including myelosuppression, mucositis, and hair loss.[34] The greatest attention, however, is given to the cardiotoxicity of these chemotherapeutic agents.[34-40] Regardless of their toxicities, nearly 60% of all children diagnosed with cancer are currently treated with anthracyclines.[34]

ANTHRACYCLINE CARDIOTOXICITY

Despite their success as antineoplastic agents, the use of anthracyclines is limited due to their known dose-dependent[35,39] cardiotoxicity.[21,41-49] The association between cardiomyopathy and anthracyclines has been noted since the late 1960s when detrimental cardiac outcomes of doxorubicin-treated patients with childhood leukemia were reported.[50] Anthracyclines, in addition to mediastinal and neck radiation, are the most common causes of therapy-related cardiovascular complications. However, other chemotherapeutic agents such as ifosfamide, cisplatin, carmustine, busulfan, mechlorethamine, high-dose cyclophosphamide,[51] and mitomycin may also be associated with cardiotoxicity.[52] Stem-cell transplantation has also been associated with

pulmonary complications, including idiopathic pneumonia syndrome and bronchiolitis obliterans.[51]

The pathogenesis of anthracycline-induced cardiotoxicity is not well understood, though there have been a number of molecular mechanisms proposed.[53,54] The mechanisms most widely accepted involve the formation of free radicals that lead to oxidative stress.[34] Because of their highly oxidative metabolism and low levels of antioxidant enzyme defenses, cardiac cells are particularly susceptible to free radical damage.[55] However, the inability to separate primary mechanisms of toxicity from secondary molecular events have hindered the development of cardio-protective agents and less cardiotoxic analogs of the currently used anthracyclines.[56]

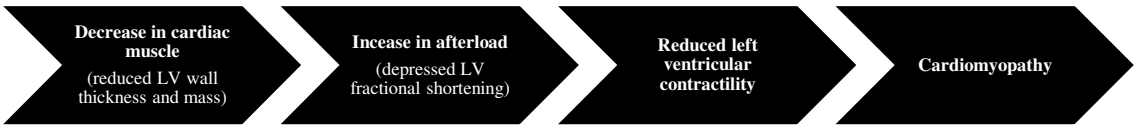
Anthracycline cardiotoxicity is often divided into three types of damage: acute, early onset chronic progressive, and late onset chronic progressive.[34] Acute cardiotoxicity is a depression of myocardial function that occurs immediately following, or within a week of, infusion of the drug. Early onset chronic progressive cardiotoxicity is characterized by myocardial dysfunction that occurs during treatment or within the first year after the end of therapy. Both acute and early onset chronic progressive cardiotoxicities are dose- and schedule-dependent.[57] Late onset chronic progressive cardiotoxicity is observed more than one year after the end of therapy[58-62] and correlates with the administered lifetime cumulative dose of anthracyclines.[58] Late cardiotoxicity may not be apparent until decades after the administration of anthracyclines.[9,63,64]

Cardiotoxicity can be subclinical or can be diagnosed as overt clinical heart failure.[34,65] Subclinical findings are any abnormalities detected through various diagnostic techniques in asymptomatic patients. Once symptomatic, recovery from clinical heart failure occurs very rarely.[66] Treatment of anthracycline cardiomyopathy involves standard medical therapy for heart failure including diuretics for volume overload, ACE inhibition, and beta-blockage.[20]

Anthracycline cardiotoxicity can manifest as cardiomyopathy with or without overt congestive heart failure, pericarditis, valvular heart disease, premature coronary artery disease,

endothelial dysfunction, or arrhythmias.[51,52] The most common clinical pathway of anthracycline cardiotoxicity in childhood cancer survivors is depicted in Figure 2.1. Patients typically have reduced left ventricular mass and wall thickness, mass index, and ventricular compliance which makes them susceptible to other cardiac stressors.[62] Reduced left ventricular wall thickness and mass, relative to body surface area, is indicative of decreased cardiac muscle, which increases afterload (measured as a depressed left ventricular fractional shortening) and results in reduced contractility ultimately leading to the development of cardiomyopathy.[40,64,67-69] Cardiomyopathy can then manifest as congestive heart failure due to left ventricular systolic dysfunction (i.e. left ventricular dilation and left ventricular ejection fraction depression).[60]

FIGURE 2.1: Typical clinical cascade of anthracycline cardiotoxicity in childhood cancer survivors



LV = Left ventricular

Our understanding of the cardiovascular outcomes related to low dose anthracycline chemotherapy regimens is limited.[70-76] Studies of late onset anthracycline cardiotoxicity in childhood cancer survivors have shown that doses as low as 100 g/m^2 increase the risk of higher afterload and reduced shortening fraction.[69,77]

FREQUENCY OF ANTHRACYCLINE CARDIOTOXICITY

Long-term data from childhood cancer survivors exposed to anthracyclines demonstrate that cardiotoxicity incidence within 15 years after chemotherapy may be as high as 71%.[62] The incidence of specific anthracycline-induced cardiac abnormalities varies according to the population studied and formal estimates of the national or worldwide prevalence of anthracycline cardiotoxicity are lacking. The lack of uniformity in detecting and reporting cardiac events and the necessity of evaluating a large number of patients with long follow-up after primary treatment make such estimates difficult.[56,78,79]

The frequency of clinical anthracycline cardiotoxicity in children varies widely by the amount of cumulative anthracycline exposure and time since exposure.[59,64,77,80-87] Regardless of time since exposure, clinical evidence of anthracycline cardiotoxicity typically presents as overt congestive heart failure and occurs in up to 30% of patients receiving cumulative doxorubicin doses of >550 mg/m^2.[40,62,88] These events are much less frequent (0.01% to 0.27%) in those treated with lower cumulative doses. Van Dalen *et al*.[87] recently studied 830 children treated with a mean cumulative anthracycline dose of 288 mg/m^2 and a mean follow-up time of 8.5 years after first dose. In their study, they found a cumulative incidence of clinical heart failure of 2.5% and the risk increased with time from 2% at 2 years to 5.5% at 20 years after treatment. As expected, they also confirmed that the risk of developing clinical heart failure was dose-dependent, increasing from 0% for those treated with up to 150 mg/m^2 of anthracyclines up to 14.3% for those treated with 600 mg/m^2.

Similarly, the frequency of subclinical cardiotoxicity varies widely by study. Numerous cross-sectional and longitudinal studies indicate that patients treated with high doses of anthracyclines (≥300 mg/m^2) are at increased risk of exhibiting subclinical cardiovascular dysfunction when compared to those not exposed to anthracyclines.[11,24,40,62,68-73,75,76,86,89-95] Table 2.1 shows the results of various studies investigating the prevalence of subclinical cardiac outcomes among anthracycline-treated pediatric cancer survivors.

TABLE 2.1: Summary of studies on the prevalence of subclinical outcomes in childhood cancer survivors exposed to anthracyclines

Source	n	Anthracycline Dose (mg/m^2)	Time since treatment (years)	Frequency of outcome
Lipshultz, *et al*. [40]	115	Range: 45-50	Median: 6.4 Range: 1-15	57% had abnormal afterload (end-systolic wall stress more than 2 SD above the mean for age in normal population) or contractility (relation between end-systolic wall stress and velocity of shortening less than -2)
Steinherz, *et al*.[62]	201	Median: 450 Range: 200-1275	Median: 7 Range: 4-20	23% had SF <25%
Hudson, *et al*. [77]	278	Median: 202	Median: 9 Range: 3-18	13.6% had SF <28% 13.8% had afterload >74 g/cm^2
Pein, *et al*.[86]	205	Mean: 333 Range: 40-600	Mean: 18	6% had SF <25% 8% had EF <50%
Roodpeyma, *et al*.[96]	58	Median: 128.5 Range: 30-557	Median: 9 Range: 5-20	50% had either EF <55% or SF <30%

SD = Standard deviations; SF = shortening fraction; EF = ejection fraction

The incidence of cardiac abnormalities detected by echocardiogram or radionucleotide angiography has been shown to increase with time since treatment.[3,64,97] Lipshultz *et al*.[64] demonstrated that previous exposure to anthracyclines induces a progressive long-term decrease in cardiac function even among patients who received doses less than 300 mg/m^2.

RISK FACTORS FOR ANTHRACYCLINE CARDIOTOXICITY

One of the strongest predictors of anthracycline cardiotoxicity is the total lifetime cumulative dose administered.[8,22,98] Although any dosage of anthracyclines is associated with cardiac damage,[64] doses of >400 mg/m^2 are associated with the greatest risk.[8,98] Currently, the maximum lifetime cumulative dose that is recommended is 550 mg/m^2.[64] However, susceptibility is largely individual and a subset of patients develop cardiomyopathy even at low anthracycline doses.[47]

In addition to the total cumulative dose, the incidence of both early and late onset cardiotoxicity may be associated with the rate of administration of the anthracyclines during each infusion,[99] peak dose intensity, and the infusion schedule.[9,70,73,99-101] Anthracyclines used in combination with other cardiotoxins such as mediastinal radiation therapy can exacerbate the risk for cardiac injury.[86] In some studies, an increase of late cardiotoxicity incidence has been seen in relation to follow-up time,[40,59,68,102,103] with longer time since completion of treatment being an independent risk factor of late increased afterload.[9,59,84]

Patient-specific risk factors for anthracycline cardiotoxicity include age at time of treatment, female gender, African American ancestry, and genetic factors including trisomy 21.[24,40,64,99,104,105] Younger age at the start of chemotherapy is associated with the thinning of the left ventricular wall which can lead to afterload increases.[9,62,64,70] Female sex has been found to be an independent risk factor for late cardiotoxicity.[68] One hypothesis for why this occurs is that women's myocardial cells retain higher concentrations of anthracyclines, which are poorly absorbed by body fat.[9,106] In addition to the increased risk of idiopathic cardiomyopathy among people of African American ancestry,[107-109] they also have an increased risk of developing anthracycline-induced cardiomyopathy as compared to whites .[24] High inter-patient variability in development and progression of anthracycline-induced cardiomyopathy suggests that genetic factors play a role in anthracycline metabolism and eventual toxic effects.[110]

The risk of anthracycline cardiotoxicity is increased by pre-existing cardiovascular disease or cardiac risk factors.[110] Children with existing hypertension, ischemic, myocardial and valvular heart disease, and drug hypersensitivity are at an increased risk for developing more severe complications due to anthracycline administration. Co-morbid conditions such as diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, and pregnancy also increase the risk for late-onset anthracycline cardiotoxicity.[110]

SCREENING FOR ANTHRACYCLINE CARDIOTOXICITY

Because anthracycline cardiotoxicity is such a serious side effect of treatment, varies widely by individual, and increases over time, the early detection and continued monitoring of cardiotoxic side effects is essential to avoid further cardiac injury and ensure early treatment. There have been no prospective, randomized clinical trials to compare different cardiac monitoring techniques to determine evidence based guidelines for routine monitoring of anthracycline cardiotoxicity.[20,110] Endomyocardial biopsy is considered the most sensitive indicator of chronic anthracycline cardiotoxicity. Due to its invasive nature, however, it cannot be recommended for routine monitoring.[111] Elevation of biochemical markers such as atrial and brain natriuretic peptides (BNP) and cardiac toponin-T (cTnT) have been suggested as having the potential to serve as surrogates for myocardial injury.[112-116] The diagnostic value of these biomarkers in the early assessment of subclinical anthracycline cardiotoxicity remains elusive.[22] Currently, the most common methods utilized in the detection of clinical or subclinical anthracycline-induced cardiomyopathy are multiple gated acquisition (MUGA) scans or resting echocardiography.[40,45,62,117-120]

Serial monitoring of cardiac function in children receiving anthracyclines permits early identification of heart damage.[34,104] Recently, the Children's Oncology Group (COG) provided recommendations for screening and management of late effects in survivors of pediatric malignancies.[121] The recommended frequency and timing of tests depends on the child's age at time of exposure, cumulative lifetime dose of anthracyclines, chest irradiation, pre-existing cardiac abnormalities, symptoms, and other stressors.[122] Although these recommendations provide much-needed guidance to clinicians who are following childhood cancer survivors, comparison studies of the efficacy and cost-effectiveness of different modalities have never been conducted.

Although no formal evidence-based guidelines exist, much work has been done to establish the existing recommendations for periodic screening. A systematic review of literature

conducted by an expert panel convened by the American Society of Clinical Oncology in 2005 found that most studies that addressed screening for long-term cardiovascular effects in anthracycline-treated asymptomatic cancer survivors were cross-sectional or retrospective by design.[51] Despite these limitations, the knowledge gained from the continued monitoring of childhood cancer survivors is anticipated to help further refine future recommendations. Feasibility studies of new cardiac surveillance modalities would be valuable to clinicians treating patients with previous anthracycline exposure.[123,124]

M-Mode and Two-Dimensional Echocardiography

The serial noninvasive surveillance of anthracycline cardiotoxicity has traditionally centered on assessment of left ventricular systolic function using motion-mode (M-mode) studies and two-dimensional resting echocardiography.[88,96] By measuring dimensional changes and utilizing volume calculations, ejection phase indices, specifically shortening fraction and ejection fraction, can be calculated. Shortening fraction measures the proportion of diastolic dimension that is lost in systole. Ejection fraction quantifies the proportion of blood pumped out of the ventricle with each heartbeat. The dimensions used in calculating these values are shown in Table 2.2.

TABLE 2.2: Common measurements and calculations utilized for the assessment of left ventricular systolic function in M-mode and two-dimensional echocardiography

Measurement	**Description**
Intraventricular septum, end diastole (IVSd)*	A measure of the ventricular septum thickness at the end of diastole, obtained from the parasternal short axis or parasternal long axis views.
Left ventricular internal diameter, end diastole (LVIDd)*	The internal dimension of the left ventricle at the end of diastole measured from the parasternal short axis or parasternal long axis views.
Left ventricular posterior wall, end diastole (LVPWd)*	The posterior wall thickness at end diastole measured from the parasternal short axis or parasternal long axis views.
Intraventricular septum, end systole (IVSs)*	A measure of the ventricular septum thickness at the end of systole, obtained from the parasternal short axis or parasternal long axis views.
Left ventricular internal diameter, end systole (LVIDs)*	The internal dimension of the left ventricle at the end of diastole measured from the parasternal short axis or parasternal long axis views.
Left ventricular posterior wall, end systole (LVPWs)*	The posterior wall thickness at the end of diastole measured from the parasternal short axis or parasternal long axis views.
Shortening Fraction (SF)	The fraction of any diastolic dimension that is lost during systole. $$SF = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$
Ejection Fraction (EF)	The fraction of blood pumped out of the ventricles with each heartbeat. Ejection fraction can be measured/calculated in various ways. In this study we used the Teichholz M-mode formula:[125,126] $$EF = \frac{\text{LV end-diastolic volume} - \text{LV end-systolic volume}}{\text{LV end-diastolic volume}} \times 100$$ where: $$\text{LV end-diastolic volume} \approx \frac{7(LVIDd)^3}{2.4 + LVIDd}$$ $$\text{LV end-systolic volume} \approx \frac{7(LVIDs)^3}{2.4 + LVIDs}$$
Left ventricular outflow tract diameter (LVOT diameter)†	A measurement of the diameter of the aortic valve annulus, which is used in the estimation of stroke volume and cardiac output. In 2D mode, parasternal long axis view, the aortic valve annulus diameter (A) is measured in systole between the outflow tract anterior and posterior endocardiums, immediately below the attachments of the anterior and posterior aortic valve leaflets.
Aortic valve area (LVOT area)†	An estimation of the area of the aortic valve utilizing the left ventricular outflow tract diameter measurement: $$\text{LVOT area} = 2\pi\left(\frac{\text{LVOT diameter}}{2}\right)^2$$

*Measurement from echocardiography M-mode image

†Measurement from two-dimensional echocardiography image

While these measures are frequently used in the cardiac monitoring of childhood cancer survivors treated with anthracyclines, they are subject to a number of limitations. These parameters are insensitive to the detection of subtle myocardial changes that occur in early cardiotoxicity. To detect a change in the global systolic function these measures require a certain amount of damaged, dysfunctional myocardium.[62,113,117,127-132] At the point when these parameters allow detection of dysfunction, further deterioration proceeds rapidly and is usually irreversible.[67,133,134] In addition, shortening fraction and ejection fraction are both dependent on ventricular loading conditions.[127,128,135-137] Loading conditions can be affected by a number of factors including fever, anemia, and sepsis, all of which may mask real changes in cardiac contractility.[7]

Doppler Echocardiography

Doppler echocardiography uses ultrasound to measure the velocity of moving red blood cells as a noninvasive way to assess hemodynamics. Doppler echocardiography can be used to measure the direction, velocity, and turbulence of blood flow across valves, within cardiac chambers, and through the vessels. The commonly measured and calculated parameters obtained from Doppler echocardiography are summarized in Table 2.3.

TABLE 2.3: Common parameters obtained from Doppler echocardiography

Measurement	**Description**
Aortic velocity time integral (LVOT VTI)	An estimate of the velocity of blood flow through the aortic valve. The amount of blood going through the aortic valve is given by the VTI of flow, obtained by tracing the pulsed Doppler left ventricular outflow tract signal's envelope.
Left ventricular outflow tract heart rate (LVOT HR)	A measure of heart rate obtained from the pulsed Doppler left ventricular outflow tract signal.
Mitral inflow E-wave velocity (E)	The velocity of blood flow through the mitral valve during early rapid filling of diastolic flow. Obtained from the pulsed wave Doppler left ventricular inflow tract signal of the apical 4-chamber view.
Mitral inflow A-wave velocity (A)	The velocity of blood flow through the mitral valve during the atrial contraction phase of diastolic flow. Obtained from the pulsed wave Doppler left ventricular inflow tract signal, of the apical 4-chamber view.
Grading of ventricular diastolic dysfunction (E/A)	A measure used to determine the level diastolic dysfunction. $$E/A = \frac{E}{A}$$ • *Normal diastolic function (0 <E/A ≥2)* • *Impaired relaxation (E/A <0)* • *Pseudo normal (E/A >0 but relaxation pattern is abnormal on pulmonary vein pulse wave Doppler)* • *Restrictive filling (E/A >2)*
Deceleration time (DT)	The time taken from the maximum E point to baseline.
Stroke Volume (SV)	The volume of blood that the heart ejects with each beat. $$SV = \text{LVOT VTI} \times \text{LVOT area}$$
Stroke Index (SI)	The stroke volume, relative to a patient's body size. $$SI = \frac{SV}{BSA}$$
Estimated Stroke Work (SW)	$$SW \approx \frac{SI}{MAP}$$
Cardiac output (CO)	The amount of blood pumped by each of the ventricles per minute. $$CO = SV \times HR$$
Cardiac Index (CI)	The cardiac output, relative to a patient's body surface area (BSA). $$CI = \frac{CO}{BSA}$$

Doppler echocardiography allows the indirect assessment of systolic and diastolic function. Several studies have suggested that diastolic dysfunction precedes systolic dysfunction and perhaps monitoring diastolic function via Doppler echocardiography may improve early detection of anthracycline cardiotoxicity.[51,138-140] Doppler echocardiography measures have been successfully applied in several clinical settings, appearing reliable in the quantification of myocardial relaxation and systolic performance.[141] Early changes in left ventricular myocardial function of cancer patients were found by pulsed Tissue Doppler early after (1-3 months) and further after (3.5 ±0.6 years) doxorubicin therapy (cumulative dose of 211 ±82 g/m^2). In these patients, myocardial systolic dysfunction was evident on Doppler imaging even in the presence of a normal ejection fraction.[139,142] However, other studies looking at left ventricular function using Doppler echocardiography in the detection of subclinical anthracycline cardiomyopathy have not been consistent with these findings.[40,62,143,144]

A commonly used indirect index to quantify diastolic dysfunction is the early peak flow velocity/atrial velocity ratio (E/A ratio). Evaluation of mitral valve inflow Doppler has demonstrated decreased peak E and increased A-phase filling velocities with decreased E/A ratios in patients treated with anthracyclines even in the presence of normal shortening fraction.[145,146] Though, it should be noted that this standard Doppler measurement is influenced by the preload, afterload, frequency, atrioventricular delay, ventricular interaction, viscoelastic properties, and pericardial limiting factors.[146]

Tissue Doppler and Strain Rate Imaging

Tissue Doppler imaging (TDI) measures the velocity of regional myocardial wall motion, which may help in the early detection of local abnormalities before global dysfunction is apparent.[139,142,146-150] Additionally, in the evaluation of diastolic performance, TDI is more reliable than conventional Doppler because it is less influenced by loading conditions, tethering, translational artifact, and traction.[119,151-154] The velocity of myocardium is several magnitudes

lower than the velocity of moving red blood cells. In TDI, the principles of Doppler echocardiography are used to quantify the higher amplitude, lower velocity signals of myocardial tissue motion. Tissue Doppler methods help define the extent of either mitral annular or ventricular wall motion, independent of intra-cardiac flow velocity. The relationship between the two may be useful for defining diastolic pressure elevation or identifying abnormalities in ventricular contraction or diastolic relaxation.

Tissue Doppler velocities cannot differentiate between active contraction and passive motion, a limitation when assessing regional myocardial function.[155] Strain rate imaging on the other hand, corresponds to the rate of regional myocardial deformation. Regional strain represents the percent of deformation (fractional change in length) caused by an applied force and is calculated by integrating the strain rate curve over time during the cardiac cycle. Strain measures the total amount of deformation in either the radial or the longitudinal direction. Strain rate calculates the velocity of shortening.

Both TDI and strain rate imaging may be more sensitive in characterizing diastolic left ventricular relaxation.[39,117,134,148-150,156-164] Yet, limited data are currently available on the usefulness of these techniques when evaluating patients exposed to anthracyclines.

A variety of cardiac conditions that can cause subclinical impairment of left ventricular contractility have been evaluated using TDI including coronary disease, hypertrophic cardiomyopathy, arrhythmias, hypertensive heart disease, and myocardial storage disorders.[132,150,165-171] TDI has also been used for the detection of allograft rejection in heart transplant recipients.[151,172]

Neilan *et al*. (2006)[173] examined a murine model of doxorubicin-induced cardiac injury and showed that TDI-derived parameters can detect left ventricular dysfunction prior to alterations in conventional indices (e.g., heart rate, left ventricular end-diastolic pressure, or blood pressure). The TDI parameters correlated with invasive hemodynamic measures and histological evidence of cardiac apoptosis, while the ejection fraction and shortening fraction measures did

not. Moreover, the TDI parameters predicted development of late cardiac dysfunction and mortality after treatment with doxorubicin.

In a population of anthracycline-treated children, conventional echocardiography failed to show any decline in left ventricular ejection fraction or shortening fraction after the first two cycles of treatment, even though myocardial deformation parameters from strain rate imaging techniques had already changed.[129] Regional left ventricular strain rate and systolic strain were reduced within two hours after the first dose of anthracycline in both the longitudinal and radial directions. Similarly, in a study of 56 childhood cancer survivors, late (median of 5.2 years after completion of therapy) radial and longitudinal myocardial strain was reduced by 15% in patients compared to controls while ejection fraction remained within normal limits. Several other studies have added convergent data on the usefulness of TDI for detecting subclinical myocardial damage in apparently healthy survivors. [23,119,139,142,149,162,174-178] Many of these studies were limited, at least in part, by the number of enrolled patients and the variable length of follow-up. Thus, further studies are needed to determine the most feasible TDI parameters and their cutoff values. [134] Furthermore, more clinical research and larger trials are necessary in order to evaluate the prognostic role of TDI parameters in childhood cancer survivors.

Exercise Stress Testing

Exercise stress testing has been reported as a promising test of cardiac function.[74,85,88,179-181] Exercise testing has the potential to reveal abnormalities that are not seen on resting studies.[52] Both anthracycline-induced cardiomyopathy and radiation-induced cardiovascular disease are associated with exercise decompensation. Signs of ischemia and significant coronary artery disease were found to be highly prevalent on exercise imaging of adult Hodgkin's lymphoma survivors treated with mediastinal radiation.[182] Exercise echocardiography has also been used to identify asymptomatic individuals at high risk for acute myocardial infarction or sudden death.[182] Thus exercise stress testing, with or without imaging, can be a useful screening tool.[52]

Doppler echocardiography with exercise or pharmacologic stress has also been shown in asymptomatic children previously treated with anthracyclines to uncover small decreases in systolic function or decreased systolic reserve.[74,183-186] Additionally, dobutamine stress echocardiography has been examined in several studies to detect subclinical abnormalities of left ventricular function induced by anthracycline cardiotoxicity.[183,187-193] However, the findings of these studies appear to be insufficient or are viewed as controversial. Lansarini *et al*.[193] found that among young oncologic patients who had undergone high dose anthracycline therapy (>400 mg/m^2), no significant modifications during the modified/accelerated dobutamine protocol were found compared to the left ventricular structure and functional findings at rest. On the other hand, Hamada *et al* (2006)[183] found evidence of altered posterior wall thickness, factional shortening and E/A ratios during the dobutamine protocol in asymptomatic patients treated with high dose anthracyclines.

PREVENTION

Measures used to mitigate or prevent anthracycline-induced cardiac damage include setting limits on lifetime cumulative and peak doses, and use of pharmacologic agents in conjunction with anthracycline administration. There is evidence that concomitant use of dexrazoxane, a cardio-protective agent approved by the Food and Drug Administration in 2007 for use with anthracyclines, significantly reduces the risk of cardiac damage.[42,67] Studies in long-term survivors also showed that enalapril, an ACE inhibitor, may prevent cardiac deterioration on a short term basis, but the benefits are not sustained.[67]

For childhood cancer survivors who do not benefit from cardio-protective strategies during treatment, secondary and tertiary prevention of cardiac disease should be considered.[194] These non-pharmacologic strategies include traditional “heart healthy” lifestyle changes.[110,195] Smoking avoidance, daily physical activity, healthy diet, moderate alcohol consumption, and attaining a healthy weight have been found to dramatically reduce the risk of coronary heart

disease events.[196] These preventive measures may be of particular benefit to cancer survivors,[110,197,198] but there is limited scientific evidence on the effects of a modified diet and lifestyle in patients specifically exposed to anthracyclines.[105,199,200]

RISK FACTORS FOR NON-ANTHRACYCLINE-INDUCED CARDIOMYOPATHY IN SURVIVORS

Long-term childhood cancer survivors are at increased risk of developing heart failure secondary to anthracycline-induced cardiomyopathy.[201] Survivors have been found to be less physically active, which may be due to advice from physicians or protective parents. This approach leads to an often unnecessary sedentary lifestyle associated with obesity, skeletal muscle atrophy, diminished exercise tolerance, and subsequently a heightened risk of premature cardiovascular disease.[40,192,202-214]

Reduced exercise tolerance is a universal phenomenon in long-term cancer survivors, with maximal oxygen consumption averaging only 50% to 70% of an age- and gender-matched normal population.[206] The sedentary lifestyle of many childhood cancer survivors may also contribute to the conditions characteristic of metabolic syndrome, a common occurrence in this group.[207] Obesity is very common in survivors of childhood cancer[210] and compared to age-matched controls, this group is universally at risk of increased fasting plasma glucose and insulin levels, as well as type 2 diabetes.[215]

A growing body of literature shows that exercise interventions can help cancer survivors both during and after treatment. Exercise may attenuate the effects of treatment including anemia, pain, nausea, vomiting, and sleep disorders through mechanisms such as suppression of inflammatory response, as well as improved insulin sensitivity, protein syntheses, and antioxidant activities.[216-219] Other potential benefits of exercise in cancer patients include improved functional capacity and cardiopulmonary function with concomitant decreases in depression, fatigue, and other symptoms in cancer survivors both during and following treatment.[220-225] In long-term

cancer survivors, there is also evidence that there are considerable advantages to regular moderate exercise including improvements in aerobic power and maximum oxygen uptake, blood lipid levels and glucose tolerance, as well as an enhanced sense of psychological and physical well-being, leading to an improved overall quality of life.[226-228]

QUALITY OF LIFE AMONG CHILDHOOD CANCER SURVIVORS

There is a growing interest in assessing health related issues outside the purview of only the physical well-being in childhood cancer survivors.[229] To date, studies have yielded varying results and have often led to contradictions across reports.[230] Generally though, data show that childhood cancer survivors have overall good physical, psychological, and social health.[231] Reviews focusing specifically on psychological or social well-being of childhood cancer survivors find that survivors do not differ from controls in terms of anxiety, depression, or self-esteem.[232,233]

A recent analysis of the Childhood Cancer Survivor Study found that survivors were more likely than their siblings to report symptoms of global distress and poorer physical health, but did not differ in the health-related quality of life (HRQoL) emotional domains.[234] However, certain groups of childhood cancer survivors were at higher risk for psychological distress, neurocognitive dysfunction, and poor HRQoL.[231-234] Additionally, certain subgroups continue to report problems such as pain, fatigue, depression, mood disturbances, tension, anger, confusion, anxiety, lack of friends and involvement in social activities, difficulties in obtaining work or health insurance, and lower rates of marriage and parenthood.[231-233] These findings suggest a need for targeted interventions for groups at highest risk for adverse quality of life and HRQoL outcomes.

CHAPTER 3 – DISSERTATION GOALS AND DATA SOURCES

DISSERTATION GOALS

The overall goal of this dissertation is to explore cardiac and morbidity-related late effects of anthracyclines in childhood cancer survivors utilizing different screening techniques, and estimate the proportion of cardiac events preventable through exercise intervention. Specifically, the following research questions will be examined:

1. How does heart muscle function, as assessed by exercise echocardiography, differ in pediatric cancer survivors treated with different doses of anthracyclines compared to cancer survivors not treated with anthracyclines?
2. How do the Pediatric Quality of Life Inventory (PedsQL) scores of long-term childhood cancer survivors differ with varying anthracycline exposure? Is this association modified by physical activity level?
3. What, if any, indirect effects does exercise deconditioning have on the relationship between treatment with anthracyclines and late cardiac outcomes in pediatric cancer survivors?

DATA SOURCES

This research used data from two separate sources. The first two research questions of this dissertation were answered using original data collected from a clinical study of exercise echocardiography results among childhood cancer survivors treated with and without anthracyclines. The third research question was answered utilizing data from the Childhood Cancer Survivor Study.

Childhood Cancer Survivor Exercise Echocardiography Study

This was a cross-sectional study of long-term childhood cancer survivors treated with anthracyclines and followed at Children's Healthcare of Atlanta (CHOA). Exercise echocardiography with Doppler imaging was conducted on cancer survivors with varying degrees of cumulative lifetime exposure to anthracyclines. This study was conducted in collaboration with the Aflac Cancer Center and the Sibley Heart Center at CHOA. Patients were identified from data maintained through the tumor registrar and the Cancer Survivor Program at CHOA. Exercise echocardiography was performed through the Sibley Heart Center at CHOA. Funding was provided through an Emory-Egleston Children's Research Center (EECRC) grant as well as CHOA philanthropic research donations from the Scott Hudgens Family Foundation. The study was reviewed and approved by the Emory Institutional Review Board.

Recruitment and enrollment occurred from March 2010 through September 2011. Patients were recruited in one of two ways. The first recruitment was carried out during routine clinic visits to the CHOA Cancer Survivor Program. As patients came in for their previously scheduled cancer survivor routine follow-up appointment, they were approached by study staff, consented, and scheduled for an exercise echocardiogram. As the patients routinely followed by the Cancer Survivor Program may differ from those who are not followed, we also recruited participants from a random sample of all cancer survivors treated at CHOA, regardless of follow-up status. With this approach eligible patients were identified through abstracted medical records and contacted via a letter mailed to their last known address. A member of the study team conducted follow-up phone calls to recruit participants and schedule exercise echocardiogram appointments. Informed consent for these patients was obtained at the beginning of their cardiac examination.

To be eligible for this study, patients must have met the following criteria:

- Confirmed malignancy

- Completed cancer treatment at least five years prior to their scheduled echocardiogram
- Alive at the time of the study
- No evidence of current malignancy
- Age 8 to 21 years at time of exercise echocardiogram
- English or Spanish speaking
- No history of radiotherapy with potential impact to the heart
- No diagnosis of trisomy 21
- At least 125 cm in height (for use of exercise bicycle)
- No known acute or chronic respiratory conditions or other conditions precluding safe use of exercise bicycle
- No cardiac symptoms, or known cardiomyopathy
- Not pregnant (self-reported) at time of study

Because we wanted to obtain a sample balanced on anthracycline cardiotoxicity risk status, we stratified the sample based on cumulative lifetime anthracycline exposure. The Children's Oncology Group (COG) currently makes Long Term Follow-Up (LTFU) recommendations on the frequency of resting echocardiogram or MUGA scans based on the patient's age at first anthracycline exposure, their cumulative lifetime dose, and presence of radiation with potential impact to the heart.[33] To focus study outcome measures on anthracycline exposure, patients with a history of radiation therapy with potential impact to the heart were excluded from this study. The COG LTFU Guidelines and the study's stratified risk status can be seen in Table 3.1.

TABLE 3.1: Children's Oncology Group long-term follow-up recommendations on the frequency of echocardiogram or MUGA scan

Age at Treatment*	Radiation with Potential Impact to the Heart	Anthracycline Dose (mg/m^2)†	Recommended Frequency	*Study Risk Status*
<1 year old	Yes	Any	Every year	*Not eligible*
	No	<200	Every 2 years	*Moderate*
		≥200	Every year	*High*
1-4 years old	Yes	Any	Every year	*Not eligible*
	No	<100	Every 5 years	*Low*
		≥100 to <300	Every 2 years	*Moderate*
		≥300	Every year	*High*
≥5 years old	Yes	<300	Every 2 years	*Not eligible*
		≥300	Every year	*Not eligible*
	No	<200	Every 5 years	*Low*
		≥200 to <300	Every 2 years	*Moderate*
		≥300	Every year	*High*
Any age with decrease in serial function			Every year	*Not eligible*

*Age at time of first cardiotoxic therapy (anthracycline or radiation whichever was given first)
†Based on doxorubicin isotoxic equivalent dose: doxorubicin (x1), daunorubicin (x0.833), epirubicin (x0.67), idarubicin (x5), mitoxantrone (x4)

Sample size estimation was performed using OpenEpi v2.3.[235] Data from the study by De Souza *et al*.[236] were used, where anthracycline-treated pediatric patients and healthy controls were examined by echocardiography and Doppler imaging during progressive exercise (Appendix I). The mean shortening fraction (SF) among controls in that study increased from 38 ±5 to 53 ±4 from rest to peak exercise, and increased from 38 ±6 to 48 ±7 for patients receiving low anthracycline doses (≤260 mg/m^2) and from 29 ±6 to 37 ±7 for patients receiving high anthracycline doses (≥260 mg/m^2). The mean velocity of circumferential fiber shortening (MVCFc) in the controls increased from 1.26 ±0.18 to 1.71 ±0.19 from rest to peak exercise and from 1.09 ±0.24 to 1.42 ±0.47 for patients receiving anthracyclines. Finally, the stress at peak systole (σPS) in the controls decreased from 73 ±31 to 50 ±13 from rest to peak exercise for all patients, from 73 ±22 to 66 ±19 for patients receiving low anthracycline doses, and from 104 ±28 to 104 ±42 for patients receiving high anthracycline doses.

From these data, and assuming a two-sided significance level of 0.05, 20 patients in the no risk profile group and 20 in each of the three anthracycline risk profile groups provide a minimum of 79% power to detect a difference in SF at peak exercise across all comparisons: >99% for controls vs. any risk group, 79% for controls vs. low risk group, >99% for controls vs. high risk group, and 99% for low vs. high risk groups. In addition, this sample size would have 97% power to detect a difference in MVCFc at peak exercise between the no risk group and any risk group (combined), and a minimum of 87% power to detect a difference in σPS at peak exercise across risk groups.

At their scheduled echocardiogram, patients were asked to complete two self-administered questionnaires. The first was a health behaviors questionnaire based on a subset of questions routinely obtained through either the Centers for Disease Control and Prevention's Youth Behavioral Risk Factor Surveillance System[237] or the Adult Behavioral Risk factor Surveillance System.[238] This questionnaire collected information on age, sex, race, ethnicity, school grade level, tobacco use, physical activity, and general health status (Appendix II). The second questionnaire was the Pediatric Quality of Life Inventory (PedsQL). The PedsQL Generic Core scales are multidimensional validated child self-report scales encompassing the domains of physical functioning (8 items), emotion functioning (5 items), social functioning (5 items), and school functioning (5 items). Participants were given the PedsQL 4.0 version most appropriate for their age group (i.e., 8-12, 13-17, or 18-5 years of age) (Appendix III). The PedsQL has a standard, easily-implemented scoring algorithm. The items of the four scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) are grouped together so it is easy to create Scale Scores. A Psychosocial Health Summary Score was calculated from each of the Emotional, Social, and School Functioning Scales. A Total Scale Score was calculated as the mean of all four Scales.

The baseline physical exam measurements included height, weight, heart rate (HR), blood pressure, and a baseline 12-lead electrocardiogram (ECG) to document normal sinus

rhythm. A standard resting echocardiogram was performed in the supine position using a GE Vivid 7 5 MHz probe.

Prior to the initiation of exercise, echocardiography was repeated with the patients in the upright position. Subjects then began pedaling at a cadence of 50-60 rpm on an electronically braked cycle ergometer (Corival Pediatric Ergometer). The initial and incremental workload was 25 Watts and was applied at 3-minute intervals. Echocardiography was performed at the 1.5-minute mark of each stage and at the termination of exercise. The MedGraphics Ultima™ CARDIO2 Cardiopulmonary Exercise System was utilized to continuously monitor ECG tracings and to obtain gas exchange values and aerobic indices. An inability to maintain 50 rpm, HR >85% predicted, or respiratory exchange ratio (RER) >1 was deemed an exhaustive effort. Though never needed, the safety protocol called for termination of studies if there were concerning changes on electrocardiogram, significant symptoms of shortness of breath or chest pain, severe hypertension or hypotension, or syncope.

Continuous heart rate, ECG, and blood pressure recordings were taken at rest and throughout the exercise protocol. A breath-by-breath metabolic measurement cart was utilized to obtain standard gas exchange values and aerobic parameters, including:

- Oxygen consumption (VO_2)
- Carbon dioxide output (VCO_2)
- Minute ventilation (VE)
- Respiratory exchange ratio (RER): VCO_2/VO_2

All echocardiography images were saved and analyzed offline using the GE EchoPAC™ Dimension ‘06 Software. Off-line measurements of the echocardiography measures were made later, removed from the time of data acquisition. Although the study personnel analyzing these images were aware of the patient’s inclusion in the study (and thus aware of their prior cancer diagnosis), they were blinded to subject risk status. The measurements obtained from this offline

analysis included the following: at rest, within each stage of exercise, and immediately post exercise (unless otherwise noted):

M-mode analysis of the left ventricle [parasternal short axis (PSS) or parasternal long axis (PSL)]:

- Intraventricular septum thickness, end diastole (IVSd)
- Intraventricular septum thickness, end systole (IVSs)
- Left ventricular posterior wall thickness, end diastole (LVPWd)
- Left ventricular posterior wall thickness, end systole (LVPWs)
- Left ventricular internal diameter, end diastole (LVIDd)
- Left ventricular internal diameter, end systole (LVIDs)
- Diameter of the aortic valve annulus (LVOT diameter)

Doppler blood flow analysis:

- Mitral inflow E-wave velocity (E) [apical 4-chamber view]
- Mitral inflow A-wave velocity (A) [apical 4-chamber view] – *rest only*
- Aortic velocity time integral (LVOT VTI) [apical 5-chamber view in LVOT]
- Left ventricular outflow tract heart rate (LVOT HR) [apical 5-chamber view in LVOT]
- Ejection time (ET) [apical 5-chamber view in LVOT]

Color TDI analysis (lateral mitral, septal, and lateral tricuspid annulus):

- Systolic septal velocity (Ss) [apical 4-chamber view]
- Systolic lateral velocity (Sl) [apical 4-chamber view]
- Systolic inferior velocity (Si) [apical 2-chamber view]
- Systolic anterior velocity (Sa) [apical 2-chamber view]
- Early diastolic septal velocity (Es) [apical 4-chamber view]
- Early diastolic lateral velocity (El) [apical 4-chamber view]

- Early diastolic inferior velocity (Ei) [apical 2-chamber view]
- Early diastolic anterior velocity (Ea) [apical 2-chamber view]
- Late diastolic septal velocity (As) [apical 4-chamber view]
- Late diastolic lateral velocity (Al) [apical 4-chamber view]
- Late diastolic inferior velocity (Ai) [apical 2-chamber view]
- Late diastolic anterior velocity (Aa) [apical 2-chamber view]

Strain Rate Imaging (natural strain using sample volumes of 5-10 mm) – *conducted at rest only*

- Radial strain (SR-S, SR-E, SR-A from LV short axis)
- Circumferential strain (SR-S, SR-E, SR-A from LV short axis)
- Longitudinal strain (SR-S, SR-E, SR-A from LV apical 4C)

Data were entered into a custom Microsoft Access database on personal computers and were thoroughly checked for completeness and correctness before and after entry. Once complete, the data were exported to the SAS® statistical software package for analysis.

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is an ongoing, multi-institutional cohort study designed to assess the late adverse effects following treatment for childhood and adolescent cancer. Detailed descriptions of the study design and early cohort characteristics have been published previously.[239] The CCSS consortium consists of 26 participating clinical centers in the United States and Canada (Table 3.2). Each participating institution identified all patients meeting the following eligibility criteria:

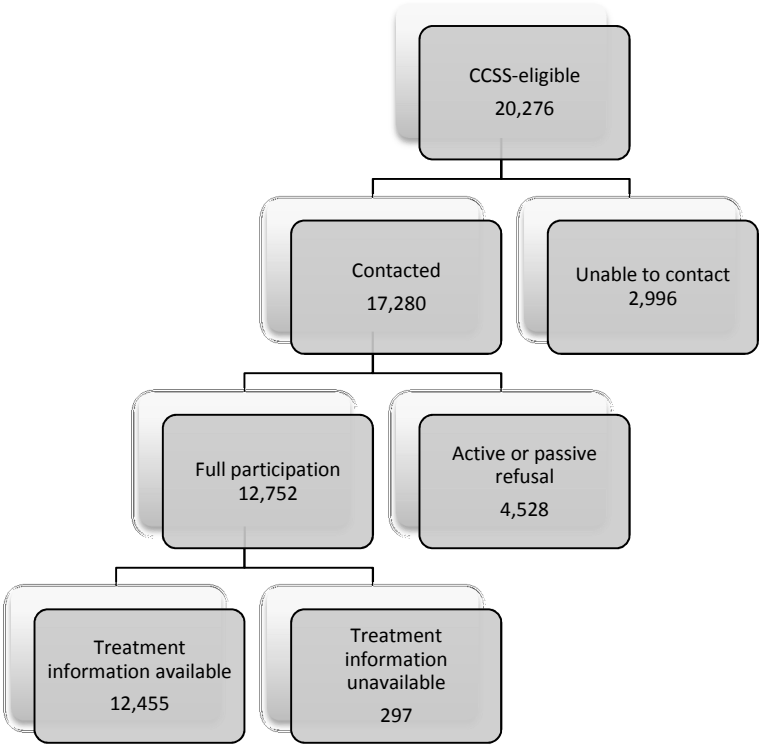
- Diagnosed and initially treated for leukemia, central nervous system malignancy (excluding meningioma and craniopharyngioma), Hodgkin disease, Non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer, or bone cancer
- Diagnosed between January 1, 1970 and December 31, 1986
- Less than 21 years of age at time of diagnosis
- Alive five years from the date of diagnosis, regardless of disease or treatment status
- English or Spanish speaking
- Resident of the United States or Canada at the time of initial follow-up

TABLE 3.2: Childhood Cancer Survivor Study clinical centers contributing cases

Institution	**Location**
University of California	San Francisco, CA
University of Alabama	Birmingham, AL
UT-Southwestern Medical Cancer	Dallas, TX
Dana-Farber Cancer Institute	Boston, MA
Texas Children's Cancer	Houston, TX
Children's Hospital and Medical Center	Seattle, WA
Roswell Park Cancer Institute	Buffalo, NY
Hospital for Sick Children	Toronto, ON
St. Louis Children's Hospital	St. Louis, MO
St. Jude Children's Research Hospital	Memphis, TN
University of Michigan	Ann Arbor, MI
Stanford University School of Medicine	Stanford, CA
Children's Hospital of Philadelphia	Philadelphia, PA
Children's Hospital	Denver, CO
Children's Health-Care	Minneapolis, MN
Columbus Children's Hospital	Columbus, OH
Children's National Medical Center	Washington, DC
Children's Hospital of Pittsburgh	Pittsburgh, PA
University of Minnesota	Minneapolis, MN
Children's Hospital Los Angeles	Los Angeles, CA
Memorial Sloan-Kettering Cancer Center New York	New York, NY
Mayo Clinic	Rochester, MN
U.T.M.D. Anderson Cancer Center	Houston, TX
Riley Hospital for Children	Indianapolis, IN
University of California-Los Angeles	Los Angeles, CA
Children's Healthcare of Atlanta/Emory University	Atlanta, GA

The initial contact and recruitment of eligible participants began in August 1994. Participants were sent a baseline questionnaire in the mail. For survivors who had died after achieving 5-year survivorship status, the questionnaire was sent to next of kin. The questionnaire consisted of 289 questions on demographics and socio-economic characteristics, medical care practices and prescription medications taken during the most recent two-year period, and medical conditions diagnosed by a doctor, including subsequent malignancies (Appendix IV). The cancer-related therapy received by each eligible participant was abstracted from medical records by trained data management staff at each institution. The cohort participation and exclusion numbers can be seen in Figure 3.1.

FIGURE 3.1: Participation of CCSS cohort



We used the most recent data obtained from the 2007 follow-up questionnaire. To obtain the data, we were required to submit a concept proposal to the Childhood Cancer Survivor Study workgroup. Once the Publications Committee reviewed and approved the concept proposal, we were given access to the data.

CHAPTER 4 –

ASSESSING CARDIAC FUNCTION IN ANTHRACYCLINE-TREATED CHILDHOOD CANCER SURVIVORS UTILIZING ADVANCED EXERCISE ECHOCARDIOGRAPHY TECHNIQUES

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ABSTRACT

Purpose: The surveillance for anthracycline cardiotoxicity in cancer survivors typically utilizes measures from resting M-mode and two-dimensional echocardiography. This study sought to determine whether exercise echocardiography helps unmask more subtle functional abnormalities to allow for earlier detection of subclinical cardiac dysfunction. **Methods:** Asymptomatic survivors at least 5 years post-treatment were recruited from a Cancer Survivor Clinic. Echocardiography was performed at rest and at termination of exercise utilizing tissue Doppler techniques and strain rate imaging. Adjusted mean values are reported. **Results:** Eighty survivors participated and were characterized by cardiotoxicity risk status (high: 12, moderate: 23, low: 24, no risk [controls]: 21) as defined by recommended echocardiography frequency in the Children's Oncology Group Long Term Follow-Up Guidelines. The high-risk group had a higher resting heart rate than controls (103 vs. 87 bpm [$p = 0.0285$]). The peak aerobic capacity in all groups was similar. However, the high-risk group had a lower peak oxygen pulse of 7.7 vs. 10.7 ml/beat ($p = 0.0118$). At rest, the high-risk group had evidence of diastolic dysfunction with septal early diastolic velocities (E/E') of 12.1 vs. 9.8 ($p = 0.0870$). However, with exercise, this difference resolved and myocardial contractile reserve was preserved. **Conclusion:** High-risk anthracycline exposed pediatric cancer survivors with normal resting systolic function have some evidence of diastolic filling abnormalities at rest. With exercise, they augment their systolic and diastolic function to achieve relatively normal maximal aerobic capacity despite impaired stroke volume. These data suggest that pediatric-aged survivors are able to compensate for mild cardiac functional abnormalities.

INTRODUCTION

The serial noninvasive surveillance of anthracycline cardiotoxicity has traditionally focused on assessment of left ventricular (LV) systolic function using M-mode and two-dimensional resting echocardiography.[88,96] By measuring dimensional changes and utilizing volume calculations, ejection phase indices such as shortening fraction (SF) and ejection fraction (EF), can be calculated. While these measures are frequently used in the cardiac monitoring of childhood cancer survivors treated with anthracyclines, they are subject to a number of limitations. First, these parameters are insensitive to the detection of subtle myocardial changes which occur in early cardiotoxicity because they only detect measureable changes in the global systolic function that take place in the presence of substantially damaged, dysfunctional myocardium.[62,113,117,127-132] At the point when these parameters allow detection of dysfunction, further deterioration proceeds rapidly and is usually irreversible.[67,133,134] Second, both SF and EF are dependent on ventricular loading conditions.[127,128,135-137] Loading conditions can be affected by a number of underlying health problems including fever, anemia, and sepsis, and these may mask real changes in cardiac contractility.[7]

Feasibility studies of new cardiac surveillance modalities would be valuable to clinicians treating patients with previous anthracycline exposure.[123,124] The aim of this study is to describe how the heart muscle function measured during exercise by novel echocardiography techniques such as Tissue Doppler Imaging (TDI) and Strain Rate Imaging (SRI) differs among pediatric cancer survivors treated with varying anthracycline doses and those who did not receive anthracyclines. Although this analysis is exploratory in nature, we hypothesize that subclinical cardiac dysfunction will be detected with these novel techniques in cancer survivors treated with anthracyclines, even at low lifetime cumulative doses, and that this dysfunction will demonstrate a dose-related response to anthracycline exposure.

METHODS

Study Design

Childhood cancer survivors followed through the Cancer Survivor Program at Children's Healthcare of Atlanta (CHOA) were enrolled in this study which involved exercise echocardiography with Doppler imaging at the Sibley Heart Center at CHOA, a health status questionnaire, and a physical exam. The study was reviewed and approved by the Emory University Institutional Review Board.

Eligible participants were children, adolescents, and young adults aged 8-21 years who were diagnosed and treated for cancer at CHOA or, if diagnosed and treated elsewhere, currently followed through the CHOA Cancer Survivor Program. All participants had completed cancer treatment at least 5 years prior to enrollment and had no evidence of current malignancy, known cardiac symptoms, or cardiomyopathy. To focus our analysis on the effects of anthracyclines, subjects were excluded if they had a history of radiotherapy with potential impact to the heart. All participants, or their legal guardians, provided written informed consent.

Because we wanted to obtain a sample balanced on anthracycline cardiotoxicity risk status, we stratified our study group based on their cumulative lifetime anthracycline exposure. Based on the recommended imaging surveillance frequencies in the long-term follow-up guidelines published by the Children's Oncology Group, all participants were assigned into control (never treated with anthracyclines), low-risk (<100 mg/m^2 of doxorubicin-equivalent cumulative anthracyclines at 1 to 4 years of age, or <300 mg/m^2 at 5 years of age or older), moderate-risk (<200 mg/m^2 at less than 1 year of age, ≥100 to <300 mg/m^2 at 1 to 4 years of age, or ≥200 to <300 mg/m^2 at 5 years of age or older), and high-risk (≥200 mg/m^2 at less than 1 year of age, ≥300 mg/m^2 at 1 to 4 years of age, or ≥300 mg/m^2 at 5 years of age or older) categories.[33]

At their scheduled echocardiogram, patients were asked to complete a self-administered questionnaire on socioeconomic factors, tobacco use, physical activity levels and general health status. The questions came directly from either the Centers for Disease Control and Prevention's

Youth Behavioral Risk Factor Surveillance System[237] or the Adult Behavioral Risk factor Surveillance System[238] instruments. The baseline physical exam measurements included height, weight, heart rate (HR), blood pressure, and a baseline 12-lead electrocardiogram (ECG) to document normal sinus rhythm. Body mass index specific to age and sex (BMI-for-age) was calculated and those in the 85th to less than the 95th percentile were categorized as overweight and those in the 95th percentile or above were categorized as obese. Prior to the initiation of exercise, standard resting echocardiograms were performed in both the supine and the upright positions using a GE Vivid 7 5 MHz probe.

Subjects exercised on an electronically braked cycle ergometer (Corival Pediatric Ergometer) at a cadence of 50-60 rpm with initial and incremental workloads of 25 Watts applied at 3-minute intervals. Echocardiography was conducted at the 1.5-minute mark of each stage, and at termination of exercise. The MedGraphics Ultima^{TM} CARDIO2 Cardiopulmonary Exercise System was used to continuously monitor ECG tracings and to obtain gas exchange values and aerobic indices. An inability to maintain 50 rpm, HR >85% predicted or respiratory exchange ratio (RER) >1 was deemed an exhaustive effort.

All echocardiography images were saved and analyzed offline using the GE EchoPAC^{TM} Dimension '06 Software. Off-line measurements of the echocardiography parameters were made later, removed from the time of data acquisition. Although the study personnel analyzing these images were aware of the patient's inclusion in the study (and thus, aware of their prior cancer diagnosis), they were blind to subjects' risk status.

Intraventricular septum thickness (IVS), and left ventricle posterior wall thickness (LVPW) were measured. At rest, and within each stage of exercise, we also measured the internal diameter (LVID) both at end diastole (d) and end systole (s) using M-mode recordings in the parasternal long-axis view. SF was calculated as the fraction of diastolic dimension lost in systole:

$$SF = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

LV end-diastolic and end-systolic volumes and EF were calculated using the Teichholz M-mode formula:[125,126]

$$\text{LV end-diastolic volume} \approx \frac{7(LVIDd)^3}{2.4 + LVIDd}$$

$$\text{LV end-systolic volume} \approx \frac{7(LVIDs)^3}{2.4 + LVIDs}$$

$$EF = \frac{\text{LV end-diastolic volume} - \text{LV end-systolic volume}}{\text{LV end-diastolic volume}} \times 100$$

Mitral flow velocities were recorded in the apical four-chamber view by placing the pulsed wave Doppler sample volume between the tips of the mitral valves in the center of the flow stream. From these, the peak early (E) and atrial (A) flow velocities and E/A ratio were measured at rest. E flow velocities were also measured at each stage of exercise.

By activating the color TDI function, recordings of the mitral annular velocities were made from the apical four-chamber and two-chamber views. From the four chamber view, the septal systolic (S'_s), early diastolic (E'_s), and late diastolic (A'_s) velocities were measured by placing the TDI cursor on the septal side of the mitral annulus and tracking a sample volume through an average of three cardiac cycles. The lateral velocities were measured in a similar way in this view. The velocities at the anterior and inferior sites of the mitral annulus were recorded from the apical two-chamber view. The ratio of the early transmitral inflow Doppler signal to the lateral mitral annular early diastolic velocity (mitral E/E') were calculated as a measure of LV filling pressure.

Left ventricular natural strain and strain rate curves were obtained from different myocardial segments using sample volumes of 5-10 mm. We measured systolic, early diastolic

and late diastolic strain and strain rate in the longitudinal direction in the apical four-chamber view at rest only.

Statistical Analysis

All statistical analyses were performed using the SAS® statistical package. We utilized general linear models (GLM) to examine the associations between various outcomes and anthracycline risk category (low, moderate, and high) compared to the controls and to assess possible dose response effects. To control for potential confounding, all GLM models were adjusted for age, race/ethnicity, sex, overweight/obesity status, tumor type, and receipt of dexrazoxane. Regression diagnostic procedures included analyses of residuals, partial plots, precision assessment, and model fit statistics. No gross departures from the linearity, homoscedasticity, or independence assumptions were found.

RESULTS

A total of 80 childhood cancer survivors completed the exercise echocardiogram and had viable images available for processing. The control, low, moderate, and high cardiotoxicity risk status groups included 21, 24, 23, and 12 subjects, respectively. Table 4.1 shows the patient characteristics by anthracycline cardiotoxicity risk status. The controls were significantly younger (mean age 13.0 years) than those in the low and high-risk groups (16.0 and 16.2 years, respectively) and there was evidence of a statistically significant linear trend ($p = 0.0410$). The groups also differed overall with respect to race/ethnicity ($p = 0.0001$) with Hispanics most represented among the controls (33%) and non-Hispanic blacks most often included in the high-risk group (42%). The control and high risk groups included greater proportions of overweight or obese participants (71% and 83%, respectively) compared to those in the low (25%) or moderate (39%) risk groups (overall $p = 0.001$).

The cancer diagnosis and treatment characteristics of the study population are shown in table 4.2. Those in the low (79%), moderate (61%), and high (25%) risk groups were more likely

to have been diagnosed with leukemia than any other cancer type, whereas the majority of controls (38%) were diagnosed with other malignancies. The average number of years that participants had been off therapy ranged between 8 and 9 years and did not differ significantly by risk status. There were two patients, both in the high-risk group, who received dexrazoxane as part of their treatment protocols to protect against anthracycline cardiotoxicity.

Table 4.3 shows the cardiopulmonary data at rest and peak exercise by risk status, adjusted for age, race/ethnicity, sex, overweight/obese, tumor type, and receipt of dexrazoxane. Much of the data do not show differences by risk status but a few parameters show statistically significant linear trends or differ for the moderate and high-risk groups as compared to the controls. The resting HR showed a statistically significant upward trend by anthracycline cardiotoxicity risk status ($p = 0.0498$) with the controls having an adjusted mean HR of 87 bpm and the high risk group having a mean HR of 103 bpm. The relative resting oxygen consumption of those in the high-risk group was significantly higher than controls (7.8 mL/kg/min vs. 5.3 mL/kg/min, $p = 0.0402$); however, the data revealed no linear trend. Analyses of the relation between average oxygen pulse and anthracycline risk status demonstrated an inverse trend ($p = 0.0376$) with the moderate (8.6 mL/beat, $p = 0.435$) and high (7.7 mL/beat, $p = 0.147$) risk groups having lower estimates than the controls (10.7 mL/beat). Similarly, the change in the oxygen pulse from rest to peak exercise measurement was lower in the high-risk group than among the controls (3.5 mL/beat vs. 7.3 mL/beat, $p = 0.251$). Stroke volume at rest was inversely related to anthracycline exposure (p for trend = 0.0229), with the moderate risk group being the only one significantly different from the controls (42.0 mL vs. 57.5 mL, $p = 0.0170$). There was also evidence that the moderate-risk group and controls were different with respect to stroke volume at peak exercise, cardiac output at peak exercise, and the change in cardiac output from peak exercise and rest. No other between-group differences or trends were statistically significant for these parameters.

The M-mode and tissue Doppler results are shown in table 4.4. No significant differences were found between the groups in EF or left ventricular SF. In terms of pulsed tissue Doppler velocities, the change from rest to peak exercise in the ratio of the early diastolic velocities at the mitral valve and septal area of the mitral annulus ($\Delta E/E'_s$) showed a statistically significant downward trend with increasing anthracycline risk category ($p = 0.0052$). While the controls and low risk groups showed an increase in the ratio from rest to peak exercise (+2.8 and +1.1, respectively), the corresponding measures for moderate and high risk groups demonstrated a decrease and differed significantly from the control group (-0.7, $p = 0.0121$ and -0.4, $p = 0.0421$, respectively). There was an overall linear upward trend by exposure status for early diastolic filling velocities at the lateral area of the mitral annulus at peak exercise ($p = 0.0455$). Those in the high-risk group had significantly higher velocities than the controls (15.1 cm/s vs. 12.4 cm/s, $p = 0.0438$). Table 4.5 shows the strain and strain rate measured at rest by cardiotoxicity risk status with no remarkable findings noted.

DISCUSSION

Regular evaluation for potential cardiotoxic effects of anthracyclines is an essential element of ongoing follow-up for cancer survivors receiving this treatment. While current clinical practice mostly utilizes measurements available from M-mode and two-dimensional echocardiography at rest, more novel echocardiography techniques, both at rest and during exercise, have been explored in recent feasibility studies.

In 2007, Jarfelt *et al*. found that anthracycline-treated adult acute lymphoblastic leukemia survivors at a median of 21 years off treatment had subclinical cardiac dysfunction identified through stress echocardiography.[240] In this asymptomatic group, EF at peak exercise was significantly lower in the 23 anthracycline-exposed survivors than in the 12 healthy controls (59.5% [95% confidence interval [CI]: 32.6 – 81.1] vs. 77.3% [95% CI: 66.2 – 85.3], $p < 0.00006$), and that 10 of the patients reduced their EF at stress compared to EF at rest. These

results suggested that echocardiographic evaluation at peak exercise could uncover otherwise undiagnosed impaired systolic function. In the same year, De Souza *et al*. used Doppler techniques to retrospectively examine stress echocardiograms of 47 anthracycline-treated patients an average of 5.6 years off treatment and found some differences at peak exercise as compared to controls.[236] Specifically, the exposed group showed smaller increases in stroke volume index in response to exercise than those not treated. They also found that the LV dimensions at end-systole fell during progressive exercise even among those with abnormal resting LV dysfunction, implying some recruitment of contractile reserve during exercise.

In contrast to the above findings, a 2010 longitudinal study by Sieswerda *et al*. showed that adding exercise SF to a model containing resting SF did not improve prediction of abnormal resting SF an average of 10.5 years later and concluded that monitoring with exercise echocardiography had no added value to monitoring with resting measures alone.[241] Most recently, and most consistent with our findings, De Caro *et al*. conducted exercise tests with M-mode echocardiography on 55 childhood cancer survivors treated with anthracyclines and compared them to 63 controls.[242] They found that 30% of 55 asymptomatic survivors treated with anthracyclines exhibited some subclinical cardiac dysfunction apparent in either reduced LV posterior wall dimensions or increases in LV end systolic wall stress as compared to 63 controls but that their cardiopulmonary response to exercise did not differ significantly from the control group.

In our study, we found no clinically-meaningful differences in systolic or diastolic function between the anthracycline-exposed survivors and the control group despite the addition of both TDI and SRI techniques to the assessment. However, we did observe some differences in HR at rest as well as very subtle E/E'-based differences in diastolic function between groups. At peak exercise, while ventilatory oxygen uptake (VO_2) were normal across the groups, oxygen pulse and stroke volume among those treated at higher doses of anthracyclines appeared slightly abnormal, suggesting potential filling inadequacies at maximal exercise. Nevertheless, these

patients were able to demonstrate global compensatory mechanisms during dynamic exercise to ensure normal exercise capacity.

Although this project was designed to improve upon earlier studies, there are still limitations of the data that may affect the interpretation of results. These limitations include the characteristics of the population included in the analysis, the cross-sectional nature of the data, the relatively small sample size, and the challenges of interpretation of cardiac imaging data.

This study population is not likely to be representative of all childhood cancer survivors. Those who are actively followed through CHOA's Cancer Survivor Program may differ from other eligible patients. Additionally, in our sample, a higher proportion of the control group was overweight or obese, as compared to the survivors who were exposure to anthracyclines. It is unclear why high BMI was so common in the controls which may have led to the detection of fewer differences in cardiopulmonary data between groups, although we adjusted for this in the analysis.

Another limitation of our study is its cross-sectional design which precludes evaluation of the TDI and SRI parameters over multiple examinations. Additionally, the variability in the time from diagnosis among study participants could underestimate the clinical impact of these measures on the early detection of cardiac dysfunction. However, future evaluation of this cohort of childhood cancer survivors may be possible, allowing us to build on the current data. The sample size, particularly for the highest risk group, was also limited in this study. While the intent of the study was to conduct exploratory analyses, multiple comparisons were made; caution should be taken when interpreting the results.

It is also important to point out that the clinical utility of TDI and SRI techniques in screening for late cardiotoxic effects of anthracyclines has not been established and much of the interpretation requires both skilled sonographers for the acquisition of high quality images as well as skilled interpreters of the offline analysis. One of the strengths of this study is the use of highly skilled and blinded sonographers for the analysis of images. Another strength is that we

conducted double-abstraction of a 10% random sample of all exams that showed high concordance of measurements between abstractors. While these procedures led to high quality data for this study, this may not be the case in a clinical setting. More work needs to be done on inter- and intra-rater variability of both sonographers and interpreters.

Contributions

Our results confirm that high-risk anthracycline-exposed pediatric cancer survivors with normal resting systolic function have some evidence of diastolic filling abnormalities at rest and that TDI may be a useful addition to routine monitoring of anthracycline cardiotoxicity using resting echocardiography. With exercise, young patients appear to be able to augment their systolic and diastolic function to achieve relatively normal maximal aerobic capacity despite impaired stroke volume. Further longitudinal evaluation of these parameters may be warranted. Additionally, our findings suggest that routine exercise echocardiography may not be a viable screening solution, though it could potentially be used as a follow-up to abnormal or borderline resting echocardiography findings.

TABLE 4.1: Patient characteristics by anthracycline cardiotoxicity risk status

	Anthracycline Cardiotoxicity Risk			
	No (n = 21)	Low (n = 24)	Moderate (n = 23)	High (n = 12)
Current age in years, *Mean (SD)*[a]	*13.0 (3.44)*	*16.0 (2.89)*[b]	*14.5 (3.20)*	*16.2 (3.64)*[b]
Sex, N (%)				
Male	10 (47.62)	11 (45.83)	13 (56.52)	8 (66.67)
Female	11 (52.38)	13 (54.17)	10 (43.48)	4 (33.33)
Race/Ethnicity, N (%)[c]				
Non-Hispanic white	13 (61.90)	18 (75.00)	22 (95.65)	6 (50.00)
Non-Hispanic black	1 (4.76)	2 (8.33)	0 (0.00)	5 (41.67)
Non-Hispanic other	0 (0.00)	2 (8.33)	1 (4.35)	1 (8.33)
Hispanic	7 (33.33)	2 (8.33)	0 (0.00)	0 (0.00)
Ever Smoke, N (%)				
Yes	2 (9.52)	3 (12.50)	4 (17.39)	3 (25.00)
No	19 (90.48)	21 (87.50)	19 (82.61)	9 (75.00)
Number of days in past week active for ≥60 minutes, N (%)				
0	1 (4.76)	4 (16.67)	0 (0.00)	3 (25.00)
1-3	9 (42.86)	8 (33.33)	7 (30.43)	2 (16.67)
4-7	11 (52.38)	12 (50.00)	16 (69.57)	7 (58.33)
General Health Status, N (%)				
Excellent	6 (28.57)	10 (41.67)	10 (43.48)	2 (16.67)
Very Good	9 (42.86)	6 (25.00)	9 (39.13)	7 (58.33)
Good	6 (28.57)	6 (25.00)	3 (13.04)	1 (8.33)
Fair	0 (0.00)	2 (8.33)	1 (4.35)	2 (16.67)
Poor	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Currently insured, N (%)				
Yes	21 (100.00)	23 (95.83)	23 (100.00)	11 (91.67)
No	0 (0.00)	1 (4.17)	0 (0.00)	1 (8.33)
Number of surgeries since treatment, N (%)				
None	12 (57.14)	10 (41.67)	8 (34.78)	6 (50.00)
One or more	9 (42.86)	14 (58.33)	15 (65.22)	6 (50.00)
Overweight/Obese, N (%)[c]				
Yes	15 (71.43)	6 (25.00)	9 (39.13)	10 (83.33)
No	6 (28.57)	18 (75.00)	14 (60.87)	2 (16.67)

[a] $p < 0.05$ for linear trend across exposure categories
[b] $p < 0.05$ for difference in mean from those with no anthracycline cardiotoxicity risk
[c] $p < 0.05$ for Fisher's exact test for independence

TABLE 4.2: Patient cancer diagnosis and treatment characteristics by anthracycline cardiotoxicity risk status

	Anthracycline Cardiotoxicity Risk			
	No	Low	Moderate	High
Diagnosis, N (%)[a]				
Leukemia	5 (23.81)	19 (79.17)	14 (60.87)	3 (25.00)
Lymphoma	0 (0.00)	5 (20.83)	4 (17.39)	1 (8.33)
Sarcoma	4 (19.05)	0 (0.00)	1 (4.35)	5 (6.25)
Wilm's/Renal	3 (14.29)	0 (0.00)	0 (0.00)	1 (8.33)
Neuroblastoma	1 (4.76)	0 (0.00)	4 (17.39)	0 (0.00)
Other	8 (38.10)	0 (0.00)	0 (0.00)	2(16.67)
Years off therapy,				
Mean (SD)	*8.5 (2.73)*	*8.0 (2.73)*	*9.6 (3.43)*	*8.3 (3.03)*
Received dexrazoxane, N (%)[a]				
Yes	0 (0.00)	0 (0.00)	0 (0.00)	2 (16.67)
No	21 (100.00)	24 (100.00)	23 (100.00)	10 (83.33)

[a]$p < 0.05$ for Fisher's exact test for independence

TABLE 4.3: Adjusted[a] mean cardiopulmonary data at rest and peak exercise by anthracycline cardiotoxicity risk status

	Anthracycline Cardiotoxicity Risk			
	None	Low	Moderate	High
$Work_{(VO2Max)}$ (Watts)	148.92	131.17	121.50	134.88
$HR_{(Rest)}$ (bpm)[b]	86.59	85.81	92.42	102.52
$HR_{(VO2Max)}$ (bpm)	189.61	189.90	190.33	192.41
Δ HR [b]	103.07	104.03	97.65	89.85
Blood $Pressure_{(Rest)}$				
Systolic (mmHg)	119.95	109.49	111.62	113.86
Diastolic (mmHg)	69.01	71.21	73.28	72.76
Blood $Pressure_{(Max)}$				
Systolic (mmHg)	175.66	164.21	165.80	173.82
Diastolic (mmHg)	66.59	74.64	75.28	61.97
Δ Blood Pressure				
Δ Systolic (mmHg)	54.69	56.86	53.29	60.38
Δ Diastolic (mmHg)	-1.85	4.60	1.42	-10.31
$VO_2/kg_{(Rest)}$ (mL/kg/min)	5.27	5.30	5.13	7.81[c]
$VO_2/kg_{(VO2Max)}$ (mL/kg/min)	33.57	34.18	34.58	35.65
Δ VO_2/kg (mL/kg/min)	28.31	28.88	29.44	27.84
$RER_{(Rest)}$	0.94	0.92	0.95	0.94
$RER_{(VO2Max)}$	1.22	1.20	1.24	1.17
Δ RER	0.28	0.29	0.29	0.24
O_2 $pulse_{(Rest)}$ (mL/beat)	3.23	4.36	3.37	3.84
O_2 $pulse_{(Peak)}$ (mL/beat) [b]	10.72	8.82	8.60 [c]	7.67[c]
Δ O_2 pulse (mL/beat) [b]	7.25	4.79	4.88	3.51[c]
Stroke $Volume_{(Rest)}$ (mL) [b]	57.47	52.70	42.40 [c]	47.85
Stroke $Volume_{(Peak)}$ (mL)	76.45	65.91	58.25 [c]	65.01
Δ Stroke Volume (mL)	20.34	14.20	16.33	17.59
Cardiac $Output_{(Rest)}$ (L/min)	4.20	4.18	3.63	3.96
Cardiac $Output_{(Peak)}$ (L/min)	12.78	10.00	9.14[c]	11.47
Δ Cardiac Output (L/min)	8.46	6.22	5.60 [c]	7.44

[a]Adjusted for age, race/ethnicity, sex, overweight or obese, tumor type and receipt of dexrazoxane using generalized linear modeling.

[b]$p < 0.05$ (but ≥ 0.01) for linear trend across exposure categories

[c]$p < 0.05$ (but ≥ 0.01) for difference in mean from those with no anthracycline cardiotoxicity risk

HR = heart rate; bpm = beats per minute; VO_2 = ventilator oxygen uptake; RER = respiratory exchange ratio; Max = maximum; Δ = change in mean from rest to peak exercise; O_2 pulse = oxygen pulse

TABLE 4.4: Adjusted[a] mean M-mode and tissue Doppler data at rest and peak exercise by anthracycline cardiotoxicity risk status

	Anthracycline Cardiotoxicity Risk			
	None	Low	Moderate	High
$SF_{(Rest)}$ (%)	34.47	33.10	35.02	33.03
$SF_{(Peak)}$ (%)	46.61	44.63	44.40	48.34
Δ SF (%)	13.87	7.64	9.67	16.76
$EF_{(Rest)}$ (%)	64.56	62.94	64.64	62.33
$EF_{(Peak)}$ (%)	78.13	77.08	75.77	80.44
Δ EF (%)	15.49	7.97	11.84	19.32
MV E $Velocity_{(Rest)}$ (m/s)	76.23	83.57	80.63	84.74
MV E $Velocity_{(Peak)}$ (m/s)	155.75	154.48	147.61	159.59
Δ MV E Velocity (m/s)	78.99	73.48	66.39	75.39
$E/A_{(Rest)}$	1.93	1.60	1.71	1.43
Septal $velocities_{(Rest)}$				
Systolic (S'_s) (cm/s)	6.38	5.74	5.98	5.94
Early diastolic (E'_s) (cm/s)	7.81	7.55	7.10	7.41
E/E'_s	9.78	11.72	11.70	12.14
Septal $velocities_{(Peak)}$				
Systolic (S'_s) (cm/s)	14.17	13.80	14.46	14.97
Early diastolic (E'_s) (cm/s)	12.87	12.54	13.52	14.05
E/E'_s	12.32	12.48	10.84	11.56
Δ Septal velocities				
Δ Systolic (S'_s) (cm/s)	7.65	8.09	8.58	8.82
Δ Early diastolic (E'_s) (cm/s)	4.94	5.32	6.40	6.60
Δ E/E'_s[c]	2.78	1.08	-0.72[d]	-0.43[d]
Lateral $velocities_{(Rest)}$				
Systolic (S'_l) (cm/s)	5.85	6.49	5.98	5.45
Early diastolic (E'_l) (cm/s)[b]	7.78	8.96	7.82	8.09
E/E'_l	10.60	10.22	10.93	11.74
Lateral $velocities_{(Peak)}$				
Systolic (S'_l) (cm/s)	12.83	13.29	13.54	14.30
Early diastolic (E'_l) (cm/s)[b]	12.38	13.25	13.52	15.08[d]
E/E'_l	13.02	11.55	10.77[d]	11.47
Δ Lateral velocities				
Δ Systolic (S'_l) (cm/s)	7.13	6.93	7.42	8.69
Δ Early diastolic (E'_l) (cm/s)	4.41	4.39	5.52	6.78
Δ E/E'_l	2.49	1.75	-0.11	0.58
Anterior $velocities_{(Rest)}$				
Systolic (S'_a) (cm/s)	6.43	6.16	6.65	5.56
Early diastolic (E'_a) (cm/s)	7.71	7.68	7.64	8.15
Anterior $velocities_{(Peak)}$				
Systolic (S'_a) (cm/s)	14.68	13.62	14.42	14.04
Early diastolic (E'_a) (cm/s)	12.95	11.92	11.78	13.60
Δ Anterior velocities				
Δ Systolic (S'_a) (cm/s)	7.96	7.09	7.89	8.86
Δ Early diastolic (E'_a) (cm/s)	5.16	3.96	4.38	5.48

TABLE 4.4 (Continued)

	Anthracycline Cardiotoxicity Risk			
	None	Low	Moderate	High
Inferior velocities$_{(Rest)}$				
Systolic (S'$_i$) (cm/s)	5.06	6.41	6.91 [d]	5.91
Early diastolic (E'$_i$) (cm/s)	7.33	7.56	7.51	8.58
Inferior velocities$_{(Peak)}$				
Systolic (S'$_i$) (cm/s)	14.29	14.09	14.26	14.49
Early diastolic (E'$_i$) (cm/s)	12.88	10.58	11.76	14.17
Δ Inferior velocities				
Δ Systolic (S'$_i$) (cm/s)	8.89	7.49	7.51	8.71
Δ Early diastolic (E'$_i$) (cm/s)	5.27	2.97	4.70	5.06

[a]Adjusted for age, race/ethnicity, sex, overweight or obese, tumor type and receipt of dexrazoxane using generalized linear modeling.

[b]$p < 0.05$ (but ≥ 0.01) for linear trend across exposure categories

[c]$p < 0.01$ for linear trend across exposure categories

[d]$p < 0.05$ (but ≥ 0.01) for difference in mean from those with no anthracycline cardiotoxicity risk

SF = shortening fraction; EF = ejection fraction; MV = mitral valve; E = early diastolic mitral valve flow velocity; A = atrial flow velocity; TDI = tissue Doppler imaging ; S' = TDI systolic velocity; E' = TDI early diastolic velocity

TABLE 4.5: Adjusted[a] mean four-chamber strain and strain rate data at rest by anthracycline cardiotoxicity risk status

	Anthracycline Cardiotoxicity Risk			
	None	Low	Moderate	High
Strain (%)				
Global	-14.26	-19.21	-17.44	-15.39
Septal				
Basal	-18.38	-16.60	-16.67	-17.96
Mid	-19.75	-18.15	-17.81	-19.03
Apical	-19.15	-17.83	-19.34	-18.38
Lateral				
Basal	-17.36	-18.68	-15.04	-14.61
Mid	-15.74	-15.34	-16.09	-16.98
Apical	-15.99	-13.88	-18.46	-16.66
Strain rate (s^{-1})				
Global	-0.94	-0.98	-1.00	-0.85
Septal				
Basal	-1.07	-1.05	-1.04	-0.94
Mid	-1.08	-1.10	-1.13	-1.03
Apical	-1.30	-1.15	-1.30	-1.12
Lateral				
Basal	-1.23	-1.52	-1.46	-1.08
Mid	-0.92	-1.02	-1.04	-0.89
Apical	-1.00	-0.98	-1.25	-1.07

[a]Adjusted for age, race/ethnicity, sex, overweight or obese, tumor type and receipt of dexrazoxane using generalized linear modeling.

CHAPTER 5 –

PEDIATRIC QUALITY OF LIFE IN LONG-TERM SURVIVORS OF CHILDHOOD CANCER TREATED WITH ANTHRACYCLINES

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ABSTRACT

Purpose: Anthracyclines are a common class of antineoplastic agents used to treat pediatric cancer. While much work is done examining the cardiotoxic effects of anthracyclines, very little is known about the psychosocial and other morbidity-related late effects of these drugs. This study examines the association of anthracycline cardiotoxicity risk status to Pediatric Quality of Life (PedsQL) Inventory ™ scores in long-term childhood cancer survivors. **Methods:** We recruited childhood cancer survivors aged 8-21 years and at least 5 years post treatment from a Cancer Survivor Clinic. Participants completed the PedsQL 4.0 Generic Core Scales in addition to a separate health behaviors survey. Clinical information was abstracted directly from medical records. Linear regression procedures were used to evaluate the associations between PedsQL scores and anthracycline cardiotoxicity risk status. The interaction of varying anthracycline exposure and self-reported physical activity on PedsQL scores was also assessed. **Results:** Eighty survivors participated and were characterized by cardiotoxicity risk status (high: 12; moderate: 23, low: 24, no risk [controls]: 21) as defined by recommended echocardiography frequencies in the Children's Oncology Group Long Term Follow-Up Guidelines. Relative to normative scores, measures in all PedsQL domains (total, physical summary health, psychosocial summary health, emotional functioning, social functioning, and school functioning) in this study group were high though tended to be slightly lower for survivors exposed to anthracyclines as compared to the unexposed. The largest difference in unadjusted scores were for social functioning (96.0% for exposed vs. 91.3% for unexposed, $p = 0.0068$). There was also an inverse dose-response association between adjusted PedsQL scores and increasing anthracycline cardiotoxicity risk though this association is not modified by physical activity level. **Conclusion:** Our data indicate that regular psychosocial assessments, such as those currently recommended by the Children's Oncology Group, may be especially important for survivors exposed to anthracyclines during treatment.

INTRODUCTION

In 2009, 14,023 children and adolescents were diagnosed with cancer in the United States.[13] Over the past several decades there have been significant improvements in survival among children with cancer, largely due to the introduction of new therapeutic strategies.[14] The 5-year survival for childhood malignancies is 79%, with more than 300,000 long-term survivors of childhood cancers currently alive in the United States.[15-17] Due to these improvements in survival, a growing number of childhood cancer survivors are at increased risk for health problems related to their treatment.[3]

Anthracyclines are a common class of antineoplastic agents with nearly 60% of all children diagnosed with cancer receiving this type of chemotherapy.[34] Childhood cancer survivors who received anthracyclines are at risk for both immediate and long-term physiological outcomes such as myelosuppression, mucositis, hair loss, and cardiotoxicity.[34-40] While much work is done on the primary and secondary prevention of anthracycline cardiotoxicity, very little is known about the psychosocial and other morbidity-related late effects of these drugs.

One measure of morbidity is health-related quality of life, a multidimensional construct encompassing physical, emotional, and social domains.[243] The Pediatric Quality of Life (PedsQL) Inventory ™ is a well-established evidence-based assessment tool designed to measure quality of life among children and young adults with chronic illness.[243,244] The PedsQL Generic Core scales have been widely used to assess self-reported physical, emotional, social, and school functioning among childhood cancer survivors.[245-247]

The primary aim of this study was to compare the PedsQL measures in long-term childhood cancer survivors with no prior cardiac diagnoses at varying risks of developing long-term outcomes related to anthracycline exposure. Our previous work within this population of cancer survivors found that those exposed to high doses of anthracyclines have some evidence of diastolic filling abnormalities despite normal resting systolic function. Our hypothesis for the current study was that survivors treated with increasing doses of anthracyclines would report

lower PedsQL scores because subclinical cardiotoxicity increases with increasing anthracycline exposure and compromises to physical health may have effects on psychosocial health. Because long-term survivors of childhood cancer are less likely than age-matched controls to participate in regular physical activity,[203,204,209,212,214,248] despite evidence that it is beneficial in this population,[226-228] we examined whether any association between reported PedsQL scores and anthracycline cardiotoxicity risk status was modified by physical activity levels.

METHODS

We conducted this study at Children's Healthcare of Atlanta (CHOA). Children, adolescents, and young adults aged 8-21 years diagnosed and treated for cancer at CHOA or those diagnosed and treated elsewhere but currently followed through the CHOA Cancer Survivor Program were eligible to participate. All participants had completed cancer treatment at least 5 years prior to enrollment and had no evidence of current malignancy or cardiac dysfunction. To focus our analysis on the effects of anthracyclines, we excluded subjects if they had a history of radiotherapy with potential direct effect on the heart. All participants, or their legal guardians, provided written informed consent and the Emory University Institutional Review Board approved this study.

To obtain a sample balanced with respect to risk of anthracycline cardiotoxicity, we stratified our study group based on their cumulative lifetime anthracycline exposure and age at first infusion. Our strata were defined based on the long-term follow-up recommendations put forth by the Children's Oncology Group (COG) on cardiac imaging surveillance frequencies.[33] All participants were assigned into one of the following groups:

- Control (never treated with anthracyclines)
- Low-risk (<100 mg/m^2 of doxorubicin-equivalent cumulative anthracyclines at 1 to 4 years of age, or <300 mg/m^2 at 5 years of age or older)

- Moderate-risk (<200 mg/m^2 at less than 1 year of age, ≥100 to <300 mg/m^2 at 1 to 4 years of age, or ≥200 to <300 mg/m^2 at 5 years of age or older)
- High-risk (≥200 mg/m^2 at less than 1 year of age, ≥300 mg/m^2 at 1 to 4 years of age, or ≥300 mg/m^2 at 5 years of age or older)

Patients completed two self-administered questionnaires. The first was the PedsQL Generic Core scales, version 4.0. The PedsQL scales are validated multidimensional self-report scales encompassing the domains of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). We asked participants to complete the PedsQL version that was most appropriate for their age group (i.e., Child PedsQL for those 8-12 years of age, Adolescent PedsQL for those 13-17 years, or the Young Adults PedsQL for those 18 and older). The PedsQL has standard, easily implemented scoring algorithms transformed to a 0-100 scale so that higher scores indicate better health-related quality of life. A Psychosocial Health Summary Score is calculated using Scale Scores from each of the Emotional, Social, and School Functioning Scales. The Total Scale Score is calculated as the mean of all Scales.

The second self-administered questionnaire asked about socioeconomic factors, tobacco use, physical activity levels, and general health status. To define physical activity, we asked participants, "During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?" The American Heart Association and the American Academy of Pediatrics recommend that children and adolescents who are cancer survivors should have 60 minutes or more of physical activity each day.[249] We considered two different definitions of "physically active" for the interaction assessment in this analysis: 1) the strict definition of only those reporting physical activity on all 7 days; and 2) a less strict definition of those reporting 5 or more days of physical activity.

We abstracted each patient's cancer diagnosis, treatment, and other clinical characteristics directly from the medical record and used a basic physical examination to measure height and weight at the time of assessment. From the height and weight measurements, we calculated body mass index specific to age and sex (BMI-for-age). Consistent with definitions from the Centers for Disease Control and Prevention (CDC), we considered those at or above the 85^{th} percentile to be overweight.

All statistical analyses were performed using the SAS® statistical package. We utilized Fisher's exact tests to examine the bivariate associations between receipt of anthracyclines and various socio-demographic and clinical characteristics. Hodges-Lehmann estimates for a Wilcoxon Rank Sum Test and distribution-free 95% confidence intervals (CIs) were used to compare the differences in mean PedsQL scores within each domain and receipt of anthracyclines. We utilized ordinary least squares to examine the associations between each PedsQL domain score and anthracycline risk category (low, moderate, and high) compared to the controls (no anthracycline exposure), and to assess possible dose response effects. To control for potential confounding, each model was adjusted for age, race/ethnicity, sex, cancer diagnosis, overweight/obesity status, and receipt of dexrazoxane. To examine whether the relationship between anthracycline exposure and PedsQL scores would be modified by physical activity level, we tested whether an interaction term between anthracycline risk status and physical activity was statistically significant in the final models also containing the physical activity variable ($\alpha = 0.05$).

RESULTS

Of the 80 patients who participated in the study, 59 (73.75%) received anthracyclines as part of their cancer treatment. The demographic and cancer diagnosis characteristics of the study population overall, and stratified by receipt of anthracyclines, are presented in Table 1. Regardless of exposure status, most participants were non-Hispanic whites (73.75%), males

(52.50%), and treated for leukemia (51.25%). When stratified by exposure to anthracyclines, those exposed tended to be slightly older (p = 0.0086), more likely non-Hispanic (p = 0.0033), more likely to have had a diagnosis of leukemia or lymphoma (p <0.0001), and less likely overweight or obese than the unexposed (57.63% vs. 38.57%, p = 0.0406). Overall, only 25% of the sample was considered physically active according to CDC recommendations, though this did not differ between exposure groups (23.81% for unexposed vs. 25.42% for the exposed, p = 0.3672). Additionally, the self-reported general health status of this study population was quite good with over 93% of the participants rating their general health status as excellent, very good, or good, and this was not different between the groups (p = 0.4087).

Although the general health status was similar across the groups, we did observe some differences in PedsQL scores across exposure groups (Table 2). The total PedsQL score was higher among the unexposed but the difference was not statistically significant (difference: 3.2, 95% CI: 8.7 – -2.2). Similarly, the subscale scores among the unexposed were higher within all the PedsQL domains but, again, these differences were not statistically significant.

When we examined each quality of life domain by the varying categories of anthracycline exposure and adjusted the results for potential confounders, we observed an inverse dose-response association between PedsQL scores and anthracycline cardiotoxicity risk (Figure 1). The total and physical PedsQL scores showed the strongest trends of decreasing PedsQL scores with increasing anthracycline exposure (p for trend = 0.0475 and 0.0259, respectively). While a similar trend was observed for the psychosocial scale and its subscales, the dose response was not statistically significant. Physical activity level did not modify the associations of PedsQL score and anthracycline risk status regardless of whether we considered those reporting five or more days of physical activity in the past week as “active” or those reporting the CDC recommendation of all 7 days (results not shown).

DISCUSSION

Regardless of anthracycline exposure status, our study population of long-term childhood cancer survivors had higher PedsQL scores in all domains (except school functioning) than a sample of healthy pediatric patients previously reported by Varni et al. (total [83.91, standard deviation [SD]: 12.47], physical [87.77, SD: 13.12], psychosocial [81.83, SD: 13.97], emotional [79.21, SD: 18.02], social [84.97, SD: 16.71], and school [81.31, SD: 16.09]).[250] These findings are similar to previous studies that found equivalent or increased PedsQL 4.0 scores for childhood cancer survivors as compared to healthy peers.[245,246]

Despite the relatively high PedsQL scores reported in this study, the childhood cancer survivors who were treated with anthracyclines reported lower quality of life than those not treated with anthracycline and there was a clear dose-response for the total and physical PedsQL score domains. These data support our hypothesis that quality of life scores would be lower for patients with increasing exposure to anthracyclines. This observation may be explained by the physical or psychosocial effects of anthracycline cardiotoxicity. The data indicate that subclinical physiological effects of anthracyclines on the cardiovascular system may negatively affect survivors' energy level or their ability to perform physical activities such as walking, running, exercise, or sports. It is possible that awareness of having been exposed to a known cardiotoxic agent affects a survivors' perception of their ability to perform certain physical tasks. For example, survivors treated with cardiotoxic therapies such as anthracyclines are advised in the COG Long-Term Follow-Up Guidelines that while aerobic exercise is generally safe, intensive isometric activities such as heavy or maximal weight lifting should be avoided.[33] Thus, when asked on the PedsQL how "hard" it is to "lift something heavy," an exposed individual who is aware of their cardiac risks and associated restrictions may be more likely to perceive and report difficulty than an unexposed survivor. In addition, the guidelines suggest that patients who take part in "strenuous or varsity team sports" should be monitored by a cardiologist which may alter their perceived risk of activities.

Although the result was not statistically significant, we did observe a similar dose-response within the psychosocial PedsQL domains in our study population, particularly for the social subdomain. This may indicate that anthracycline exposure among some individuals may pose a threat to social and emotional adjustment. These results may be a direct effect of anthracycline exposure on psychosocial functioning or they may be an indirect effect, secondary to decreased physical quality of life or physical restrictions.

As far as we are aware, this is the first study examining the association of long-term health related quality of life and anthracycline exposure among childhood cancer survivors. However, limitations of these data warrant additional confirmatory studies. The dose-dependent trend seen for PedsQL scores with increasing anthracycline exposure may reflect an overall increase in the intensity of treatment and long-term morbidity rather than the specific effect of anthracycline exposure. As mentioned previously, this study population may not be representative of all childhood cancer survivors. In terms of demographics, our sample was largely non-Hispanic white and previous research has shown ethnic minority status to be associated with lower PedsQL scores.[246] As part of this study, patients were tested with exercise echocardiography, which may have attracted a more active group of participants. Thus, PedsQL scores may be lower in a more representative population of pediatric cancer survivors. Another limitation of our study is the relatively small sample size, particularly for the highest risk group. Regardless, we still observed statistically significant effects and trends in these data and might expect greater effects in a larger study. Lastly, relying on self-reported physical activity levels by pediatric patients may have resulted in misclassification.

Our results are the first to show a dose-response effect of childhood exposure to anthracyclines on overall and physical health-related quality of life during survivorship. These findings underscore the continued need to monitor survivors exposed to anthracyclines for cardiotoxicity long after treatment. In addition, the COG Long-Term Follow-Up guidelines also recommend yearly psychosocial assessment of childhood cancer survivors for fatigue and

functional disability, mental health disorders, and social withdrawal. Our health-related quality of life data indicate that these psychosocial assessments may be especially important for survivors exposed to anthracyclines during treatment. Overall, these data emphasize the need for cancer survivors to have comprehensive physical and psychosocial services available to them throughout their life.

TABLE 5.1: Demographic and cancer diagnosis characteristics of study population by receipt of anthracyclines

	Total No. (%)	No Anthracyclines No. (%)	Anthracyclines No. (%)	P^1
Total	80 (100.00)	21 (26.25)	59 (73.75)	
Current age (years)				
8-10	12 (15.00)	6 (28.57)	6 (10.17)	
11-14	26 (32.50)	8 (38.10)	18 (30.51)	0.089
15-17	22 (27.50)	5 (23.81)	17 (28.81)	
18-21	20 (25.00)	2 (9.52)	18 (30.51)	
Race/Ethnicity				
Non-Hispanic, white	59 (73.75)	13 (61.90)	46 (77.97)	
Non-Hispanic, black	8 (10.00)	1 (4.76)	7 (11.86)	0.003
Non-Hispanic, other	4 (5.00)	0 (0.00)	4 (6.78)	
Hispanic	9 (11.25)	7 (33.33)	2 (3.39)	
Sex				
Female	38 (47.50)	11 (52.38)	27 (45.76)	0.621
Male	42 (52.50)	10 (47.62)	32 (54.24)	
Diagnosis				
Leukemia	41 (51.25)	5 (23.81)	36 (61.02)	
Lymphoma	10 (12.50)	0 (0.00)	10 (16.95)	<0.0
Sarcoma	10 (12.50)	4 (19.05)	6 (10.17)	01
Wilm's/Renal	4 (5.00)	3 (14.29)	1 (1.69)	
Neuroblastoma	5 (6.25)	1 (4.76)	4 (6.78)	
Other	10 (12.50)	8 (38.10)	2 (3.39)	
Age at diagnosis (years)				
0-2	31 (38.75)	12 (57.14)	19 (32.20)	0.140
3-5	30 (37.50)	5 (23.81)	25 (42.37)	
6-15	19 (23.75)	4 (19.05)	15 (25.42)	
Years off treatment				
5-6	26 (32.50)	7 (33.33)	19 (32.20)	0.999
7-11	42 (52.50)	11 (52.38)	31 (52.54)	
12-19	12 (15.00)	3 (14.29)	9 (15.25)	
Received dexrazoxane				
No	78 (97.50)	21 (100.00)	57 (96.61)	0.999
Yes	2 (2.50)	0 (0.00)	2 (3.39)	
Days active in past 7[2]				
0	8 (10.00)	1 (4.76)	7 (11.86)	
1-4	37 (46.25)	13 (61.90)	24 (40.68)	0.367
5-6	15 (18.75)	2 (9.52)	13 (22.03)	
7	20 (25.00)	5 (23.81)	15 (25.42)	
General health status				
Excellent	28 (35.00)	6 (28.57)	22 (37.29)	
Very good	31 (38.75)	9 (42.86)	22 (37.29)	0.409
Good	16 (20.00)	6 (28.57)	10 (16.95)	
Fair	5 (6.25)	0 (0.00)	5 (8.47)	

TABLE 5.1 (Continued)

	Total No. (%)	No Anthracyclines No. (%)	Anthracyclines No. (%)	*P*[1]
Ever smoke				
No	68 (85.00)	19 (90.48)	49 (83.05)	0.502
Yes	12 (15.00)	2 (9.52)	10 (16.95)	
Overweight or obese				
No	40 (50.00)	6 (28.57)	34 (57.63)	0.041
Yes	40 (50.00)	15 (71.43)	25 (42.37)	

[1]Fisher's exact test

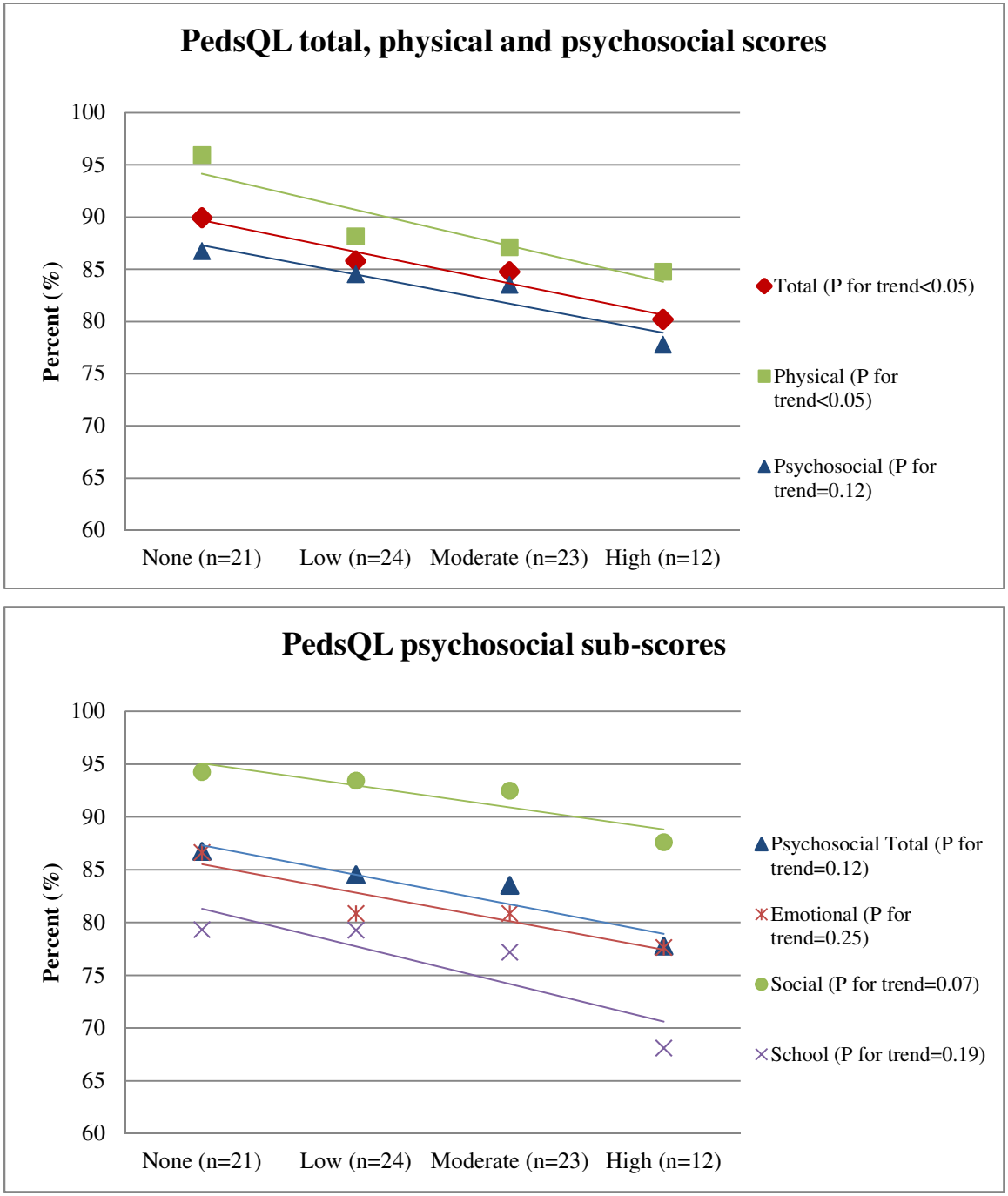
[2]Number of days in the past week physically active for a total of ≥60 minutes

TABLE 5.2: PedsQL 4.0 Generic score by receipt of anthracyclines (crude mean [95% confidence interval])

PedsQL Score	No Anthracyclines	Anthracyclines	Difference Between Groups (95% CI)[1]
Total score	89.03	84.56	3.2 (8.7, -2.2)
Physical health	92.58	88.25	0.0 (6.3, -3.1)
Psychosocial health	87.15	82.60	3.3 (10.0, -3.3)
Emotional functioning	85.24	80.68	0.0 (10.0, -5.0)
Social functioning	95.95	91.27	0.0 (10.0, 0.0)
School functioning	80.24	75.85	5.0 (15.0, -5.0)

[1]Hodges-Lehmann estimate for a Wilcoxon Rank Sum Test of the difference between two treatment groups, and accompanying nonparametric 95% confidence interval (CI)

FIGURE 5.1: Adjusted[1] mean PedsQL scores by anthracycline cardiotoxicity risk status



[1]Adjusted for age, race/ethnicity, sex, cancer diagnosis, overweight/obese and receipt of dexrazoxane

CHAPTER 6 –

THE EFFECT EXERCISE HAS ON PREVENTING LATE CARDIAC OUTCOMES AMONG CHILDHOOD CANCER SURVIVORS TREATED WITH ANTHRACYCLINES

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ABSTRACT

Purpose: Long-term **c**hildhood cancer survivors are at risk for cardiac deconditioning and those treated with anthracyclines are at further risk for cardiac outcomes related to their treatment. The purpose of this study was to estimate the contribution of exercise deconditioning relative to the total effect of anthracycline cardiotoxicity in order to determine the relative importance of exercise interventions in this population. **Methods:** We utilized 2003-2007 follow-up data from the Childhood Cancer Survivor Study. Naïve bivariate and multivariable analyses were conducted to understand the associations of anthracyclines and physical inactivity, separately, on cardiac outcomes. To decompose the total effect of anthracyclines on cardiac outcomes into the direct and indirect effects (through physical inactivity), we used a method developed by Robert Erikson and extended to the logistic model by Maarten Buis. **Results:** Of the 3,358 eligible survivors who reported no cardiac outcomes prior to 2003, 11.2% had at least one cardiac diagnosis between 2003 and 2007. Overall, the survivors who were treated with anthracyclines were more likely than the unexposed to have been diagnosed with any cardiac outcome (12.8% versus 10.2%, p = 0.0173). Myocardial dysfunction was the only outcome with a statistically significant total effect (OR: 9.59, 95% CI: 1.84-49.30). The decomposition analysis demonstrated that the indirect effect attributable to physical inactivity was negligible with an OR of 1.00 (95% CI: 0.98-1.02) and the overall association was driven entirely by the direct effect of anthracyclines (OR: 9.55; 95% CI: 1.83-49.84). Similarly, no associations between anthracycline exposure and the other cardiac outcomes could be explained by the differences in physical activity between the groups. **Conclusion:** While the findings from our data indicate that very little, if any, of the increased incidence of cardiac outcomes among this cohort of long-term childhood cancer survivors treated with anthracyclines can be explained by physical inactivity, results of this study help better define the mechanism by which anthracyclines may affect cardiac outcomes and clarify the role of exercise deconditioning among this population.

INTRODUCTION

Long-term survivors of childhood cancer, even those who were not treated with cardiotoxic therapy, are at increased risk for obesity and are usually less active in sports than age-matched controls.[203,204,209,212,214,248] It has been shown that childhood cancer survivors have higher fasting plasma glucose and insulin levels than age-matched controls and type 2 diabetes is reported to be nearly twice more common in childhood cancer survivors than among sibling controls.[215] Reductions in cardiac output and lower cardio-respiratory fitness are also prevalent among cancer survivors.[205,251]

Childhood cancer survivors continue to be in danger of systemic deconditioning resulting from restrained physical activity long after remission. Despite evidence that regular moderate exercise and fitness in this population is beneficial,[226-228] parents and physicians may not emphasize the importance of physical activity perhaps due to concerns about treatment-related cardiac damage. This approach may lead to a more sedentary lifestyle, further increasing their risk of cardiovascular disease.

From a public health point of view, it is important to understand what fraction of early cardiac outcomes among childhood cancer survivors treated with anthracyclines could be prevented by improving physical fitness. Using data from the Childhood Cancer Survivor Study (CCSS), we assessed the total, direct, and indirect cardiac effects of anthracycline use among long-term childhood cancer survivors. The analytic approach is illustrated in the simplified directed acyclic graph (DAG) in Figure 6.1. We hypothesized that while anthracyclines are known to be cardiotoxic, part of the observed effect may occur because a cancer diagnosis also influences exercise deconditioning, a known risk factor for many cardiac outcomes. Within this framework the effect of anthracyclines on the outcome, excluding all effects of exercise deconditioning, is the direct effect. The indirect effect is the effect of anthracycline exposure explained by subsequent exercise deconditioning. The indirect and direct effects together form the total effect of anthracycline exposure on the outcome. The aim was to estimate the

contribution of exercise deconditioning relative to the total effect of anthracycline cardiotoxicity in order to determine the relative importance of exercise interventions targeting childhood cancer survivors previously exposed to anthracyclines.

METHODS

Study Design

This analysis utilized data from the Childhood Cancer Survivor Study (CCSS). The CCSS is an ongoing, multi-institutional cohort study designed to assess the late adverse effects following treatment for childhood and adolescent cancer. A detailed description of the study design and early cohort characteristics have been published previously.[239] The CCSS consortium consists of 26 participating clinical centers in the United States and Canada who identified patients meeting the following eligibility criteria:

- Diagnosed and initially treated for leukemia, central nervous system malignancy (excluding meningioma and craniopharyngioma), Hodgkin disease, Non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer, or bone cancer
- Diagnosed between January 1, 1970 and December 31, 1986
- Less than 21 years of age at the time of diagnosis
- Alive five years from the date of diagnosis, regardless of disease or treatment status
- English or Spanish speaking
- Resident of the United States or Canada at the time of initial follow-up

The initial contact and recruitment of eligible participants began in August 1994. Participants were sent a baseline questionnaire in the mail. For survivors who had died after achieving 5-year survivorship status, the questionnaire was sent to the next of kin. The baseline study instrument consisted of 289 questions on demographic and socio-economic characteristics,

medical care practices and prescription medications taken during the most recent two-year period, and medical conditions diagnosed by a doctor, including subsequent malignancies. The cancer-related therapy received by each eligible participant was abstracted from medical records by trained data management staff at each institution. Various follow-up questionnaires have been conducted since the baseline. Our analysis focuses on information collected on either the 2003 or 2007 surveys.

Those eligible for this analysis were all active CCSS cohort members alive in 2007 who reported no current or past cardiac abnormalities prior to 2003. There are two exposures of interest in this analysis: cumulative lifetime exposure to anthracyclines (dichotomous) and exercise deconditioning measured at the time of the 2003 survey. To focus our analysis on the effects of anthracyclines, survivors were excluded if they had any history of radiotherapy with potential impact to the heart.

Outcomes

The outcomes of interest in this analysis were any cardiac event or diagnosis occurring after the 2003 survey. During the 2007 survey, participants were asked a series of questions related to their cardiac health including medications and the timing of the reported events. We used the timing of these self-reported events to exclude anyone with a cardiac outcome reported prior to the 2003 survey. Using the multiple questions of interest on the 2007 survey, we grouped the questions regarding cardiac outcomes into six clinically meaningful categories (Table 6.1). The categories were selected due to differences in hypothesized causal mechanisms with anthracyclines, and/or exercise conditioning. Additionally, we reviewed the open-ended responses given to the questions related to “any other heart or circulatory problems” and “other heart surgery” in consultation with a cardiologist to determine categorization of these responses into one of the groupings of interest.

Exposure Variables

The medical record abstraction data were used to determine exposure to anthracyclines. If participants had missing or incomplete treatment data, they were excluded from the analysis. To define physical inactivity, in 2003 the participants were asked, "During the past month, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?" Participants were then asked a series of questions to quantify the amount of time spent in moderate (activities causing small increases in breathing or heart rate) or vigorous (activities causing large increases in breathing or heart rate) physical activity during a usual week. We used the Centers for Disease Control and Prevention (CDC) definition of physical activity.[238] The participants were considered to not have met the CDC guidelines for physical activity if they did not report moderate intensity physical activities for at least 30 minutes on at least 5 days of the week or vigorous intensity physical activity for at least 20 minutes on at least 3 days of the week.

Covariates and confounding assessment

We assessed confounding using both the DAG methodology and the data-based methods. The socio-demographic variables included in this assessment were sex, race/ethnicity, age at the time of the 2003 survey, highest level of education completed, current income, health insurance status and employment status. Possible clinical confounders in this analysis included cancer diagnosis and chemotherapeutic agents other than anthracyclines. Other cardiovascular risk factors examined as potential confounders were current body mass index, family history of cardiovascular disease, smoking status, and general health status. Although diabetes, hypertension, and elevated cholesterol are known risk factors for the outcomes of interest in this study, they are likely on the causal pathway between deconditioning and cardiac problems and for this reason these variables were not included in the multivariable models but assessed only in the bivariate analyses. We chose to assess a Cardiovascular Risk Factor Cluster (CVRFC), a variable

defined previously by Meacham et al. as a surrogate for metabolic syndrome in the CCSS.[252] Restrictions on physical activity levels among some of the cancer survivors receiving certain lower extremity or amputation surgeries may confound the relationships of interest, so we controlled for history of these treatments in the analysis.

Statistical Analysis

All descriptive, bivariate, and total effect multivariable analyses were conducted using SAS v9.2 (SAS Institute Inc., Cary, North Carolina). To decompose the total effect multivariable analyses into the direct and indirect effects of anthracycline exposure on cardiac outcomes we used a method developed in Stata 12.0 (StataCorp LP, College Station, Texas) by Erikson et al.[253] and generalized for a logistic model by Buis.[254] The parameters estimates were calculated using the following 12-step procedure:

1. Perform a logistic regression analysis using both anthracycline and physical inactivity (deconditioning) in the following model:

$$\text{Cardiac Outcome} = \beta_0 + \beta_1(\text{Anth}) + \beta_2(\text{Decondit}) + \sum_{i=1}^{p} \gamma_i(\text{Covariates}) + E$$

   Where:
   Anth = dichotomous variable for anthracycline exposure
   Decondit = dichotomous variable for deconditioning
   Covariates = ***p*** covariates identified for appropriate confounding control

2. For each individual in the dataset, calculate the log odds of a cardiac outcome.
3. Transform the individual log odds into probabilities, fixing the value of all covariates in the model to the sample mean.
4. For anthracycline exposed and unexposed, separately:
   a. Compute the average predicted probability of a cardiac outcome using the arithmetic mean of the predicted probabilities.
   b. Transform these probabilities to log odds.

5. Calculate the difference in the average predicted log odds between anthracycline exposed and unexposed (with their own physical activity distributions) to estimate the ***total effect***.

$$\textbf{Total Effect} = \ln(\overline{\widehat{Odds_{anth=1,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=0}}})$$

**Note: In this notation, the first subscript represents the logistic regression coefficients and the second subscript represents the distribution of physical activity.*

6. Create a counterfactual scenario by predicting the log odds of a cardiac outcome among anthracycline unexposed, assuming they were exposed to anthracyclines.
7. Transform the individual counterfactual log odds to probabilities, fixing the value of all covariates in the model to the sample mean.
8. Compute the average of the individual counterfactual probabilities using the arithmetic mean of the counterfactual probabilities. This is the counterfactual probability of a cardiac outcome for anthracycline exposed if they had the distribution of physical activity of the unexposed survivors.
9. Transform the counterfactual probability to the log odds.
10. Compute the difference in the log odds of a cardiac outcome among the anthracycline unexposed and the log odds of a cardiac outcome among the counterfactual group. These groups differ with respect to the distribution of physical activity, but the probabilities of a cardiac outcome conditional on both anthracycline exposure and physical activity, are kept constant. Therefore this difference gives the effect of anthracycline exposure caused by the differences in the distribution of physical activity, or, the ***indirect effect***.

$$\textbf{Indirect Effect} = \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=0}}})$$

11. Compute the difference in the log odds of a cardiac outcome among the anthracycline exposed and the counterfactual group. These groups now differ with respect to the probabilities of a cardiac outcome conditional on anthracycline exposure and physical

activity, but the distribution of physical activity is kept constant. This difference gives the effect of anthracycline exposure while controlling for the distribution of physical activity, or the ***direct effect***.

$$\textbf{Direct Effect} = \ln(\overline{\widehat{Odds_{anth=1,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=1}}})$$

12. Transform the decomposition results in terms of odds ratios (ORs).

$$\text{Total Effect} = \text{Indirect Effect} + \text{Direct Effect} \rightarrow$$

$$\left[\ln(\overline{\widehat{Odds_{anth=1,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=0}}})\right]$$

$$= \left[\ln(\overline{\widehat{Odds_{anth=0,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=0}}})\right]$$

$$+ \left[\ln(\overline{\widehat{Odds_{anth=1,decondit|anth=1}}}) - \ln(\overline{\widehat{Odds_{anth=0,decondit|anth=1}}})\right] \rightarrow$$

$$ln\left(\frac{\overline{\widehat{(Odds_{anth=1,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=0})}}}\right)$$

$$= ln\left(\frac{\overline{\widehat{(Odds_{anth=0,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=0})}}}\right) + ln\left(\frac{\overline{\widehat{(Odds_{anth=1,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=1})}}}\right) \rightarrow$$

$$\frac{\overline{\widehat{(Odds_{anth=1,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=0})}}} = \frac{\overline{\widehat{(Odds_{anth=0,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=0})}}} \times \frac{\overline{\widehat{(Odds_{anth=1,decondit|anth=1})}}}{\overline{\widehat{(Odds_{anth=0,decondit|anth=1})}}}$$

13. Compute standard errors and accompanying 95% confidence intervals (CIs) using the bootstrap procedure.[255]

RESULTS

A total of 7,304 survivors responded to both the 2003 and 2007 CCSS surveys. Of those, approximately half were eligible to participate in the study. The exclusions and key cardiac outcomes during the follow-up period are outlined in Figure 6.2. Because we were interested in six separate outcomes in addition to the combination of any cardiac outcome, we conducted seven unique analyses with varying eligible (or "at-risk") individuals. For example, there were 3,358 individuals eligible for the *any cardiac outcome* analysis since these cohort members reported

none of the six cardiac outcomes of interest prior to the 2003 survey. The *myocardial dysfunction* analysis included slightly more people (4,041) because while they could not have reported myocardial dysfunction prior to 2003, they may have reported some other cardiac diagnosis prior to the follow-up period (e.g., dysrhythmias).

Of the 3,358 eligible survivors who reported no cardiac outcomes prior to 2003, 11.2% had at least one cardiac diagnosis between 2003 and 2007. The most common outcome relative to each at-risk population was arteriosclerosis (9.4% of 3,612 at-risk) followed by dysrhythmias (1.7% of 3,928 at-risk). The least common diagnoses during follow-up were pericardial disease (0.2% of 4,093 at-risk) and valve disease (0.4% of 4,056 at-risk).

The characteristics of the population at risk for each outcome are shown in Table(s) 6.2. Regardless of the slight differences in the total at-risk population for each analysis, similar characteristics were observed. Those receiving anthracyclines were older at the time of the study ($p < 0.01$), more likely to be male ($p < 0.01$), and had slightly higher self-reported household incomes ($p < 0.01$) than those not receiving anthracyclines. Additionally, the survivors exposed to anthracyclines were more likely to have reported at least one echocardiogram in the past ($p < 0.0001$). Diagnosis and other treatment characteristics also differed between the groups. Those receiving anthracyclines were more likely than the unexposed to: have been diagnosed with either a leukemia or lymphoma ($p < 0.0001$); have had an amputation ($p < 0.0001$); be older at their time of diagnosis ($p < 0.0001$); have been treated with platinum ($p < 0.0001$) or non-platinum alkylating agents ($p < 0.0001$); have received radiation not involving the heart ($p < 0.0001$); have been diagnosed with some other (e.g., congenital) heart condition ($p < 0.01$); have received cardiac medication ($p < 0.001$); or have had heart surgery unrelated to the cardiac outcomes of interest ($p < 0.05$).

Overall, the survivors who were treated with anthracyclines were more likely than the unexposed to have been diagnosed with any cardiac outcome (12.8% versus 10.2%, $p = 0.0173$). Table 6.3 provides the frequency and percent of each cardiac outcome reported during the

follow-up period, relative to the population at risk for that diagnosis. All cardiac outcomes, regardless or type, were more likely to occur among survivors who received anthracyclines though only the differences for myocardial dysfunction ($p < 0.0001$), dysrhythmias ($p = 0.0009$), and valve disease ($p = 0.0077$) were statistically significant across the two groups.

The crude and adjusted associations of each cardiac outcome with anthracyclines and physical inactivity separately are provided in Table 6.4. There were statistically significant crude associations between anthracyclines and myocardial dysfunction (OR: 9.6, 95% CI: 3.3-27.5), dysrhythmias (OR: 2.3, 95% CI: 1.4-3.7), and valve disease (OR: 3.7, 95% CI: 1.3-10.4). Independent of anthracycline exposure, those with arteriosclerosis (OR: 1.5, 95% CI: 1.2-1.9) and any cardiac outcome (OR: 1.4, 95% CI: 1.1-1.7) were more likely to be inactive than those without the outcome. After controlling for confounders, myocardial dysfunction was the only outcome associated with anthracycline exposure (adjusted OR: 9.6, 95% CI: 2.9-31.4) and arteriosclerosis was the only outcome associated with physical inactivity (adjusted OR: 1.3, 95% CI: 1.1-1.7).

Table 6.5 provides the estimated indirect, direct, and total adjusted effects of anthracycline exposure and physical inactivity on each cardiac outcome. Myocardial dysfunction was the only outcome with a statistically significant total effect (OR: 9.59, 95% CI: 1.84-49.30). The decomposition analysis demonstrated that the indirect effect attributable to physical inactivity was negligible with an OR of 1.00 (95% CI: 0.98-1.02) and the overall association was driven entirely by the direct effect of anthracyclines (OR: 9.55; 95% CI: 1.83-49.84). Similarly, no associations between anthracycline exposure and the other cardiac outcomes could be explained by the differences in physical activity between the groups.

DISCUSSION

Many consensus-based physical activity recommendations for cancer survivors have traditionally emphasized restriction rather than activity due to the absence of definitive

evidence-based guidelines, particularly for survivors with the highest risk for treatment cardiotoxicities.[256] While the findings from our data indicate that very little, if any, of the increased incidence of cardiac outcomes among this cohort of long-term childhood cancer survivors treated with anthracyclines can be explained by physical inactivity, regular physical activity still remains essential in ameliorating additive risk factors for cardiac outcomes such as obesity and vascular health.[226-228]

While the CCSS is the largest and most comprehensive and diverse cohort of cancer survivors in North America, both the study data and the current analysis may be subject to limitations. First, not all eligible survivors participate in these surveys. However, the proportion of survivors who elect not to participate in the CCSS does not differ substantially from other similar cohort studies of cancer survivors.[4,257-259]

Second, both the cardiac outcomes and physical activity levels were assessed using self-reported data which may be subject to bias and imprecision. Strath et al.[260] compared physical activity questions with an objective measure (heart rate motion sensor technique) and showed that under-reporting and over-reporting were only apparent for moderate intensity activities and these balanced each other out such that there were no differences between the self-reported and the objective data. Sensitivity for meeting CDC recommendations was 91% with a specificity of 71%. Similarly, the self-report of outcomes may also present a problem. Even assuming accurate reporting, it is possible that some of the subjects had undiagnosed anthracycline-induced cardiac problems.

Third, the simplified causal diagram in Figure 6.1 ignores the possible bidirectional relationship between cardiac outcomes and physical activity levels. As people develop subclinical cardiac dysfunction, they may respond by decreasing their activity levels. Lastly, the methodology used in this study is relatively new and there are other ways of estimating direct and indirect effects. [261-264]

Despite the limitations, results of this study help better define the mechanism by which anthracyclines may affect cardiac outcomes and clarify the role of exercise deconditioning among long-term childhood cancer survivors. Additionally, this analysis provides an example of how a relatively new methodology can be used in epidemiologic research to help understand the inter-relation of two or more causal pathways.

FIGURE 6.1: Simplified DAG depicting the association of anthracyclines, exercise deconditioning, and cardiac outcomes

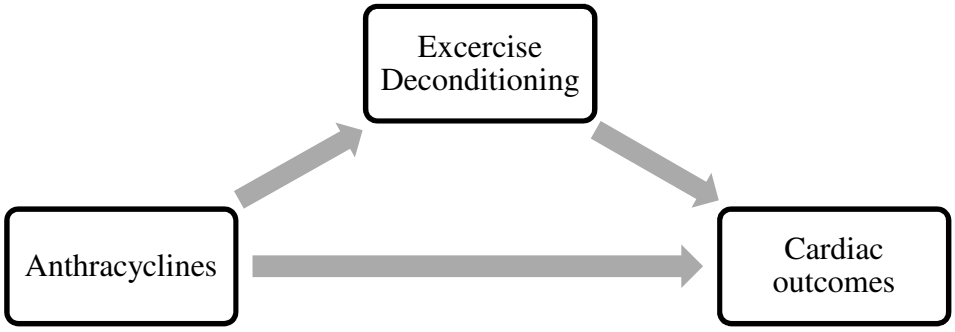

TABLE 6.1: Grouping of cardiac outcomes

Grouping	**Defined as a positive answer to at least one of the following questions:**
Myocardial dysfunction	Have you ever been told by a doctor or other health care professional that you have, or have had **congestive heart failure** or **cardiomyopathy** (weak heart muscle)? Have you ever had a **heart transplant**?
Dysrhythmias	Have you ever been told by a doctor or other health care professional that you have, or have had **irregular heartbeat** or **palpitations** (Arrhythmia) requiring mediation or follow-up by a doctor? Have you ever had surgery for **pacemaker**?
Pericardial disease	Have you ever been told by a doctor or other health care professional that you have, or have had **pericarditis** or fluid around the heart? Have you ever been told by a doctor or other health care professional that you have, or have had **pericardial constriction** (scarring or tightness of the sac around the heart)? Have you ever had surgery for **pericardiectomy** (stripping of the sac around the heart)?
Valve disease	Have you ever been told by a doctor or other health care professional that you have, or have had **stiff or leaking heart valves**? Have you ever had surgery for **heart valve replacement**?
Coronary artery disease	Have you ever been told by a doctor or other health care professional that you have, or have had a **myocardial infarction** (heart attack)? Have you ever been told by a doctor or other health care professional that you have, or have had **coronary heart disease**? Have you ever been told by a doctor or other health care professional that you have, or have had **angina pectoris** (chest pains due to lack of oxygen to the heart requiring medication such as nitroglycerin)? Have you ever had **coronary artery bypass surgery**? Have you ever had a **heart catheterization** ("heart cath")? Have you ever had **angioplasty** (enlarging a heart vessel using a balloon)?
Arteriosclerosis	Have you ever been told by a doctor or other health care professional that you have, or have had **hypertension** (high blood pressure) requiring medication? Have you ever been told by a doctor or other health care professional that you have, or have had **high cholesterol** (or triglyceride) requiring prescription medication? Have you ever been told by a doctor or other health care professional that you have, or have had **blood clot** in head, lung, arm, leg, or pelvis?

FIGURE 6.2: Study population and exclusions

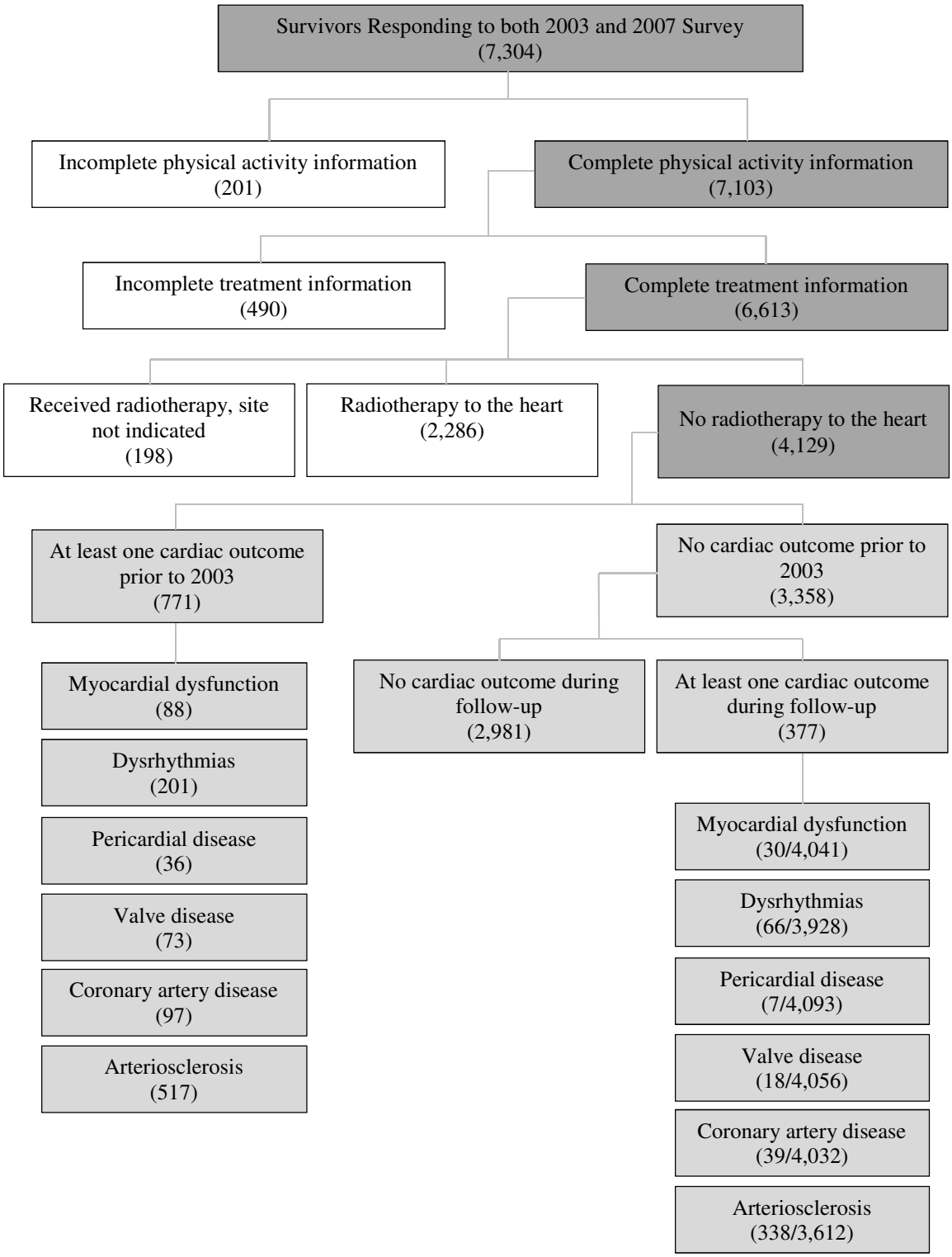

TABLE 6.2.1 (Any Cardiac Outcome): Characteristics of study population with no cardiac outcome prior to 2003 (n = 3,358), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,042)	Anthracyclines, N (%) Yes (n = 1,316)	*P**
Age at beginning of follow-up			
17-24 years	630 (63.70)	359 (36.30)	0.0066
25-34 years	940 (61.28)	594 (38.72)	
35-54 years	472 (56.53)	363 (43.47)	
Sex			
Male	962 (58.55)	681 (41.45)	0.0087
Female	1,080 (62.97)	635 (37.03)	
Race/Ethnicity			
White, non-Hispanic	1,853 (61.01)	1,184 (38.99)	0.4560
Other	189 (58.88)	132 (41.12)	
Household income			
$40,000 or more	1,067 (58.12)	769 (41.88)	0.0017
<$40,000	668 (63.50)	384 (36.50)	
Unknown/missing	307 (65.32)	163 (34.68)	
Highest Education Level			
More than high school	1,622 (60.30)	1,068 (39.70)	0.2376
High school or less	392 (62.32)	237 (37.68)	
Unknown/missing	28 (71.79)	11 (28.21)	
General Health Status			
Excellent	427 (59.47)	291 (40.53)	
Very good	809 (60.92)	519 (39.08)	
Good	578 (60.59)	376 (39.41)	0.6845
Fair	190 (63.76)	108 (36.24)	
Poor	28 (59.57)	19 (40.43)	
Unknown/missing	10 (76.92)	3 (23.08)	
CVRFC			
Yes	25 (58.14)	18 (41.86)	0.7181
No	2,017 (60.84)	1,298 (39.16)	
Last Echocardiogram			
Never	1,437 (78.31)	398 (21.69)	
Less than 5 years ago	200 (34.90)	373 (65.10)	<0.0001
5 or more years ago	154 (30.37)	353 (69.63)	
Unknown/missing	251 (56.66)	192 (43.34)	
Amputation			
Yes	49 (24.02)	155 (75.98)	<0.0001
No	1,993 (63.19)	1,161 (36.81)	
Does not meet activity recommendations			0.5858
Yes	1,051 (60.37)	690 (39.63)	
No	991 (61.29)	626 (38.71)	

TABLE 6.2.1 (Any Cardiac Outcome): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,042)	Anthracyclines, N (%) Yes (n = 1,316)	*P**
Cancer Diagnosis			
Leukemia	851 (53.45)	741 (46.55)	
Lymphoma	97 (44.70)	120 (55.30)	
Sarcoma	231 (63.81)	131 (36.19)	<0.0001
Wilm's tumor	174 (89.23)	21 (10.77)	
Neuroblastoma	165 (73.99)	58 (26.01)	
Other	524 (68.14)	245 (31.86)	
Age at Cancer Diagnosis			
<5 years	1,099 (67.76)	523 (32.24)	<0.0001
5 to <10 years	476 (62.96)	280 (37.04)	
10 to <21 years	467 (47.65)	513 (52.35)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	531 (33.42)	1,058 (66.58)	
No	1,511 (85.42)	258 (14.58)	
Received Platinum			
Yes	26 (17.93)	119 (82.07)	<0.0001
No	2,016 (62.75)	1,197 (37.25)	
Received Radiation not involving heart			
Yes	846 (55.77)	671 (44.23)	<0.0001
No	1,196 (64.96)	645 (35.04)	
Other heart condition			
Yes	122 (51.05)	117 (48.95)	0.0013
No	1,920 (61.56)	1,199 (38.44)	
Other heart surgery			
Yes	7 (35.00)	13 (65.00)	0.0177
No	2,035 (60.96)	1,303 (39.04)	
Ever take medications for heart conditions			<0.0001
Yes	8 (24.24)	25 (75.76)	
No	2,034 (61.17)	1,291 (38.83)	

*Pearson chi-square test of homogeneity

TABLE 6.2.2 (Myocardial Dysfunction): Characteristics of study population with no myocardial dysfunction prior to 2003 (n = 4,041), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,395)	Anthracyclines, N (%) Yes (n = 1,646)	*P**
Age at beginning of follow-up			
17-24 years	692 (62.91)	408 (37.09)	0.0003
25-34 years	1,078 (59.92)	721 (40.08)	
35-54 years	625 (54.73)	517 (45.27)	
Sex			
Male	1,115 (56.57)	856 (43.43)	0.0007
Female	1,280 (61.84)	790 (38.16)	
Race/Ethnicity			
White, non-Hispanic	2,186 (59.56)	1,484 (40.44)	0.2276
Other	209 (56.33)	162 (43.67)	
Household income			
$40,000 or more	1,266 (56.09)	991 (43.91)	<0.0001
<$40,000	776 (62.73)	461 (37.27)	
Unknown/missing	353 (64.53)	194 (35.47)	
Highest Education Level			
More than high school	1,907 (58.82)	1,335 (41.18)	0.1884
High school or less	456 (60.48)	298 (39.52)	
Unknown/missing	32 (71.11)	13 (28.89)	
General Health Status			
Excellent	479 (58.41)	341 (41.59)	
Very good	918 (59.07)	636 (40.93)	
Good	703 (58.93)	490 (41.07)	0.6451
Fair	242 (62.86)	143 (37.14)	
Poor	43 (57.33)	32 (42.67)	
Unknown/missing	10 (71.43)	4 (28.57)	
CVRFC			
Yes	56 (57.73)	41 (42.27)	0.7554
No	2,339 (59.31)	1,605 (40.69)	
Last Echocardiogram			
Never	1,602 (77.58)	463 (22.42)	
Less than 5 years ago	307 (36.94)	524 (63.06)	<0.0001
5 or more years ago	208 (32.35)	435 (67.65)	
Unknown/missing	278 (55.38)	224 (44.62)	
Amputation			
Yes	73 (24.09)	230 (75.91)	<0.0001
No	2,322 (62.12)	1,416 (37.88)	
Does not meet activity recommendations			0.2687
Yes	1,241 (58.46)	882 (41.54)	
No	1,154 (60.17)	764 (39.83)	

TABLE 6.2.2 (Myocardial Dysfunction): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,395)	Anthracyclines, N (%) Yes (n = 1,646)	*P**
Cancer Diagnosis			
Leukemia	982 (52.68)	882 (47.32)	
Lymphoma	121 (42.01)	167 (57.99)	
Sarcoma	274 (63.72)	156 (36.28)	<0.0001
Wilm's tumor	197 (88.34)	26 (11.66)	
Neuroblastoma	183 (74.09)	64 (25.91)	
Other	638 (64.51)	351 (35.49)	
Age at Cancer Diagnosis			
<5 years	1,224 (67.22)	597 (32.78)	<0.0001
5 to <10 years	558 (62.14)	340 (37.86)	
10 to <21 years	613 (46.37)	709 (53.63)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	629 (32.36)	1,315 (67.64)	
No	1,766 (84.22)	331 (15.78)	
Received Platinum			
Yes	28 (14.81)	161 (85.19)	<0.0001
No	2,367 (61.45)	1,485 (38.55)	
Received Radiation not involving heart			
Yes	1,013 (55.36)	817 (44.64)	<0.0001
No	1,382 (62.51)	829 (37.49)	
Other heart condition			
Yes	197 (51.84)	183 (48.16)	0.0020
No	2,198 (60.04)	1,463 (39.96)	
Other heart surgery			
Yes	18 (43.90)	23 (56.10)	0.0442
No	2,377 (59.43)	1,623 (40.58)	
Ever take medications for heart conditions			0.0003
Yes	30 (38.96)	47 (61.04)	
No	2,365 (59.66)	1,599 (40.34)	

*Pearson chi-square test of homogeneity

TABLE 6.2.3 (Dysrhythmias): Characteristics of study population with no dysrhythmias prior to 2003 (n = 3,928), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,327)	Anthracyclines, N (%) Yes (n = 1,601)	*P**
Age at beginning of follow-up			
17-24 years	672 (62.45)	404 (37.55)	0.0008
25-34 years	1,056 (60.07)	702 (39.93)	
35-54 years	599 (54.75)	495 (45.25)	
Sex			
Male	1,097 (56.58)	842 (43.42)	0.0008
Female	1,230 (61.84)	759 (38.16)	
Race/Ethnicity			
White, non-Hispanic	2,125 (59.61)	1,440 (40.39)	0.1435
Other	202 (55.65)	161 (44.35)	
Household income			
$40,000 or more	1,225 (56.14)	957 (43.86)	<0.0001
<$40,000	757 (62.46)	455 (37.54)	
Unknown/missing	345 (64.61)	189 (35.39)	
Highest Education Level			
More than high school	1,850 (58.79)	1,297 (41.21)	0.2169
High school or less	446 (60.52)	291 (39.48)	
Unknown/missing	31 (70.45)	13 (29.55)	
General Health Status			
Excellent	469 (58.33)	335 (41.67)	
Very good	898 (59.31)	616 (40.69)	
Good	684 (59.22)	471 (40.78)	0.9031
Fair	228 (61.29)	144 (38.71)	
Poor	38 (55.88)	30 (44.12)	
Unknown/missing	10 (66.67)	5 (33.33)	
CVRFC			
Yes	56 (58.33)	40 (41.67)	0.8546
No	2,271 (59.26)	1,561 (40.74)	
Last Echocardiogram			
Never	1,583 (77.79)	452 (22.21)	
Less than 5 years ago	271 (34.65)	511 (65.35)	<0.0001
5 or more years ago	197 (32.08)	417 (67.92)	
Unknown/missing	276 (55.53)	221 (44.47)	
Amputation			
Yes	71 (24.57)	218 (75.43)	<0.0001
No	2,256 (62.00)	1,383 (38.00)	
Does not meet activity recommendations			0.3939
Yes	1,212 (58.61)	856 (41.39)	
No	1,115 (59.95)	745 (40.05)	

TABLE 6.2.3 (Dysrhythmias): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,327)	Anthracyclines, N (%) Yes (n = 1,601)	*P**
Cancer Diagnosis			
Leukemia	955 (52.59)	861 (47.41)	
Lymphoma	118 (42.14)	162 (57.86)	
Sarcoma	264 (63.77)	150 (36.23)	<0.0001
Wilm's tumor	189 (88.32)	25 (11.68)	
Neuroblastoma	179 (73.66)	64 (26.34)	
Other	622 (64.72)	339 (35.28)	
Age at Cancer Diagnosis			
<5 years	1,197 (66.72)	597 (33.28)	<0.0001
5 to <10 years	538 (62.12)	328 (37.88)	
10 to <21 years	592 (46.69)	676 (53.31)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	613 (32.43)	1,277 (67.57)	
No	1,714 (84.10)	324 (15.90)	
Received Platinum			
Yes	28 (15.22)	156 (84.78)	<0.0001
No	2,299 (61.40)	1,445 (38.60)	
Received Radiation not involving heart			
Yes	985 (55.21)	799 (44.79)	<0.0001
No	1,342 (62.59)	802 (37.41)	
Other heart condition			
Yes	170 (51.36)	161 (48.64)	0.0023
No	2,157 (59.97)	1,440 (40.03)	
Other heart surgery			
Yes	16 (39.02)	25 (60.98)	0.0081
No	2,311 (59.45)	1,576 (40.55)	
Ever take medications for heart conditions			<0.0001
Yes	19 (30.16)	44 (69.84)	
No	2,308 (59.72)	1,557 (40.28)	

*Pearson chi-square test of homogeneity

TABLE 6.2.4 (Pericardial Disease): Characteristics of study population with no pericardial disease prior to 2003 (n = 4,093), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,397)	Anthracyclines, N (%) Yes (n = 1,696)	*P**
Age at beginning of follow-up			
17-24 years	695 (62.33)	420 (37.67)	0.0001
25-34 years	1,079 (59.29)	741 (40.71)	
35-54 years	623 (53.80)	535 (46.20)	
Sex			
Male	1,117 (55.91)	881 (44.09)	0.0008
Female	1,280 (61.10)	815 (38.90)	
Race/Ethnicity			
White, non-Hispanic	2,188 (58.90)	1,527 (41.10)	0.1752
Other	209 (55.29)	169 (44.71)	
Household income			
$40,000 or more	1,268 (55.47)	1,018 (44.53)	<0.0001
<$40,000	775 (61.90)	477 (38.10)	
Unknown/missing	354 (63.78)	201 (36.22)	
Highest Education Level			
More than high school	1,905 (57.99)	1,380 (42.01)	0.0848
High school or less	460 (60.21)	304 (39.79)	
Unknown/missing	32 (72.73)	12 (27.27)	
General Health Status			
Excellent	477 (57.82)	348 (42.18)	
Very good	916 (58.57)	648 (41.43)	
Good	708 (58.37)	505 (41.63)	0.7404
Fair	243 (61.06)	155 (38.94)	
Poor	43 (54.43)	36 (45.57)	
Unknown/missing	10 (71.43)	4 (28.57)	
CVRFC			
Yes	58 (56.31)	45 (43.69)	0.6383
No	2,339 (58.62)	1,651 (41.38)	
Last Echocardiogram			
Never	1,601 (77.53)	464 (22.47)	
Less than 5 years ago	314 (35.36)	574 (64.64)	<0.0001
5 or more years ago	204 (31.88)	436 (68.13)	
Unknown/missing	278 (55.60)	222 (44.40)	
Amputation			
Yes	74 (23.49)	241 (76.51)	<0.0001
No	2,323 (61.49)	1,455 (38.51)	
Does not meet activity recommendations			0.2383
Yes	1,247 (57.70)	914 (42.30)	
No	1,150 (59.52)	782 (40.48)	

TABLE 6.2.4 (Pericardial Disease): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,397)	Anthracyclines, N (%) Yes (n = 1,696)	*P**
Cancer Diagnosis			
Leukemia	982 (52.26)	897 (47.74)	
Lymphoma	120 (41.24)	171 (58.76)	
Sarcoma	275 (62.93)	162 (37.07)	<0.0001
Wilm's tumor	197 (87.95)	27 (12.05)	
Neuroblastoma	185 (74.00)	65 (26.00)	
Other	638 (63.04)	374 (36.96)	
Age at Cancer Diagnosis			
<5 years	1,226 (66.56)	616 (33.44)	<0.0001
5 to <10 years	558 (61.12)	355 (38.88)	
10 to <21 years	613 (45.81)	725 (54.19)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	630 (31.80)	1,351 (68.20)	
No	1,767 (83.66)	345 (16.34)	
Received Platinum			
Yes	28 (14.07)	171 (85.93)	<0.0001
No	2,369 (60.84)	1,525 (39.16)	
Received Radiation not involving heart			
Yes	1,015 (54.84)	836 (45.16)	<0.0001
No	1,382 (61.64)	860 (38.36)	
Other heart condition			
Yes	197 (50.90)	190 (49.10)	0.0013
No	2,200 (59.36)	1,506 (40.64)	
Other heart surgery			
Yes	20 (38.46)	32 (61.54)	0.0031
No	2,377 (58.82)	1,664 (41.18)	
Ever take medications for heart conditions			<0.0001
Yes	33 (30.56)	75 (69.44)	
No	2,364 (59.32)	1,621 (40.68)	

*Pearson chi-square test of homogeneity

TABLE 6.2.5 (Valve Disease): Characteristics of study population with no valve disease prior to 2003 (n = 4,056), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,378)	Anthracyclines, N (%) Yes (n = 1,678)	*P**
Age at beginning of follow-up			
17-24 years	693 (62.66)	413 (37.34)	0.0001
25-34 years	1,069 (59.16)	738 (40.84)	
35-54 years	616 (53.89)	527 (46.11)	
Sex			
Male	1,114 (56.23)	867 (43.77)	0.0025
Female	1,264 (60.92)	811 (39.08)	
Race/Ethnicity			
White, non-Hispanic	2,169 (58.99)	1,508 (41.01)	0.1480
Other	209 (55.15)	170 (44.85)	
Household income			
$40,000 or more	1,253 (55.37)	1,010 (44.63)	<0.0001
<$40,000	774 (61.97)	475 (38.03)	
Unknown/missing	351 (64.52)	193 (35.48)	
Highest Education Level			
More than high school	1,887 (57.95)	1,369 (42.05)	0.0617
High school or less	459 (60.71)	297 (39.29)	
Unknown/missing	32 (72.73)	12 (27.27)	
General Health Status			
Excellent	477 (58.10)	344 (41.90)	
Very good	908 (58.69)	639 (41.31)	
Good	701 (58.56)	496 (41.44)	0.8158
Fair	239 (60.20)	158 (39.80)	
Poor	43 (53.75)	37 (46.25)	
Unknown/missing	10 (71.43)	4 (28.57)	
CVRFC			
Yes	57 (55.88)	45 (44.12)	0.5683
No	2,321 (58.70)	1,633 (41.30)	
Last Echocardiogram			
Never	1,600 (77.67)	460 (22.33)	
Less than 5 years ago	300 (34.68)	565 (65.32)	<0.0001
5 or more years ago	201 (31.90)	429 (68.10)	
Unknown/missing	277 (55.29)	224 (44.71)	
Amputation			
Yes	74 (23.72)	238 (76.28)	<0.0001
No	2,304 (61.54)	1,440 (38.46)	
Does not meet activity recommendations			0.2803
Yes	1,236 (57.84)	901 (42.16)	
No	1,142 (59.51)	777 (40.49)	

TABLE 6.2.5 (Valve Disease): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,378)	Anthracyclines, N (%) Yes (n = 1,678)	*P**
Cancer Diagnosis			
Leukemia	975 (52.33)	888 (47.67)	
Lymphoma	119 (41.46)	168 (58.54)	
Sarcoma	273 (62.47)	164 (37.53)	<0.0001
Wilm's tumor	196 (88.29)	26 (11.71)	
Neuroblastoma	184 (74.19)	64 (25.81)	
Other	631 (63.16)	368 (36.84)	
Age at Cancer Diagnosis			
<5 years	1,223 (66.79)	608 (33.21)	<0.0001
5 to <10 years	551 (60.82)	355 (39.18)	
10 to <21 years	604 (45.79)	715 (54.21)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	625 (31.84)	1,338 (68.16)	
No	1,753 (83.76)	340 (16.24)	
Received Platinum			
Yes	28 (14.14)	170 (85.86)	<0.0001
No	2,350 (60.91)	1,508 (39.09)	
Received Radiation not involving heart			
Yes	1,008 (54.63)	837 (45.37)	<0.0001
No	1,370 (61.96)	841 (38.04)	
Other heart condition			
Yes	183 (50.69)	178 (49.31)	0.0013
No	2,195 (59.40)	1,500 (40.60)	
Other heart surgery			
Yes	17 (33.33)	34 (66.67)	0.0002
No	2,361 (58.95)	1,644 (41.05)	
Ever take medications for heart conditions			<0.0001
Yes	29 (27.10)	78 (72.90)	
No	2,349 (59.48)	1,600 (40.52)	

*Pearson chi-square test of homogeneity

TABLE 6.2.6 (Coronary Artery Disease): Characteristics of study population with no coronary artery disease prior to 2003 (n = 4,032), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,369)	Anthracyclines, N (%) Yes (n = 1,663)	*P**
Age at beginning of follow-up			
17-24 years	682 (62.63)	407 (37.37)	0.0001
25-34 years	1,074 (59.44)	733 (40.56)	
35-54 years	613 (53.96)	523 (46.04)	
Sex			
Male	1,100 (56.24)	856 (43.76)	0.0016
Female	1,269 (61.13)	807 (38.87)	
Race/Ethnicity			
White, non-Hispanic	2,160 (59.05)	1,498 (40.95)	0.2361
Other	209 (55.88)	165 (44.12)	
Household income			
$40,000 or more	1,256 (55.72)	998 (44.28)	<0.0001
<$40,000	767 (62.00)	470 (38.00)	
Unknown/missing	346 (63.96)	195 (36.04)	
Highest Education Level			
More than high school	1,889 (58.18)	1,358 (41.82)	0.1190
High school or less	448 (60.54)	292 (39.46)	
Unknown/missing	32 (71.11)	13 (28.89)	
General Health Status			
Excellent	476 (58.12)	343 (41.88)	
Very good	911 (58.89)	636 (41.11)	
Good	696 (58.34)	497 (41.66)	0.6649
Fair	236 (61.46)	148 (38.54)	
Poor	40 (53.33)	35 (46.67)	
Unknown/missing	10 (71.43)	4 (28.57)	
CVRFC			
Yes	54 (56.84)	41 (43.16)	0.7015
No	2,315 (58.80)	1,622 (41.20)	
Last Echocardiogram			
Never	1,595 (77.58)	461 (22.42)	
Less than 5 years ago	299 (35.14)	552 (64.86)	<0.0001
5 or more years ago	200 (31.80)	429 (68.20)	
Unknown/missing	275 (55.44)	221 (44.56)	
Amputation			
Yes	73 (23.93)	232 (76.07)	<0.0001
No	2,296 (61.60)	1,431 (38.40)	
Does not meet activity recommendations			0.3474
Yes	1,228 (58.06)	887 (41.94)	
No	1,141 (59.52)	776 (40.48)	

TABLE 6.2.6 (Coronary Artery Disease): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,369)	Anthracyclines, N (%) Yes (n = 1,663)	*P**
Cancer Diagnosis			
Leukemia	977 (52.61)	880 (47.39)	
Lymphoma	121 (41.72)	169 (58.28)	
Sarcoma	271 (62.73)	161 (37.27)	<0.0001
Wilm's tumor	193 (87.73)	27 (12.27)	
Neuroblastoma	181 (74.49)	62 (25.51)	
Other	626 (63.23)	364 (36.77)	
Age at Cancer Diagnosis			
<5 years	1,213 (66.94)	599 (33.06)	<0.0001
5 to <10 years	554 (61.15)	352 (38.85)	
10 to <21 years	602 (45.81)	712 (54.19)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	622 (31.98)	1,323 (68.02)	
No	1,747 (83.71)	340 (16.29)	
Received Platinum			
Yes	28 (14.29)	168 (85.71)	<0.0001
No	2,341 (61.03)	1,495 (38.97)	
Received Radiation not involving heart			
Yes	1,002 (54.93)	822 (45.07)	<0.0001
No	1,367 (61.91)	841 (38.09)	
Other heart condition			
Yes	187 (51.09)	179 (48.91)	0.0018
No	2,182 (59.52)	1,484 (40.48)	
Other heart surgery			
Yes	14 (36.84)	24 (63.16)	0.0058
No	2,355 (58.96)	1,639 (41.04)	
Ever take medications for heart conditions			<0.0001
Yes	26 (27.96)	67 (72.04)	
No	2,343 (59.48)	1,596 (40.52)	

*Pearson chi-square test of homogeneity

TABLE 6.2.7 (Arteriosclerosis): Characteristics of study population with no arteriosclerosis prior to 2003 (n = 3,612), by anthracycline exposure status

Characteristic	Anthracyclines, N (%) No (n = 2,145)	Anthracyclines, N (%) Yes (n = 1,467)	*P**
Age at beginning of follow-up			
17-24 years	666 (62.71)	396 (37.29)	0.0037
25-34 years	973 (59.51)	662 (40.49)	
35-54 years	506 (55.30)	409 (44.70)	
Sex			
Male	997 (57.13)	748 (42.87)	0.0077
Female	1,148 (61.49)	719 (38.51)	
Race/Ethnicity			
White, non-Hispanic	1,950 (59.61)	1,321 (40.39)	0.3846
Other	195 (57.18)	146 (42.82)	
Household income			
$40,000 or more	1,130 (56.67)	864 (43.33)	0.0011
<$40,000	694 (62.52)	416 (37.48)	
Unknown/missing	321 (63.19)	187 (36.81)	
Highest Education Level			
More than high school	1,703 (58.81)	1,193 (41.19)	0.1303
High school or less	413 (61.09)	263 (38.91)	
Unknown/missing	29 (72.50)	11 (27.50)	
General Health Status			
Excellent	448 (58.79)	314 (41.21)	
Very good	841 (59.60)	570 (40.40)	
Good	613 (58.89)	428 (41.11)	0.7685
Fair	201 (61.85)	124 (38.15)	
Poor	32 (54.24)	27 (45.76)	
Unknown/missing	10 (71.43)	4 (28.57)	
CVRFC			
Yes	26 (55.32)	21 (44.68)	0.5678
No	2,119 (59.44)	1,446 (40.56)	
Last Echocardiogram			
Never	1,462 (77.97)	413 (22.03)	
Less than 5 years ago	247 (34.59)	467 (65.41)	<0.0001
5 or more years ago	181 (31.75)	389 (68.25)	
Unknown/missing	255 (56.29)	198 (43.71)	
Amputation			
Yes	53 (22.46)	183 (77.54)	<0.0001
No	2,092 (61.97)	1,284 (38.03)	
Does not meet activity recommendations			0.3894
Yes	1,099 (58.71)	773 (41.29)	
No	1,046 (60.11)	694 (39.89)	

TABLE 6.2.7 (Arteriosclerosis): (Continued)

Characteristic	Anthracyclines, N (%) No (n = 2,145)	Anthracyclines, N (%) Yes (n = 1,467)	*P**
Cancer Diagnosis			
Leukemia	893 (52.53)	807 (47.47)	
Lymphoma	102 (42.50)	138 (57.50)	
Sarcoma	240 (62.18)	146 (37.82)	<0.0001
Wilm's tumor	185 (88.10)	25 (11.90)	
Neuroblastoma	175 (74.15)	61 (25.85)	
Other	550 (65.48)	290 (34.52)	
Age at Cancer Diagnosis			
<5 years	1,148 (66.63)	575 (33.37)	<0.0001
5 to <10 years	497 (61.51)	311 (38.49)	
10 to <21 years	500 (46.25)	581 (53.75)	
Received (non-Platinum) Alkylating Agents			<0.0001
Yes	557 (32.16)	1,175 (67.84)	
No	1,588 (84.47)	292 (15.53)	
Received Platinum			
Yes	26 (16.15)	135 (83.85)	<0.0001
No	2,119 (61.40)	1,332 (38.60)	
Received Radiation not involving heart			
Yes	882 (54.88)	725 (45.12)	<0.0001
No	1,263 (62.99)	742 (37.01)	
Other heart condition			
Yes	173 (49.86)	174 (50.14)	0.0001
No	1,972 (60.40)	1,293 (39.60)	
Other heart surgery			
Yes	16 (33.33)	32 (66.67)	0.0002
No	2,129 (59.74)	1,435 (40.26)	
Ever take medications for heart conditions			<0.0001
Yes	20 (25.97)	57 (74.03)	
No	2,125 (60.11)	1,410 (39.89)	

*Pearson chi-square test of homogeneity

TABLE 6.3: Cardiac outcomes reported during follow-up, by anthracycline exposure status

Reported outcome during follow-up	Anthracyclines, N (%)		*P**
	No	Yes	
Any cardiac outcome (n = 3,358)			
Yes	208 (55.17)	169 (44.83)	0.0173
No	1,834 (61.52)	1,147 (38.48)	
Myocardial dysfunction (n = 4,041)			
Yes	4 (13.33)	26 (86.67)	<0.0001
No	2,391 (59.61)	1,620 (40.39)	
Dysrhythmias (n = 3,928)			
Yes	26 (39.39)	40 (60.61)	0.0009
No	2,301 (59.58)	1,561 (40.42)	
Pericardial disease (n = 4,093)			
Yes	2 (28.57)	5 (71.43)	0.1342†
No	2,395 (58.61)	1,691 (41.39)	
Valve disease (n = 4,056)			
Yes	5 (27.78)	13 (72.22)	0.0077
No	2,373 (58.77)	1,665 (41.23)	
Coronary artery disease (n = 4,032)			
Yes	19 (48.72)	20 (51.28)	0.2007
No	2,350 (58.85)	1,643 (41.15)	
Arteriosclerosis (n = 3,612)			
Yes	187 (55.33)	151 (44.67)	0.1104
No	1,958 (59.80)	1,316 (40.20)	

* Pearson chi-square test of homogeneity

† Fisher's exact test

TABLE 6.4: Crude odds ratios (cOR), adjusted odds ratios (aOR), and 95% confidence intervals (CI) for the association of each outcome by anthracycline and inactivity exposure

	Outcome association with **Anthracycline Exposure**		Outcome association with **Inactivity Exposure**	
Outcome	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)
Any cardiac outcome*	1.3 (1.0-1.6)	1.0 (0.8-1.3)	1.4 (1.1-1.7)	1.3 (1.0-1.6)
Myocardial dysfunction†	9.6 (3.3-27.5)	9.6 (2.9-31.4)	1.2 (0.6-2.4)	0.9 (0.4-2.0)
Dysrhythmias‡	2.3 (1.4-3.7)	1.3 (0.7-2.3)	1.0 (0.6-1.6)	0.8 (0.5-1.3)
Pericardial disease¶	3.5 (0.7-18.3)	1.0 (0.1-6.7)	5.4 (0.6-44.7)	4.1 (0.5-36.2)
Valve disease**	3.7 (1.3-10.4)	2.4 (0.8-7.3)	3.2 (1.0-9.6)	2.8 (0.9-8.7)
Coronary artery disease††	1.5 (0.8-2.8)	0.7 (0.3-1.5)	1.3 (0.7-2.5)	1.0 (0.5-1.9)
Arteriosclerosis‡‡	1.2 (1.0-1.5)	1.0 (0.8-1.3)	1.5 (1.2-1.9)	1.3 (1.1-1.7)

*Adjusted for age, sex, race, income, education, receipt of (non-platinum) alkylating agents, receipt of platinum, other heart conditions, and other heart medications.

†Adjusted for age, sex, income, amputation, diagnosis, non-cardiac radiation, other heart medication

‡Adjusted for age, sex, race, income, general health status, timing of last echocardiogram, receipt of platinum, other heart surgery

¶Adjusted for age, sex, income, amputation, diagnosis, receipt of platinum, other heart surgery and other heart medication

**Adjusted for age, sex, income, timing of last echocardiogram, diagnosis, other heart medication

††Adjusted for age, sex, income, CVRFC, diagnosis, receipt of platinum, other heart conditions, other heart surgery, and other heart medication

‡‡Adjusted for age, sex, race, income, general health status, receipt of (non-platinum) alkylating agents

TABLE 6.5: Estimating the adjusted direct and indirect effect in the logit models

Outcome	**Total** aOR (95% CI)	**Indirect** aOR (95% CI)	**Direct** aOR (95% CI)
Any cardiac outcome*	1.02 (0.80-1.31)	1.00 (0.99-1.01)	1.02 (0.80-1.31)
Myocardial dysfunction†	9.53 (1.84-49.30)	1.00 (0.98-1.02)	9.55 (1.83-49.84)
Dysrhythmias‡	1.33 (0.68-2.58)	0.99 (0.98-1.01)	1.34 (0.69-2.60)
Pericardial disease¶	0.98 (0.10-9.42)	1.02 (0.99-1.06)	0.96 (0.10-9.24)
Valve disease**	2.21 (0.47-10.29)	1.02 (0.98-1.06)	2.16 (0.47-10.04)
Coronary artery disease††	0.70 (0.29-1.71)	1.00 (0.98-1.02)	0.70 (0.29-1.72)
Arteriosclerosis‡‡	1.01 (0.81-1.25)	1.00 (0.99-1.02)	1.00 (0.80-1.25)

aOR = adjusted odds ratio; CI = confidence interval

*Adjusted for age, sex, race, income, education, receipt of (non-platinum) alkylating agents, receipt of platinum, other heart conditions, and other heart medications.

†Adjusted for age, sex, income, amputation, diagnosis, non-cardiac radiation, other heart medication

‡Adjusted for age, sex, race, income, general health status, timing of last echocardiogram, receipt of platinum, other heart surgery

¶Adjusted for age, sex, income, amputation, diagnosis, receipt of platinum, other heart surgery and other heart medication

**Adjusted for age, sex, income, timing of last echocardiogram, diagnosis, other heart medication

††Adjusted for age, sex, income, CVRFC, diagnosis, receipt of platinum, other heart conditions, other heart surgery, and other heart medication

‡‡Adjusted for age, sex, race, income, general health status, receipt of (non-platinum) alkylating agents

CHAPTER 7 – CONCLUSIONS AND FUTURE DIRECTIONS

SUMMARY OF FINDINGS

Over the past few decades, there have been marked improvements in the survival rates of children diagnosed with cancer. These improvements have resulted in an ever-growing and aging population of childhood cancer survivors. Most of these survivors will experience at least one disease- or treatment-related late effect over their lifetime and their risk of developing long-term complications increases as they age. Physicians, patients, and research institutions have begun to recognize the need for lifelong surveillance of cancer survivors based on individualized assessment of therapeutic, genetic, and behavioral risk factors and comorbid conditions. The Children's Oncology Group (COG) has developed a set of guidelines for the long-term follow-up of childhood cancer survivors. These guidelines were the result of a collaborative effort of national experts in the field to provide recommendations for screening and management of late effects that may arise because of treatment. The primary goals of the guidelines are intended to increase quality of life and decrease complication-related healthcare costs by promoting healthy lifestyles, providing surveillance of health status, facilitating early identification of late effects, and offering timely interventions.

Although the COG recommendations are a useful source of information for clinicians and represent an important step towards improving the health and well-being of childhood cancer survivors, the recommendations are primarily based on consensus and not necessarily on specific clinical studies. In addition, the relatively small size of the survivor population and low rate of outcomes limits the ability to provide evidence-based recommendations for certain outcomes and exposures. For this reason, it is essential to continue research on late effects of childhood cancer survivors and on the best methods for early detection and intervention.

This dissertation sought to add evidence in support of recommendations for long-term care of childhood cancer survivors exposed to anthracyclines. The recommendations specific to

this population of survivors include monitoring for cardiac toxicity, cancer recurrence, development of secondary malignancies, psychosocial and mental health disorders, risky behaviors, psychosocial disability due to pain and fatigue, and maintaining a healthy lifestyle. This dissertation focuses on screening for anthracycline cardiotoxicity and psychosocial outcomes and on the relative importance of physical activity in modifying anthracycline cardiotoxicity.

The first study included in this dissertation indicated that addition of exercise testing might not be necessary for monitoring anthracycline cardiotoxicity. We observed very few clinically meaningful differences in systolic or diastolic function between the anthracycline-exposed survivors and the control group; however, the results did provide insight into the natural history of anthracycline cardiotoxicity in childhood cancer survivors. We observed some differences in heart rate as well as subtle differences in the septal early diastolic velocities at rest, when comparing those exposed to the highest doses of anthracyclines and the controls. These findings suggest the highest risk individuals may experience mild diastolic dysfunction at rest, though future studies are recommended to confirm these preliminary results. At peak exercise, the high-risk survivors had slightly abnormal oxygen pulse and stroke volume possibly reflecting filling inadequacies at maximal exercise. Despite these minor changes, anthracycline patients did not differ from controls with respect to global compensatory mechanisms during exercise and demonstrated normal exercise capacity. With exercise, young childhood cancer survivors exposed to high doses of anthracyclines appeared to be able to augment their systolic and diastolic function and achieve relatively normal maximal aerobic capacity.

The second study of the dissertation examined the effect of anthracyclines on reported quality of life (QoL) in long-term childhood cancer survivors. We used the Pediatric Quality of Life Inventory (PedsQL) to measure different domains of health-related QoL and found that the survivors treated with anthracyclines reported lower QoL than those not treated with anthracyclines and that there was a clear dose-response for overall (total) and physical QoL

domains. These data supported our hypothesis that survivors treated with increasing doses of anthracyclines would report lower PedsQL scores because compromised physical health, such as the subtle diastolic dysfunction and filling abnormalities found in dissertation study one, may have effects on psychosocial health. Additionally, because long-term survivors of childhood cancer are less likely than controls to participate in regular physical activity, we examined whether any association between reported PedsQL scores and anthracycline cardiotoxicity risk status was modified by physical activity levels. Contrary to expectation, we found no evidence that physical activity attenuates the associations between anthracycline exposure and PedsQL scores.

While monitoring of physical effects of the disease and its treatment in childhood cancer survivors is essential, it is also important to promote the maintenance of a healthy lifestyle in this at-risk population. The third study of the dissertation was primarily a methodological exercise to estimate the contribution of exercise deconditioning relative to the total effect of anthracycline cardiotoxicity in order to determine the relative importance that an exercise intervention may have in this population. We used data from the Childhood Cancer Survivor Study (CCSS) and applied a new decomposition method developed by Robert Erikson[253] and extended to the logistic model by Maarten Buis.[254] As expected, the survivors who were treated with anthracyclines were nearly ten times more likely than the unexposed to have been diagnosed with myocardial dysfunction. However, the decomposition analysis demonstrated that the indirect effect attributable to physical inactivity was negligible and that the observed association was driven entirely by the direct effect of anthracyclines. Despite hopes that physical activity may attenuate the effects of anthracyclines, we found that very little, if any, of the increased incidence of cardiac outcomes among this relatively young cohort of anthracycline-exposed cancer survivors can be explained by (self-reported) physical inactivity.

DISSERTATION STRENGTHS AND LIMITATIONS

For the first two studies of the dissertation, we collected primary clinical data from a sample of childhood cancer survivors. One of the main strengths of this study was the availability of detailed anthracycline exposure-related and other clinical information, obtained directly from the medical records. In addition, exposure was measured prior to the outcomes, a methodological feature that allows overcoming the limitations of cross-sectional studies.

These strengths notwithstanding, certain limitations of the data may affect the interpretation of results. The study population recruited among children diagnosed through Children's Healthcare of Atlanta (CHOA) was likely not representative of all childhood cancer survivors. While we attempted to include participants who had never or rarely been followed by the Aflac Cancer Survivorship Clinic at CHOA, many of these patients (n = 87) were unreachable (50.6%), many were subsequently deemed ineligible due to inaccuracies or incompleteness of medical records (16.1%), and about one-fifth (19.5%) declined participation. As a result, only 41% of eligible CHOA patients (n = 12) not actively followed through the Aflac Survivor Clinic participated in the study, comprising only 15% of the analysis sample. The 144 patients that were approached through the Aflac Cancer Survivor Clinic had a slightly higher participation rate of 47.2%. This resulted in 68 survivor clinic patients contributing to our final study sample (85% of sample). Those who are actively followed through Alfac's Cancer Survivor Program may differ from other eligible patients. The sample size, particularly for the highest risk group, was small, limiting our statistical power to detect differences.

In addition to methodological features discussed above, the first study is notable because, we utilized highly skilled echocardiography technicians and sonographers with clinical research experience who were blinded to patient risk status and we conducted double-abstraction of a 10% random sample of all exams that showed high concordance of measurements. While these procedures lead to high-quality data while minimizing potential outcome misclassification, the clinical utility of TDI and SRI techniques in screening for late cardiotoxic effects of

anthracyclines has not been established and the attainment of similarly high-quality data in a clinical setting may not be possible.

An additional strength of the second study is that it was the first report on the association between long-term health related quality of life and anthracycline exposure. The observed anthracycline dose-dependent trend seen for PedsQL scores may be a reflection of the overall treatment intensity rather than the specific effect of anthracycline exposure. Additionally, we relied on self-report physical activity levels which may have resulted in misclassification. For all of the above reasons our findings require confirmation by independent studies.

The third part of the dissertation utilized existing data from the Childhood Cancer Survivor Study (CCSS). While the CCSS is the largest and most comprehensive and diverse cohort of cancer survivors in North America, both the study data and the relatively new methodology may be subject to limitations. Not all eligible survivors participate in these CCSS surveys. However, the proportion of survivors who elect not to participate in the CCSS does not differ substantially from other similar cohort studies of cancer survivors.[4,257-259] In addition, both the cardiac outcomes and physical activity levels were assessed using self-reported data which may be subject to bias and imprecision. Moreover, even if we could assume accurate reporting, it is possible that some of the subjects had undiagnosed anthracycline-induced cardiac problems. Lastly, the methodology used in this study is relatively new and there are other ways of estimating direct and indirect effects. [261-264]

FUTURE DIRECTIONS

This dissertation resulted in several important observations and identified additional directions for research on late effects of anthracycline cardiotoxicity in childhood cancer survivors. The stress echocardiography study confirmed that high-risk anthracycline-exposed pediatric cancer survivors may begin showing evidence of diastolic filling abnormalities at rest, even at an early age. We found that TDI might be a useful addition to the routine monitoring of

these survivors using resting echocardiography. Future studies should examine the clinical utility, including inter- and intra-rater variability of persons who interpret for these measures. We also found that with exercise, young patients appear to be able to augment their systolic and diastolic dysfunction to achieve relatively normal maximal aerobic capacity despite impaired stroke volume. Further longitudinal evaluation of these parameters is warranted and may be possible in this cohort of childhood cancer survivors.

In addition to changes in cardiac function, we also observed interesting trends in overall and physical health-related quality of life following exposure to anthracyclines. Our results indicate that in addition to cardiac surveillance, psychosocial assessments may be especially important for pediatric cancer survivors exposed to anthracyclines during treatment. Overall, the data emphasize the need for cancer survivors to have comprehensive physical and psychosocial services available to them throughout their life. Future studies examining the relationship between anthracyclines and quality of life should rely on larger sample sizes and follow patients over time.

We utilized a new decomposition methodology to help better define the potential impact of lifestyle interventions, namely physical activity, on cardiac health outcomes among childhood cancer survivors exposed to anthracyclines. This project illustrates how decomposition methods can be used in epidemiologic research to help understand the inter-relation of two or more causal pathways. To further the development of this methodology, future work could compare various decomposition methods. To clarify the role exercise plays in survivors exposed to anthracyclines, data with reduced measurement error is warranted.

In conclusion, this dissertation extends the literature on the understanding and monitoring of various effects of anthracycline exposure in childhood. Given the obstacles in obtaining evidence from randomized trials on early detection, and prevention of anthracycline-induced damage, observational studies should continue to provide support for consensus-based recommendations such as those of the Children's Oncology Group.

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APPENDIX I – Stress Echocardiography Study, Power Calculations

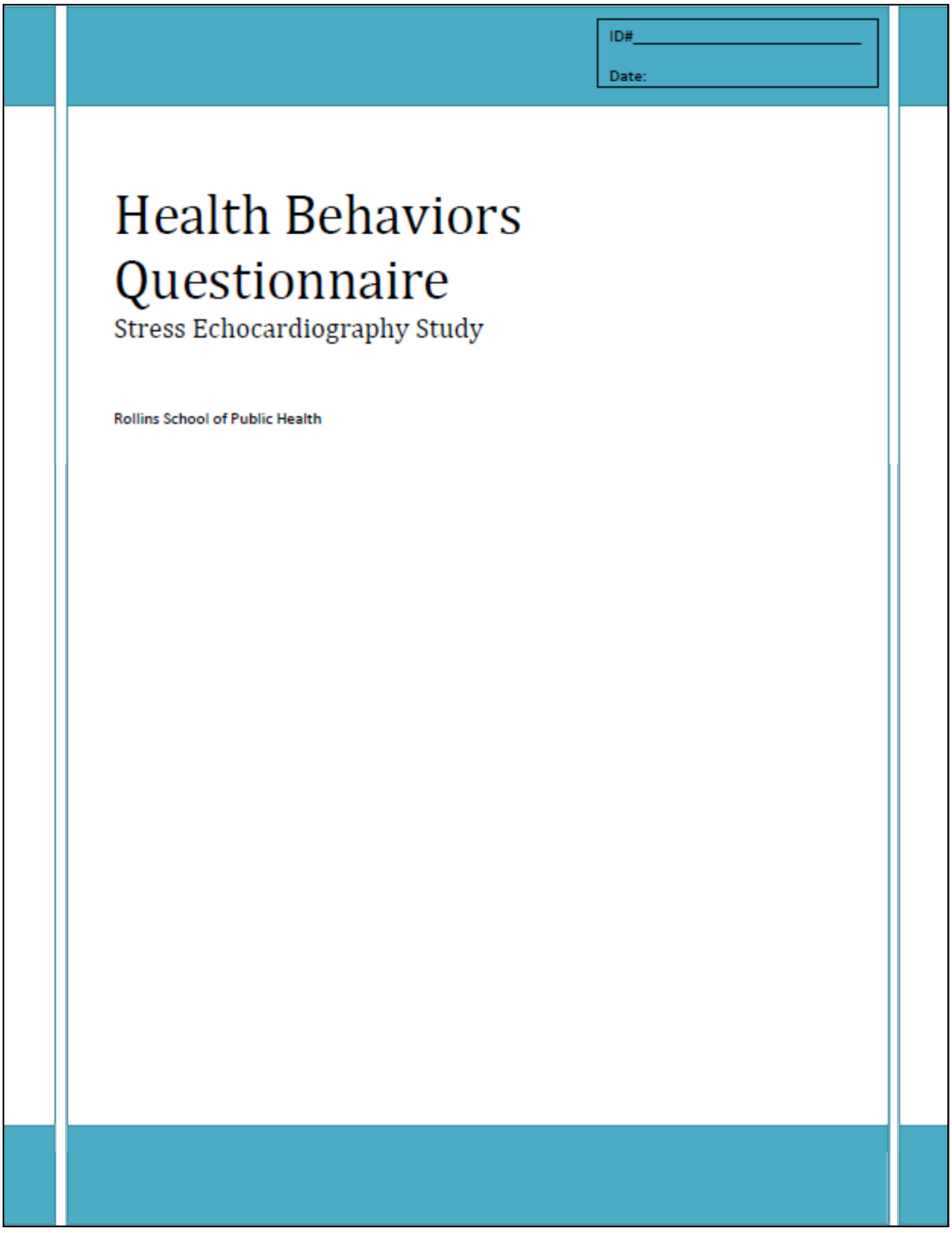
Table A1.1: Power Calculations using Indices of LV Function at Rest and Peak Exercise for Controls and Anthracycline-treated patients (AP) (De Souza *et al*, 2007, Table II)

		Control (n=20)	Total AP (n=60)	**Power (Control vs. total AP)**	Low dose AP (n=20)	**Power (Control vs. low AP)**	High dose AP (n=20)	**Power (Control vs. High AP)**	**Power (low vs. High AP)**
LVEDi	R	3.3 ±0.6	3.5 ±0.7	**23.47**	3.8 ±0.8	**60.88**	3.2 ±0.5	**8.21**	**81.18**
	P	3.1 ±0.6	3.4 ±0.8	**42.55**	3.8 ±0.9	**82.49**	3.1 ±0.5	**1.07**	**86.01**
LVESi	R	2.1 ±0.4	2.3 ±0.5	**44.17**	2.3 ±0.6	**23.59**	2.3 ±0.5	**28.67**	**1.07**
	P	1.5 ±0.4	2.0 ±0.5	**99.50**	2.0 ±0.6	**87.31**	2.0 ±0.4	**97.69**	**1.07**
SF	R	38 ±5	32 ±7	**98.66**	38 ±6	**1.07**	29 ±6	**99.93**	**99.73**
	P	53 ±4	41 ±9	**100.00**	48 ±7	**79.21**	37 ±7	**100.00**	**99.87**
LVPWs	R	1.15 ±0.4	1.02 ±0.17	**29.18**	1.06 ±0.17	**15.05**	1.01 ±0.16	**30.63**	**15.81**
	P	1.39 ±0.31	1.17 ±0.19	**84.90**	1.24 ±0.21	**43.32**	1.13 ±0.16	**91.52**	**46.16**
ET	R	0.26 ±0.02	0.25 ±0.02	**49.07**	0.25 ±0.02	**35.25**	0.26 ±0.02	**1.07**	**35.25**
	P	0.18 ±0.01	0.18 ±0.02	**1.07**	0.19 ±0.03	**29.29**	0.17 ±0.02	**51.60**	**69.88**
MVCFc	R	1.26 ±0.18	1.09 ±0.24	**91.73**	1.25 ±0.21	**2.78**	0.99 ±0.21	**99.19**	**97.47**
	P	1.71 ±0.19	1.42 ±0.47	**97.47**	1.61 ±0.36	**19.45**	1.22 ±0.27	**100.00**	**97.23**
σPS	R	73 ±31	93 ±32	**69.80**	73 ±22	**1.07**	104 ±28	**91.29**	**97.34**
	P	50 ±13	88 ±42	**100.00**	66 ±19	**87.46**	104 ±42	**99.98**	**95.79**

AP = anthracycline-treated patients; R = rest; P = peak; LVEDi = dimensions of left ventricle at end-diastole; **LVESi =** dimensions of left ventricle at end-systole; **SF =** contractility; **LVPWs =** posterior wall thickness at end-systole; ET = Ejection Time; **MVCFc =** rate-corrected mean velocity of circumferential fiber shortening; **σPS =** Stress peak systole

Power for mean differences calculated through open epi
http://www.openepi.com/Menu/OpenEpiMenu.htm
$\alpha = 0.05$

APPENDIX II: Stress Echocardiography Study, Health Behaviors Questionnaire



ID#_____

Date:

Health Behaviors Questionnaire

Stress Echocardiography Study

Rollins School of Public Health

Health Behaviors Questionnaire

Some of these questions are about your background, and some are about health behavior.
These questions were developed so you can tell us what you do that may affect your health.

The answers you give will be kept private.

Make sure to read every question and mark your answers clearly.

DIRECTIONS

- Use a pencil only
- Make dark marks
- If you change your answer, erase your old answer completely.

Health Behaviors Questionnaire

What is your date of birth? _____ _____ _____
Month Day Year

What is your sex?

- ☐ Female
- ☐ Male

In what grade are you in school?

- ☐ 2nd grade
- ☐ 3rd grade
- ☐ 4th grade
- ☐ 5th grade
- ☐ 6th grade
- ☐ 7th grade
- ☐ 8th grade
- ☐ 9th grade
- ☐ 10th grade
- ☐ 11th grade
- ☐ 12th grade
- ☐ College or technical school
- ☐ Not in school

Are you Hispanic or Latino?

- ☐ Yes
- ☐ No

Health Behaviors Questionnaire

What is your race? (Select one or more responses.)

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Other (Please specify:_____)

Have you ever tried cigarette smoking, even one or two puffs?

- ☐ Yes
- ☐ No

How old were you when you smoked a whole cigarette for the first time?

- ☐ I have never smoked a whole cigarette
- ☐ 8 years old or younger
- ☐ 9 or 10 years old
- ☐ 11 or 12 years old
- ☐ 13 or 14 years old
- ☐ 15 or 16 years old
- ☐ 17 years old or older

During the past 30 days, on how many days did you smoke cigarettes?

- ☐ 0 days
- ☐ 1 or 2 days
- ☐ 3 to 5 days
- ☐ 6 to 9 days
- ☐ 10 to 19 days
- ☐ 20 to 29 days
- ☐ All 30 days

Health Behaviors Questionnaire

During the past 30 days, on the days you smoked, how many cigarettes did you smoke **per day**?

- ☐ I did not smoke cigarettes during the past 30 days
- ☐ Less than 1 cigarette per day
- ☐ 1 cigarette per day
- ☐ 2 to 5 cigarettes per day
- ☐ 6 to 10 cigarettes per day
- ☐ 11 to 20 cigarettes per day
- ☐ More than 20 cigarettes per day

Have you ever smoked cigarettes daily, that is, at least one cigarette every day for 30 days?

- ☐ Yes
- ☐ No

During the past 12 months, did you ever try **to quit** smoking cigarettes?

- ☐ I did not smoke during the past 12 months
- ☐ Yes
- ☐ No

During the past 30 days, on how many days did you use **chewing tobacco, snuff, or dip**, such as Redman, Levi Garrett, Beechnut, Skoal, Skoal Bandits, or Copenhagen?

- ☐ 0 days
- ☐ 1 or 2 days
- ☐ 3 to 5 days
- ☐ 6 to 9 days
- ☐ 10 to 19 days
- ☐ 20 to 29 days
- ☐ All 30 days

Health Behaviors Questionnaire

During the past 30 days, on how many days did you smoke **cigars, cigarillos, or little cigars?**

- ☐ 0 days
- ☐ 1 or 2 days
- ☐ 3 to 5 days
- ☐ 6 to 9 days
- ☐ 10 to 19 days
- ☐ 20 to 29 days
- ☐ All 30 days

During the past 7 days, on how many days were you physically active for a total of **at least 60 minutes per day?** (Add up all the time you spent in any kind of physical activity that increased your heart rate and made you breathe hard some of the time.)

- ☐ 0 days
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ 4 days
- ☐ 5 days
- ☐ 6 days
- ☐ 7 days

On an average school/week day, how many hours do you watch TV?

- ☐ I do not watch TV on an average school/week day
- ☐ Less than 1 hour per day
- ☐ 1 hour per day
- ☐ 2 hours per day
- ☐ 3 hours per day
- ☐ 4 hours per day
- ☐ 5 or more hours per day

Health Behaviors Questionnaire

On an average school/week day, how many hours do you play video or computer games or use a computer for something that is not school work? (Include activities such as Nintendo, Game Boy, PlayStation, Xbox, computer games, and the Internet.)

- ☐ I do not watch TV on an average school/week day
- ☐ Less than 1 hour per day
- ☐ 1 hour per day
- ☐ 2 hours per day
- ☐ 3 hours per day
- ☐ 4 hours per day
- ☐ 5 or more hours per day

In an average week when you are in school, on how many days do you go to physical education (PE) classes?

- ☐ 0 days
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ 4 days
- ☐ 5 days

During the past 12 months, on how many sports teams did you play? (Include any teams run by your school or community groups.)

- ☐ 0 teams
- ☐ 1 team
- ☐ 2 teams
- ☐ 3 or more teams

Health Behaviors Questionnaire

Would you say that in general your health is...

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

Do you currently have health insurance coverage?

- ☐ No
- ☐ Yes

How is your current health insurance provided? (Mark all that apply)

- ☐ I do not currently have health insurance
- ☐ Through parent's place of employment
- ☐ Through parent's policy
- ☐ Through your own policy
- ☐ Medicaid or other public assistance program
- ☐ Military dependant/Veteran's benefits (CHAMPUS)
- ☐ Other [please specify:_____]

Since your cancer diagnosis, have you had any operations or surgeries?

- ☐ No
- ☐ Yes [How many time?_____]

Health Behaviors Questionnaire

The remaining questions are for FEMALES only

Have you ever become pregnant?

- ☐ No
- ☐ Yes [How many time?_____]

Are you currently pregnant now?

- ☐ Don't know
- ☐ No
- ☐ Yes

APPENDIX III: Stress Echocardiography Study, Pediatric Quality of Life Inventory

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Young Adult Quality of Life Inventory

Version 4.0

YOUNG ADULT REPORT (ages **18-25**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other young adults	0	1	2	3	4
2. Other young adults do not want to be my friend	0	1	2	3	4
3. Other young adults tease me	0	1	2	3	4
4. I cannot do things that others my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT MY WORK/STUDIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention at work or school	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my work or studies	0	1	2	3	4
4. I miss work or school because of not feeling well	0	1	2	3	4
5. I miss work or school to go to the doctor or hospital	0	1	2	3	4

APPENDIX IV: CCSS, Questionnaire

Last modified:
05/21/2010 09:56:58 AM

LTFU

Long-Term Follow-Up Study

St. Jude Children's Research Hospital
Children's Healthcare of Atlanta/Emory University
Children's Hospital at Stanford
Children's Hospital of Columbus
Children's Hospital of Orange County
Children's Hospital of Philadelphia
Children's Hospital of Los Angeles
Children's Hospital of Pittsburgh
Children's Hospitals & Clinics of Minnesota, Minneapolis and St. Paul
Children's Medical Center of Dallas
Children's National Medical Center
City of Hope National Medical Center
Dana-Farber Cancer Institute
Loma Linda University
Mattel Children's Hospital at UCLA
Mayo Clinic
Memorial Sloan-Kettering Cancer Center
Miller Children's Hospital
Riley Hospital for Children - Indiana University
Roswell Park Cancer Institute
Seattle Children's Hospital
St. Louis Children's Hospital
Texas Children's Hospital
The Denver Children's Hospital
Toronto Hospital for Sick Children
UAB/The Children's Hospital of Alabama
University of California at San Francisco
University of Michigan - Mott Children's Hospital
University of Minnesota
U.T.M.D. Anderson Cancer Center

Our mailing address is:
Long-Term Follow-Up Study
St. Jude Children's Research Hospital
Department of Epidemiology
Mail Stop 735
262 Danny Thomas Place
Memphis, TN 38105-3678

Toll-free phone number:
1-800-775-2167

e-mail: LTFU@stjude.org

www.stjude.org/ltfu

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

and

UNIVERSITY OF MINNESOTA

Thank you for participating in the Long-Term Follow-Up Study. Your participation continues to provide us with valuable information in the fight against childhood cancer and similar illnesses.

It has been about two years since we sent you our last general survey and we would like to update your information. Please fill out the following form that will bring us up-to-date on your health in the past two years. The length of time to complete varies between individuals, but generally requires 30-60 minutes.

You can be assured that we will respect your privacy at all times. Your name or other identifiers will not be used in any report of our findings, or released to any person or agency, except study investigators.

Your generosity in participating is greatly appreciated.

Sincerely,

The LTFU study staff

The questions in this booklet relate to:

Person completing this questionnaire is:

Your relationship:

☐ Self ☐ Parent ☐ Other: _____

Today's date: ☐☐ / ☐☐ / ☐☐☐☐

Please! Do not mark below this line

Edit ☐ Survey #001 Code ☐ 2458454653

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRE

Please follow these rules in completing this questionnaire. If you have any questions about completing this questionnaire, please call 1-800-775-2167.

1. Use a black ballpoint pen or a number 2 black pencil. Do not use a felt-tip or roller-ball pen. These may cause smudging. If you must erase answers, erase them completely.
2. When marking boxes, make an x inside the box (see examples below).
3. Make no stray marks of any kind. Please keep the form as clean as possible.
4. Written responses must stay within the boxes provided:

CORRECT: Grape

INCORRECT: Grape

MARKING EXAMPLES

Below are some examples of how to fill out this questionnaire. Please look these over before you begin.

Example 1

1. During the past month, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?

☐ No ☒ Yes

Example 2

2. Have you ever taken. . .

	No	Yes	Not sure	If yes, age at first use
a. BIRTH CONTROL PILLS such as Demulen, Lo-Ovral, Loestrin, Norinyl, Norplant, Ortho-Novum, Ovral, Triphasil)	☒	☐	☐	years:
If yes, specify the name of the drug(s) or indicate you do not know the specific name:				
b. MEDICATIONS TO LOWER CHOLESTEROL OR TRIGLYCERIDES, such as Zocor, Pravachol, Lipitor, Colestid (colestipol), Tricor, Lescol, Lopid (gemfibrozil), Mevacor, niacin, or Lorelco	☐	☒	☐	34
If yes, specify the name of the drug(s) or indicate you do not know the specific name: mevacor				

Example 3

3. When was this condition diagnosed?

Month (mm): 04 Year (yyyy): 1995

Please! Do not mark below this line

5159454654

In the past we have asked you questions similar to those below. We would like to update this information.

A1. What is your current height without shoes?

☐☐ Feet ☐☐ Inches

A2. What is your current weight without shoes?

☐☐☐ Pounds

A3. What is the highest grade or level of schooling you have now completed?

- ☐ 1-8 years (grade school)
- ☐ 9-12 years (high school) but did not graduate
- ☐ Completed high school/GED
- ☐ Training after high school, other than college
- ☐ Some college
- ☐ College graduate
- ☐ Post graduate level
- ☐ Other

If Other, please describe.

A4. What is your current employment status? Include unpaid work in the family business or farm. *(Mark all that apply)*

- ☐ Working full-time (30 or more hours per week)
- ☐ Working part-time (less than 30 hours per week)
- ☐ Caring for home or family (not seeking paid work)
- ☐ Unemployed and looking for work
- ☐ Unable to work due to illness or disability
- ☐ Retired
- ☐ Student
- ☐ Other

If Other, please describe.

If you are <u>not</u> currently working full or part time. . . → *Go to Question A6.*

A5. The following questions are about your present occupation. Please write your job title and brief details of what you do. If you have more than one job, please give the title of your main job:

A5a. Main job title:

A5b. Please briefly describe the primary tasks in your job:

A6. Over the last year, what was the total income of the <u>household</u> you live in?

- ☐ Less than $20,000
- ☐ $20,000 - $39,999
- ☐ $40,000 - $59,999
- ☐ $60,000 - $79,999
- ☐ $80,000 - $99,999
- ☐ Over $100,000
- ☐ Don't know

A7. During the past year, how many people in this household were supported on this income?

☐ 1	☐ 4	☐ 7
☐ 2	☐ 5	☐ 8
☐ 3	☐ 6	☐ 9 or more

A8. Over the last year, what was your personal income?

- ☐ None
- ☐ Less than $20,000
- ☐ $20,000 - $39,999
- ☐ $40,000 - $59,999
- ☐ $60,000 - $79,999
- ☐ $80,000 - $99,999
- ☐ Over $100,000

Please! Do not mark below this line

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MEDICAL CARE

The next questions are about health care received during the 2 year period between November 2007 and November 2009.

B1. During this two year period, which of the following health care providers (excluding dentists) did you see or talk to for medical care? This includes routine and sick care. *(Mark all that apply)*

- ☐ None → *Go to Question B8, next page.*
- ☐ Physician (including Osteopath)
- ☐ Nurse Practitioner/Physician's Assistant
- ☐ Nurse
- ☐ Chiropractor
- ☐ Physical therapist
- ☐ Other

If Other, please describe.

B2. Where did you receive your health care? *(Mark all that apply)*

- ☐ Doctor's office
- ☐ Oncology (cancer) center or clinic
- ☐ Other type of clinic
- ☐ Hospital
- ☐ Emergency room or urgent care center
- ☐ Long-term follow-up clinic
- ☐ Other

If Other, please describe.

B3. During this 2 year period, how many times did you see a physician?

- ☐ None
- ☐ 1-2 times
- ☐ 3-4 times
- ☐ 5-6 times
- ☐ 7-10 times
- ☐ 11-20 times
- ☐ More than 20 times

B4. As you know, you were asked to participate in this study because you were once diagnosed with a cancer, leukemia, tumor, or similar illness. How many of the visits to the physician indicated in question B3 (during the 2 year period) were related to this previous illness?

- ☐ None
- ☐ 1-2 visits
- ☐ 3-4 visits
- ☐ 5-6 visits
- ☐ 7-10 visits
- ☐ 11-20 visits
- ☐ More than 20 visits

B5. Did you discuss any of the following issues with your physician or primary health care provider during any of these visits?

	No	Yes
a. Heart disease	☐	☐
b. Osteoporosis (weak or brittle bones)	☐	☐
c. Risk of developing cancer (breast, skin, other)	☐	☐
d. Hepatitis C	☐	☐
e. Dental problems	☐	☐
f. Fertility issues	☐	☐
g. Mental health	☐	☐
h. Other issues related to your history of cancer or other serious illness during childhood	☐	☐

If Other issues, please describe.

Please! Do not mark below this line

B6. When was your MOST RECENT routine check-up where a doctor examined you and did tests to see if you had any health problems from your cancer or your cancer treatment?

- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Never → *Go to Question B8.*

B7. At this check-up did your doctor . . .

	No	Yes
a. Give you advice about what to do to reduce risks	☐	☐
b. Discuss or order medical screening tests	☐	☐
c. Suggest you see a cancer specialist	☐	☐
d. Suggest you see another type of medical subspecialist(s)	☐	☐
e. Tell you that you had nothing to worry about based on findings at the check-up	☐	☐
f. Other	☐	☐

If yes to Other, please describe.

B8. When do you plan to have your NEXT visit with a doctor in order to examine you for any health problems from your cancer or your cancer treatment?

- ☐ Less than 1 year from now
- ☐ 1-2 years from now
- ☐ 3-4 years from now
- ☐ 5 or more years from now
- ☐ Never

B9. Do you currently have health insurance coverage?

- ☐ Canadian resident
- ☐ No
- ☐ Yes

MEDICAL SCREENING TESTS

The following questions are about medical screening tests you may have received.

When was the last time you had . . .

C1. An echocardiogram (ultrasound of the heart to look at the heart muscle and heart valves) or MUGA scan?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

C2. A test to measure your bone strength or bone mineral density (such as a DEXA or quantitative CT scan)?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

Continue on next page.

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C3. A blood stool test is a test that may use a special kit at home to determine whether the stool contains blood.

When was the last time that you had a blood stool test using a home kit?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

C4. Sigmoidoscopy and colonoscopy are exams in which a tube is inserted in the rectum to view the colon for signs of cancer or other health problems.

When was the last time you had either of these exams?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

MALES → *Go to Question C8, next page.*

FEMALES

When was the last time you had . . .

C5. A mammogram?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

C6. A breast MRI?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

C7. A pap smear (test for cancer of the cervix)?

- ☐ Never
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ More than 2 years but less than 5 years ago
- ☐ 5 or more years ago
- ☐ Don't know

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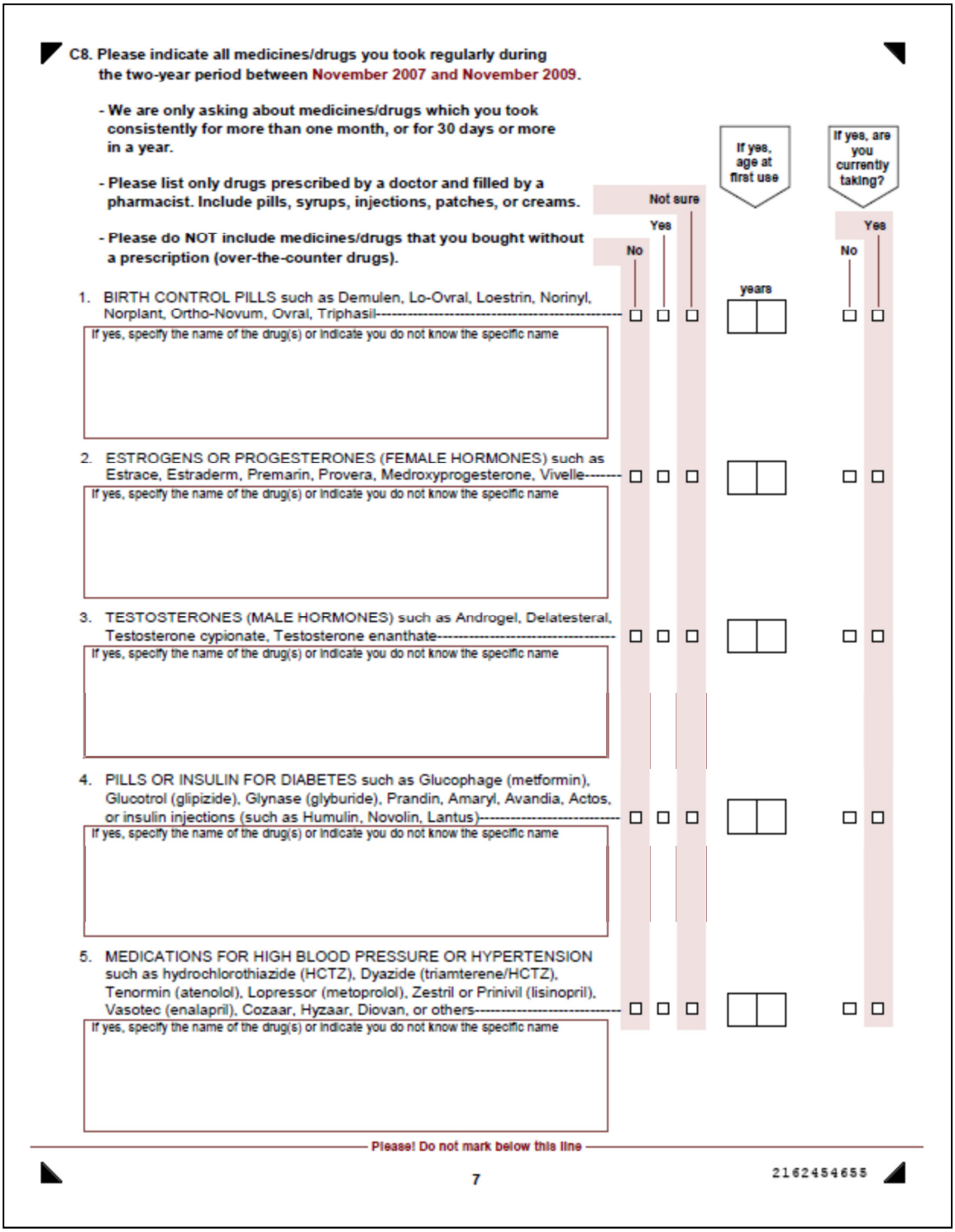

C8. Please indicate all medicines/drugs you took regularly during the two-year period between November 2007 and November 2009.

- **We are only asking about medicines/drugs which you took consistently for more than one month, or for 30 days or more in a year.**
- **Please list only drugs prescribed by a doctor and filled by a pharmacist. Include pills, syrups, injections, patches, or creams.**
- **Please do NOT include medicines/drugs that you bought without a prescription (over-the-counter drugs).**

	No	Yes	Not sure	If yes, age at first use	If yes, are you currently taking? No	If yes, are you currently taking? Yes
1. BIRTH CONTROL PILLS such as Demulen, Lo-Ovral, Loestrin, Norinyl, Norplant, Ortho-Novum, Ovral, Triphasil	☐	☐	☐	☐☐ years	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
2. ESTROGENS OR PROGESTERONES (FEMALE HORMONES) such as Estrace, Estraderm, Premarin, Provera, Medroxyprogesterone, Vivelle	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
3. TESTOSTERONES (MALE HORMONES) such as Androgel, Delatesteral, Testosterone cypionate, Testosterone enanthate	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
4. PILLS OR INSULIN FOR DIABETES such as Glucophage (metformin), Glucotrol (glipizide), Glynase (glyburide), Prandin, Amaryl, Avandia, Actos, or insulin injections (such as Humulin, Novolin, Lantus)	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
5. MEDICATIONS FOR HIGH BLOOD PRESSURE OR HYPERTENSION such as hydrochlorothiazide (HCTZ), Dyazide (triamterene/HCTZ), Tenormin (atenolol), Lopressor (metoprolol), Zestril or Prinivil (lisinopril), Vasotec (enalapril), Cozaar, Hyzaar, Diovan, or others	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						

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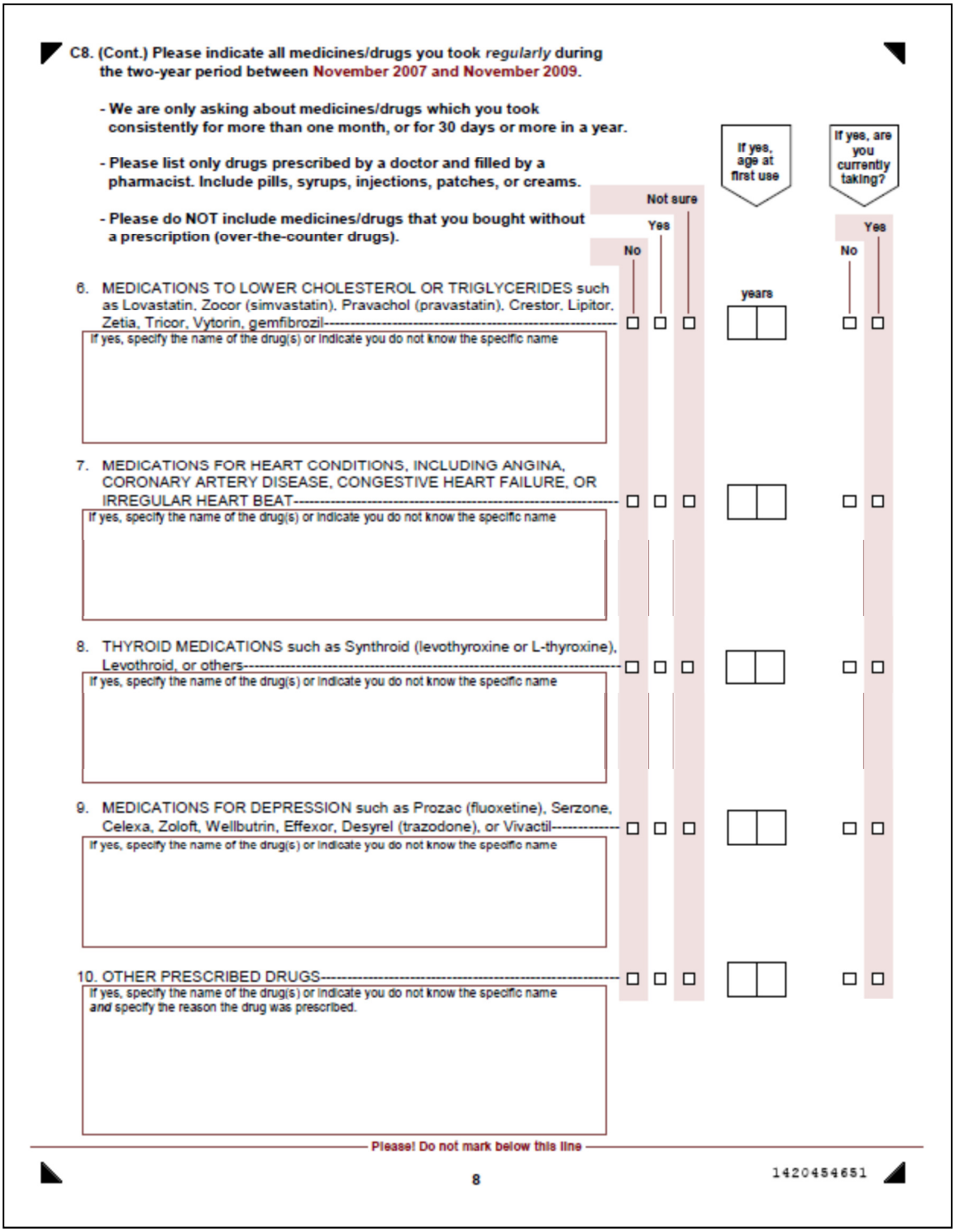

C8. (Cont.) Please indicate all medicines/drugs you took *regularly* during the two-year period between November 2007 and November 2009.

- **We are only asking about medicines/drugs which you took consistently for more than one month, or for 30 days or more in a year.**
- **Please list only drugs prescribed by a doctor and filled by a pharmacist. Include pills, syrups, injections, patches, or creams.**
- **Please do NOT include medicines/drugs that you bought without a prescription (over-the-counter drugs).**

	No	Yes	Not sure	If yes, age at first use	If yes, are you currently taking? No	If yes, are you currently taking? Yes
6. MEDICATIONS TO LOWER CHOLESTEROL OR TRIGLYCERIDES such as Lovastatin, Zocor (simvastatin), Pravachol (pravastatin), Crestor, Lipitor, Zetia, Tricor, Vytorin, gemfibrozil----------	☐	☐	☐	☐☐ years	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
7. MEDICATIONS FOR HEART CONDITIONS, INCLUDING ANGINA, CORONARY ARTERY DISEASE, CONGESTIVE HEART FAILURE, OR IRREGULAR HEART BEAT----------	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
8. THYROID MEDICATIONS such as Synthroid (levothyroxine or L-thyroxine), Levothroid, or others----------	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
9. MEDICATIONS FOR DEPRESSION such as Prozac (fluoxetine), Serzone, Celexa, Zoloft, Wellbutrin, Effexor, Desyrel (trazodone), or Vivactil----------	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name						
10. OTHER PRESCRIBED DRUGS----------	☐	☐	☐	☐☐	☐	☐
If yes, specify the name of the drug(s) or indicate you do not know the specific name *and* specify the reason the drug was prescribed.						

Please! Do not mark below this line

Medical Conditions

The next series of questions relate to medical conditions that you have ever had. You may have previously told us about some of these conditions. We are asking again to make sure our records are current and to capture occurrences of new medical conditions.

Please indicate, by marking the box (either "No", "Yes", or "Not sure") if a doctor or other health care professional has told you that you have or have had any of the following conditions. If you answer "yes", please give your age when the condition first occurred. (If more than one occurrence, please give age at first occurrence.)

Because we need definite responses, it is very important to mark an answer for each question, even if you have never had that condition. Please do not leave any questions blank (unmarked).

HEARING/VISION/SPEECH

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
D1. Hearing loss requiring a hearing aid?	☐	☐	☐	☐	☐☐
D2. Deafness in both ears not completely corrected by hearing aid?	☐	☐	☐	☐	☐☐
D3. Deafness in only one ear not completely corrected by hearing aid?	☐	☐	☐	☐	☐☐
D4. Tinnitus or ringing in the ears?	☐	☐	☐	☐	☐☐
D5. Persistent dizziness or vertigo?	☐	☐	☐	☐	☐☐
D6. Hearing loss, not requiring a hearing aid?	☐	☐	☐	☐	☐☐
D7. Any other hearing problems?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

D8. Legally blind in only one eye?	☐	☐	☐	☐	☐☐

If yes, do you have any sight in this eye? ☐ No ☐ Yes

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
D9. Legally blind in both eyes?	☐	☐	☐	☐	☐☐

If yes, do you have any sight? ☐ No ☐ Yes

D10. Cataracts?	☐	☐	☐	☐	☐☐
D11. Glaucoma (excess pressure in the eyeball)?	☐	☐	☐	☐	☐☐
D12. Problems with double vision?	☐	☐	☐	☐	☐☐
D13. A detached retina or any other condition of the retina?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

D14. Crossed or turned eyes (strabismus)?	☐	☐	☐	☐	☐☐
D15. Lazy eye (amblyopia)?	☐	☐	☐	☐	☐☐
D16. Any other trouble seeing with one or both eyes even when wearing glasses?	☐	☐	☐	☐	☐☐
D17. Very dry eyes requiring eye drops or ointment?	☐	☐	☐	☐	☐☐
D18. Any other eye problems?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

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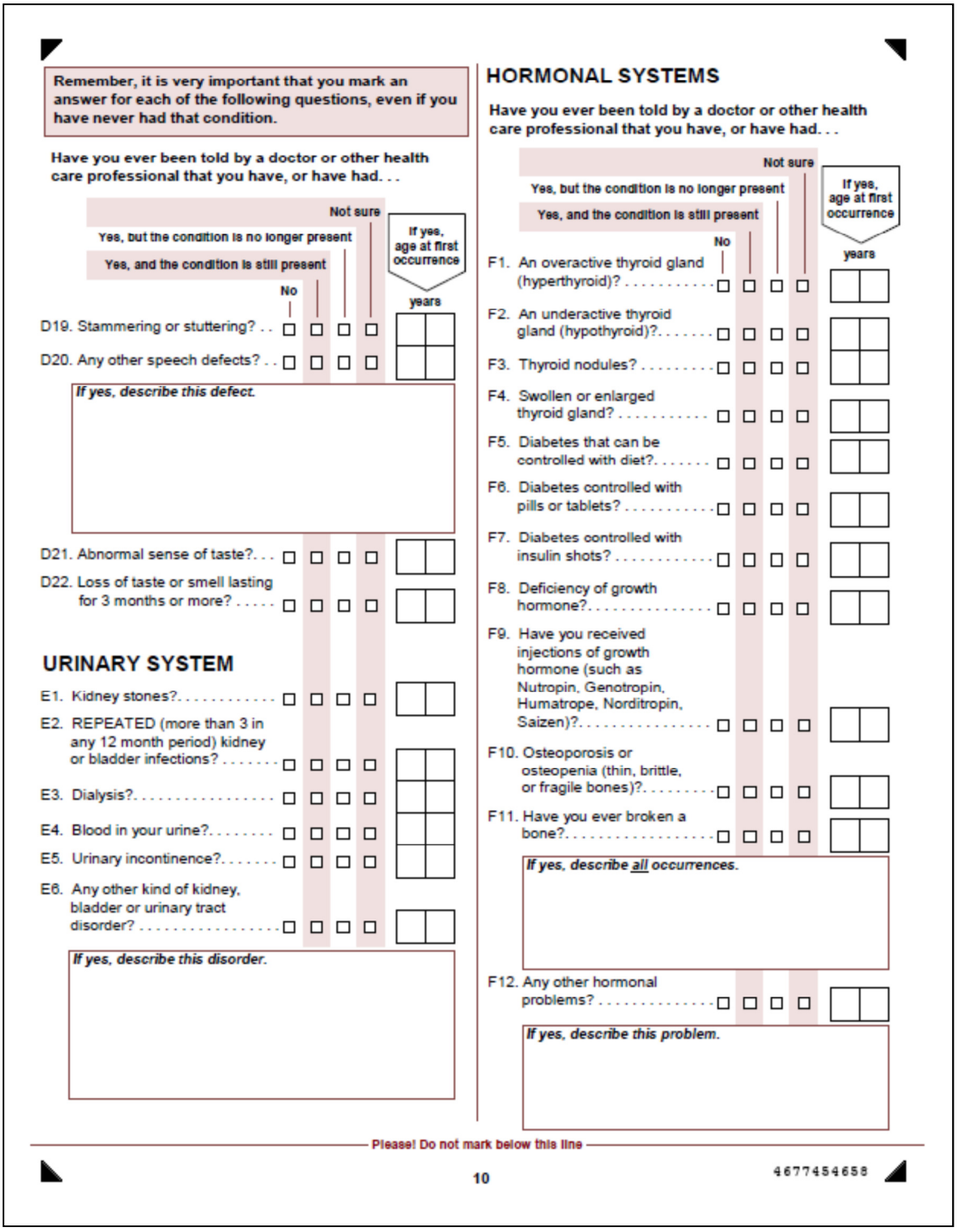

Remember, it is very important that you mark an answer for each of the following questions, even if you have never had that condition.

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
D19. Stammering or stuttering?	☐	☐	☐	☐	
D20. Any other speech defects?	☐	☐	☐	☐	

If yes, describe this defect.

D21. Abnormal sense of taste?	☐	☐	☐	☐	
D22. Loss of taste or smell lasting for 3 months or more?	☐	☐	☐	☐	

URINARY SYSTEM

E1. Kidney stones?	☐	☐	☐	☐	
E2. REPEATED (more than 3 in any 12 month period) kidney or bladder infections?	☐	☐	☐	☐	
E3. Dialysis?	☐	☐	☐	☐	
E4. Blood in your urine?	☐	☐	☐	☐	
E5. Urinary incontinence?	☐	☐	☐	☐	
E6. Any other kind of kidney, bladder or urinary tract disorder?	☐	☐	☐	☐	

If yes, describe this disorder.

HORMONAL SYSTEMS

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
F1. An overactive thyroid gland (hyperthyroid)?	☐	☐	☐	☐	
F2. An underactive thyroid gland (hypothyroid)?	☐	☐	☐	☐	
F3. Thyroid nodules?	☐	☐	☐	☐	
F4. Swollen or enlarged thyroid gland?	☐	☐	☐	☐	
F5. Diabetes that can be controlled with diet?	☐	☐	☐	☐	
F6. Diabetes controlled with pills or tablets?	☐	☐	☐	☐	
F7. Diabetes controlled with insulin shots?	☐	☐	☐	☐	
F8. Deficiency of growth hormone?	☐	☐	☐	☐	
F9. Have you received injections of growth hormone (such as Nutropin, Genotropin, Humatrope, Norditropin, Saizen)?	☐	☐	☐	☐	
F10. Osteoporosis or osteopenia (thin, brittle, or fragile bones)?	☐	☐	☐	☐	
F11. Have you ever broken a bone?	☐	☐	☐	☐	

If yes, describe <u>all</u> occurrences.

F12. Any other hormonal problems?	☐	☐	☐	☐	

If yes, describe this problem.

Please! Do not mark below this line

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Males ⟶ *Go to Question F17.*

F13. **FEMALES** - Have you had a menstrual period naturally, that is, without needing hormones or medication?

☐ No ☐ Yes **If yes, age at first occurrence:** ☐☐

If no, ⟶ *Go to Question F15.*

F14. **FEMALES** - At what age did you last have a menstrual period naturally, without needing hormones or medication?

☐☐ **years and** ☐☐ **months old**

F15. **FEMALES** - Which one of the following statements best describes you? **(Select only one)**

- ☐ a. I am having regular periods and I am not taking birth control pills or female hormones (example: Premarin, estrogen)
- ☐ b. I am having regular periods but I am using birth control pills to prevent a pregnancy
- ☐ c. My menstrual periods are irregular and I am taking birth control pills or female hormones to regulate my periods
- ☐ d. I am currently pregnant
- ☐ e. I am not having menstrual periods naturally but I am taking birth control pills or female hormones
- ☐ f. I am not having menstrual periods naturally and I am not taking birth control pills or female hormones
- ☐ g. Other

If Other, please describe.

If you selected a, b, c, or d ⟶ *Go to Question G1.*
If you selected e, f, or g ⟶ *Go to Question F16.*

F16. **FEMALES** - What caused your menstrual periods to stop? **(Select only one)**

- ☐ Normal or early menopause
- ☐ Surgery (example: a hysterectomy)
- ☐ Pregnancy
- ☐ Don't know
- ☐ Other

If Other, please describe.

Females ⟶ *Go to Question G1.*

F17. **MALES** -

LTFU Questionnaire on Men's Health

We are conducting an additional study funded by the Lance Armstrong Foundation to better understand fertility and sexual function in males. Participation would require 30-40 minutes. Because some of the questions are of a personal nature we would send you a separate questionnaire. Would you consider participating?

☐ Yes ☐ No ☐ Not Sure

Remember, it is very important that you mark an answer for each of the following questions, even if you have never had that condition.

HEART AND CIRCULATORY SYSTEM

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
G1. Congestive heart failure or cardiomyopathy (weak heart muscle)?	☐	☐	☐	☐	☐☐
G2. A myocardial infarction (heart attack)?	☐	☐	☐	☐	☐☐
G3. Irregular heartbeat or palpitations, (Arrhythmia) requiring medication or follow-up by a doctor?	☐	☐	☐	☐	☐☐
G4. Coronary heart disease?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

G5. Hypertension (high blood pressure) requiring medication?	☐	☐	☐	☐	☐☐

If yes, do you currently take hypertension medication?
☐ No ☐ Yes

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Remember, it is very important that you mark an answer for each of the following questions, even if you have never had that condition.

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
G6. Angina pectoris (chest pains due to lack of oxygen to the heart requiring medication such as nitroglycerin)?	☐	☐	☐	☐	☐☐
G7. Pericarditis or fluid around the heart?	☐	☐	☐	☐	☐☐
G8. Pericardial constriction (scarring or tightness of the sac around the heart)?	☐	☐	☐	☐	☐☐
G9. Stiff or leaking heart valves?	☐	☐	☐	☐	☐☐
G10. Blood clot in head, lung, arm, leg, or pelvis?	☐	☐	☐	☐	☐☐
G11. Does exercise cause severe chest pain, shortness of breath, or irregular heart beat?	☐	☐	☐	☐	☐☐
G12. High cholesterol (or triglyceride) requiring prescription medication?	☐	☐	☐	☐	☐☐
If yes, do you currently take medication for this? ☐ No ☐ Yes					
G13. Any other heart or circulatory problems?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

G14. Has anyone in your immediate family (biological mother, father, brothers, sisters) had a heart attack before the age of 55?

☐ No ☐ Yes

RESPIRATORY SYSTEM

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
H1. Asthma?	☐	☐	☐	☐	☐☐
H2. Chronic cough or shortness of breath for more than one month?	☐	☐	☐	☐	☐☐
H3. Have you had a need for extra oxygen?	☐	☐	☐	☐	☐☐
H4. Pneumonia, 3 or more times in the past 2 years?	☐	☐	☐	☐	☐☐
H5. Emphysema?	☐	☐	☐	☐	☐☐
H6. Lung fibrosis or "scarring" of the lung?	☐	☐	☐	☐	☐☐
H7. Problems with breathing while at rest that lasted for more than 3 months?	☐	☐	☐	☐	☐☐
H8. Any other breathing or lung problems?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

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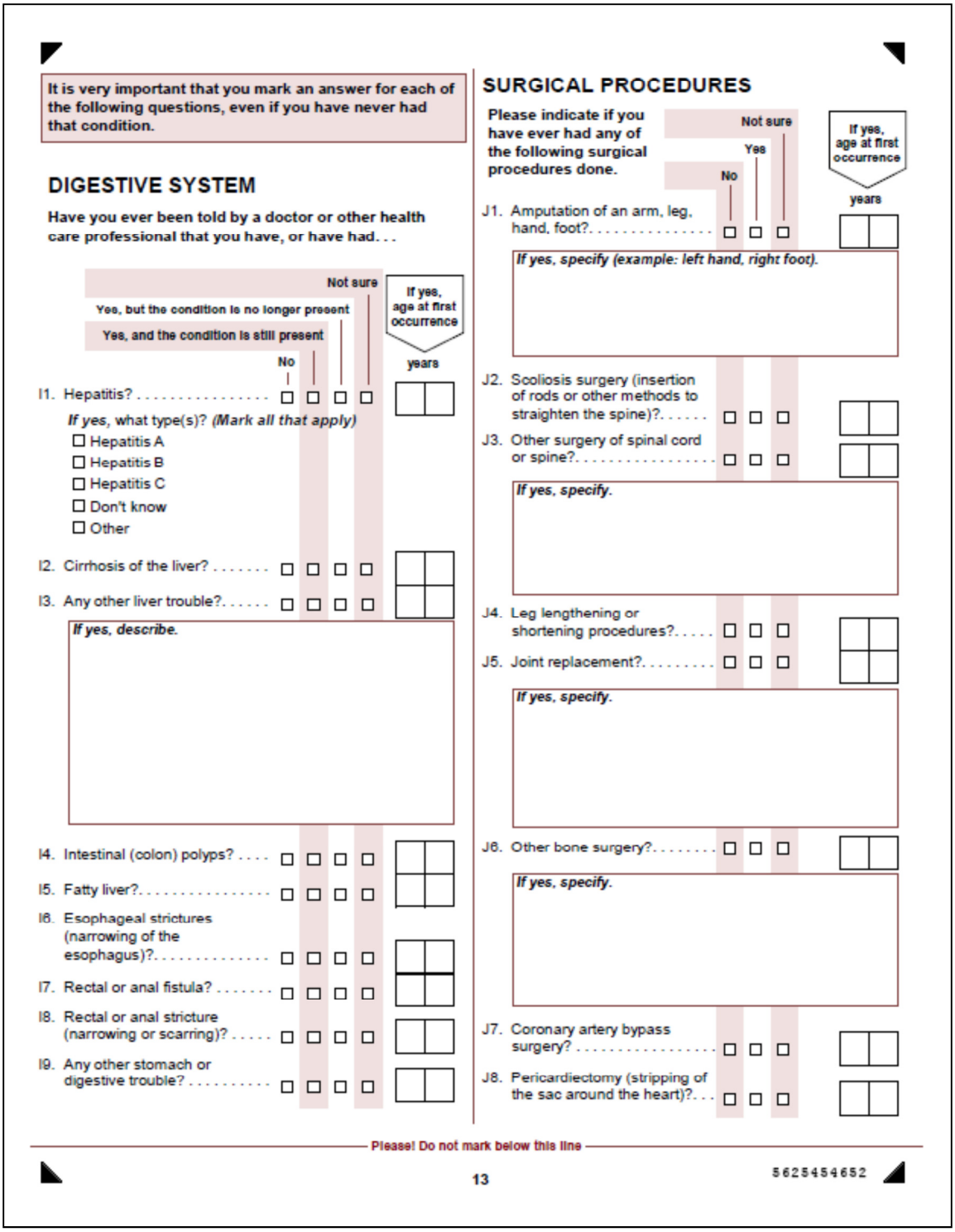

It is very important that you mark an answer for each of the following questions, even if you have never had that condition.

DIGESTIVE SYSTEM

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
I1. Hepatitis?	☐	☐	☐	☐	
If yes, what type(s)? *(Mark all that apply)* ☐ Hepatitis A ☐ Hepatitis B ☐ Hepatitis C ☐ Don't know ☐ Other					
I2. Cirrhosis of the liver?	☐	☐	☐	☐	
I3. Any other liver trouble?	☐	☐	☐	☐	
If yes, describe.					
I4. Intestinal (colon) polyps?	☐	☐	☐	☐	
I5. Fatty liver?	☐	☐	☐	☐	
I6. Esophageal strictures (narrowing of the esophagus)?	☐	☐	☐	☐	
I7. Rectal or anal fistula?	☐	☐	☐	☐	
I8. Rectal or anal stricture (narrowing or scarring)?	☐	☐	☐	☐	
I9. Any other stomach or digestive trouble?	☐	☐	☐	☐	

SURGICAL PROCEDURES

Please indicate if you have ever had any of the following surgical procedures done.

	No	Yes	Not sure	If yes, age at first occurrence (years)
J1. Amputation of an arm, leg, hand, foot?	☐	☐	☐	
If yes, specify (example: left hand, right foot).				
J2. Scoliosis surgery (insertion of rods or other methods to straighten the spine)?	☐	☐	☐	
J3. Other surgery of spinal cord or spine?	☐	☐	☐	
If yes, specify.				
J4. Leg lengthening or shortening procedures?	☐	☐	☐	
J5. Joint replacement?	☐	☐	☐	
If yes, specify.				
J6. Other bone surgery?	☐	☐	☐	
If yes, specify.				
J7. Coronary artery bypass surgery?	☐	☐	☐	
J8. Pericardiectomy (stripping of the sac around the heart)?	☐	☐	☐	

Please! Do not mark below this line

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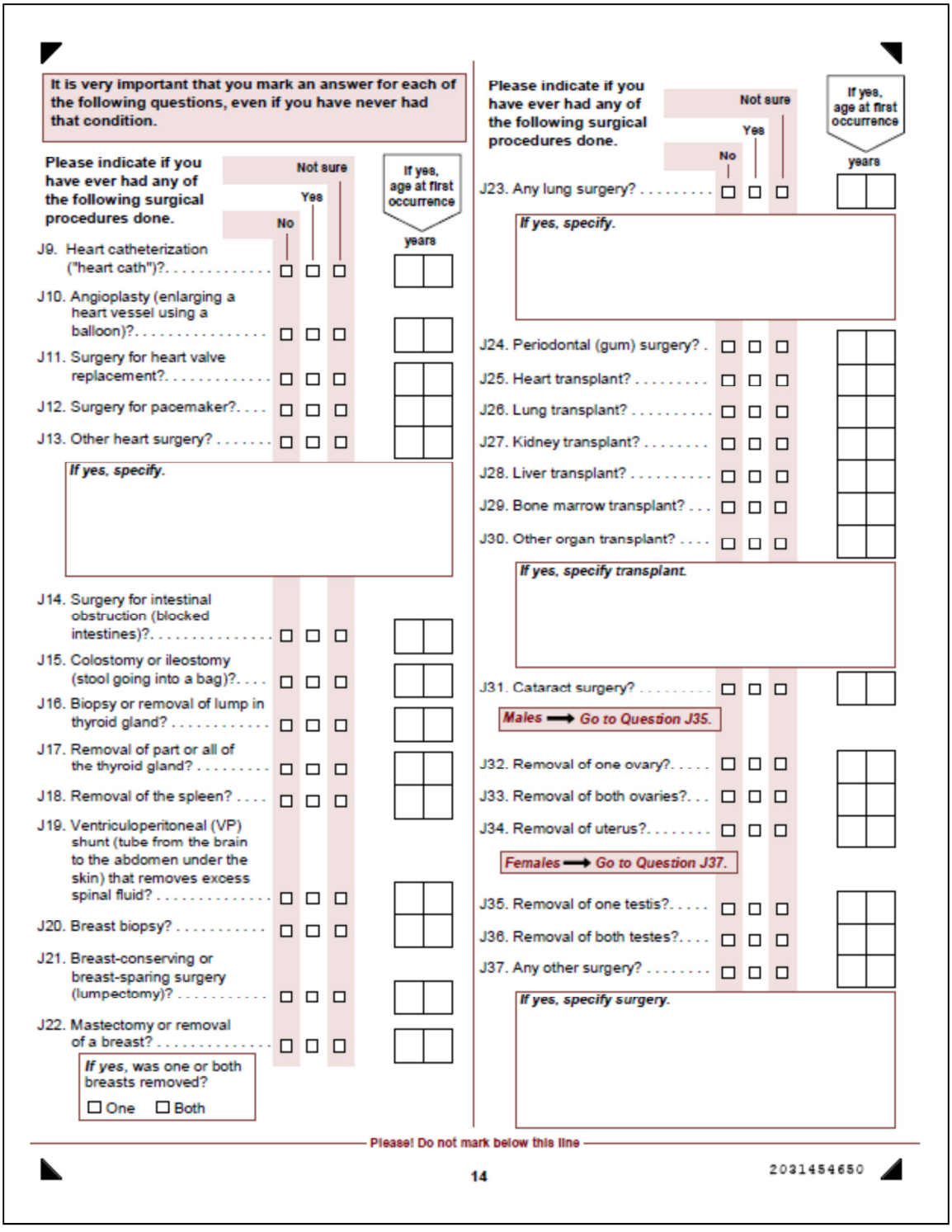

It is very important that you mark an answer for each of the following questions, even if you have never had that condition.

Please indicate if you have ever had any of the following surgical procedures done.

	No	Yes	Not sure	If yes, age at first occurrence (years)
J9. Heart catheterization ("heart cath")?	☐	☐	☐	
J10. Angioplasty (enlarging a heart vessel using a balloon)?	☐	☐	☐	
J11. Surgery for heart valve replacement?	☐	☐	☐	
J12. Surgery for pacemaker?	☐	☐	☐	
J13. Other heart surgery?	☐	☐	☐	

If yes, specify.

J14. Surgery for intestinal obstruction (blocked intestines)?	☐	☐	☐	
J15. Colostomy or ileostomy (stool going into a bag)?	☐	☐	☐	
J16. Biopsy or removal of lump in thyroid gland?	☐	☐	☐	
J17. Removal of part or all of the thyroid gland?	☐	☐	☐	
J18. Removal of the spleen?	☐	☐	☐	
J19. Ventriculoperitoneal (VP) shunt (tube from the brain to the abdomen under the skin) that removes excess spinal fluid?	☐	☐	☐	
J20. Breast biopsy?	☐	☐	☐	
J21. Breast-conserving or breast-sparing surgery (lumpectomy)?	☐	☐	☐	
J22. Mastectomy or removal of a breast?	☐	☐	☐	

If yes, was one or both breasts removed?
☐ One ☐ Both

Please indicate if you have ever had any of the following surgical procedures done.

	No	Yes	Not sure	If yes, age at first occurrence (years)
J23. Any lung surgery?	☐	☐	☐	

If yes, specify.

J24. Periodontal (gum) surgery?	☐	☐	☐	
J25. Heart transplant?	☐	☐	☐	
J26. Lung transplant?	☐	☐	☐	
J27. Kidney transplant?	☐	☐	☐	
J28. Liver transplant?	☐	☐	☐	
J29. Bone marrow transplant?	☐	☐	☐	
J30. Other organ transplant?	☐	☐	☐	

If yes, specify transplant.

J31. Cataract surgery?	☐	☐	☐	

Males → Go to Question J35.

J32. Removal of one ovary?	☐	☐	☐	
J33. Removal of both ovaries?	☐	☐	☐	
J34. Removal of uterus?	☐	☐	☐	

Females → Go to Question J37.

J35. Removal of one testis?	☐	☐	☐	
J36. Removal of both testes?	☐	☐	☐	
J37. Any other surgery?	☐	☐	☐	

If yes, specify surgery.

Please! Do not mark below this line

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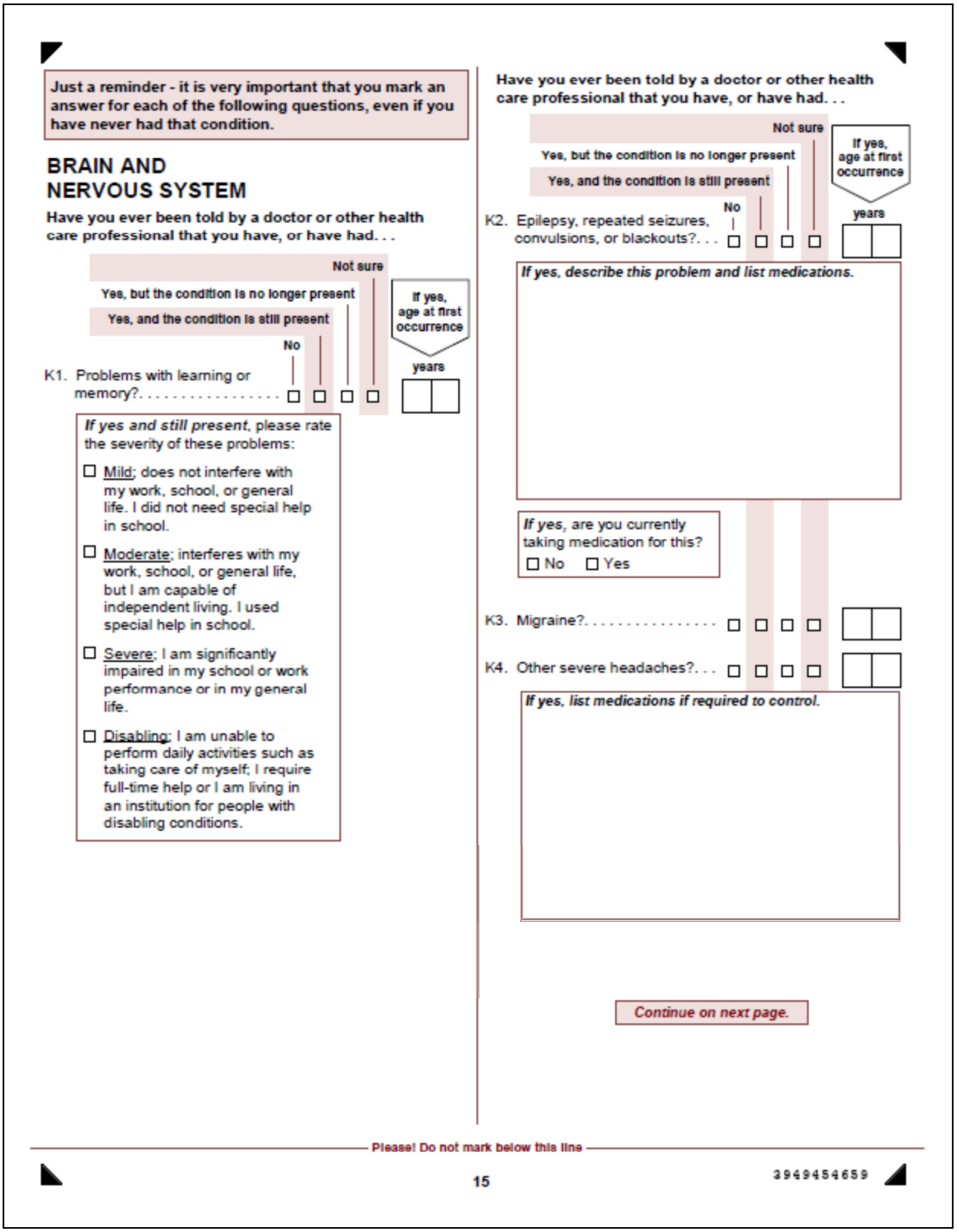

Just a reminder - it is very important that you mark an answer for each of the following questions, even if you have never had that condition.

BRAIN AND NERVOUS SYSTEM

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, and the condition is still present	Yes, but the condition is no longer present	Not sure	If yes, age at first occurrence (years)
K1. Problems with learning or memory?	☐	☐	☐	☐	

If yes and still present, please rate the severity of these problems:

- ☐ Mild; does not interfere with my work, school, or general life. I did not need special help in school.
- ☐ Moderate; interferes with my work, school, or general life, but I am capable of independent living. I used special help in school.
- ☐ Severe; I am significantly impaired in my school or work performance or in my general life.
- ☐ Disabling; I am unable to perform daily activities such as taking care of myself; I require full-time help or I am living in an institution for people with disabling conditions.

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, and the condition is still present	Yes, but the condition is no longer present	Not sure	If yes, age at first occurrence (years)
K2. Epilepsy, repeated seizures, convulsions, or blackouts?	☐	☐	☐	☐	

If yes, describe this problem and list medications.

If yes, are you currently taking medication for this?
☐ No ☐ Yes

K3. Migraine?	☐	☐	☐	☐	
K4. Other severe headaches?	☐	☐	☐	☐	

If yes, list medications if required to control.

Continue on next page.

Please! Do not mark below this line

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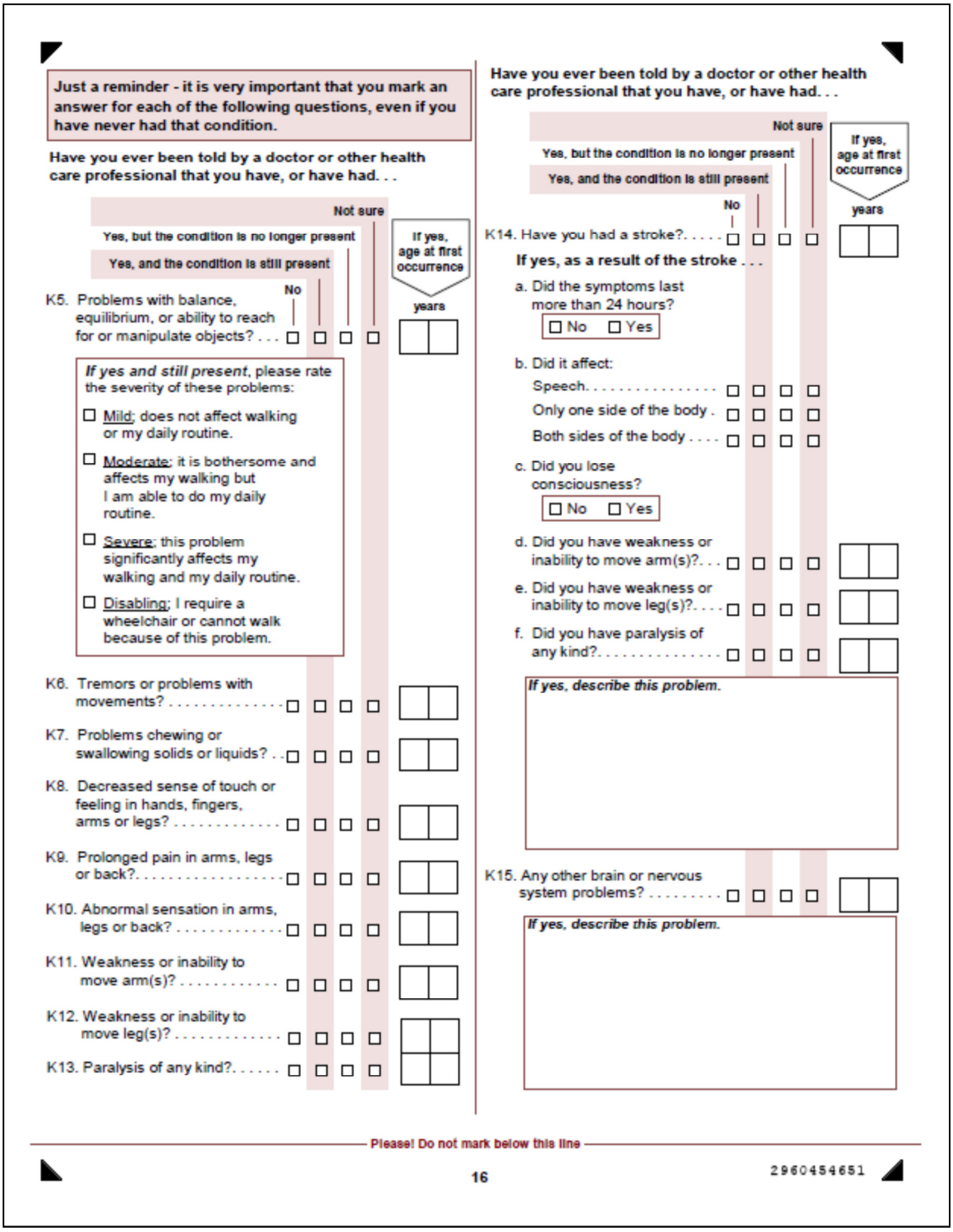

Just a reminder - it is very important that you mark an answer for each of the following questions, even if you have never had that condition.

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
K5. Problems with balance, equilibrium, or ability to reach for or manipulate objects?	☐	☐	☐	☐	☐☐
K6. Tremors or problems with movements?	☐	☐	☐	☐	☐☐
K7. Problems chewing or swallowing solids or liquids?	☐	☐	☐	☐	☐☐
K8. Decreased sense of touch or feeling in hands, fingers, arms or legs?	☐	☐	☐	☐	☐☐
K9. Prolonged pain in arms, legs or back?	☐	☐	☐	☐	☐☐
K10. Abnormal sensation in arms, legs or back?	☐	☐	☐	☐	☐☐
K11. Weakness or inability to move arm(s)?	☐	☐	☐	☐	☐☐
K12. Weakness or inability to move leg(s)?	☐	☐	☐	☐	☐☐
K13. Paralysis of any kind?	☐	☐	☐	☐	☐☐

If yes and still present, please rate the severity of these problems:

- ☐ Mild: does not affect walking or my daily routine.
- ☐ Moderate: it is bothersome and affects my walking but I am able to do my daily routine.
- ☐ Severe: this problem significantly affects my walking and my daily routine.
- ☐ Disabling: I require a wheelchair or cannot walk because of this problem.

Have you ever been told by a doctor or other health care professional that you have, or have had. . .

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
K14. Have you had a stroke?	☐	☐	☐	☐	☐☐

If yes, as a result of the stroke . . .

a. Did the symptoms last more than 24 hours? ☐ No ☐ Yes

b. Did it affect:

Speech	☐	☐	☐	☐	
Only one side of the body	☐	☐	☐	☐	
Both sides of the body	☐	☐	☐	☐	

c. Did you lose consciousness? ☐ No ☐ Yes

d. Did you have weakness or inability to move arm(s)?	☐	☐	☐	☐	☐☐
e. Did you have weakness or inability to move leg(s)?	☐	☐	☐	☐	☐☐
f. Did you have paralysis of any kind?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

	No	Yes, but the condition is no longer present	Yes, and the condition is still present	Not sure	If yes, age at first occurrence (years)
K15. Any other brain or nervous system problems?	☐	☐	☐	☐	☐☐

If yes, describe this problem.

Please! Do not mark below this line

Questions L1 to L18 relate to the past 7 days.

Below is a list of problems people sometimes have. Please read each one carefully and mark the box that best describes how much that problem has distressed or bothered you during the past 7 days including today.

Mark only one answer for each problem and try not to skip any items.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
L1. Nervousness or shaking inside	☐	☐	☐	☐	☐
L2. Faintness or dizziness	☐	☐	☐	☐	☐
L3. Pains in heart or chest	☐	☐	☐	☐	☐
L4. Thoughts of ending your life	☐	☐	☐	☐	☐
L5. Suddenly scared for no reason	☐	☐	☐	☐	☐
L6. Feeling lonely	☐	☐	☐	☐	☐
L7. Feeling blue	☐	☐	☐	☐	☐
L8. Feeling no interest in things	☐	☐	☐	☐	☐
L9. Feeling fearful	☐	☐	☐	☐	☐
L10. Nausea or upset stomach	☐	☐	☐	☐	☐
L11. Trouble getting your breath	☐	☐	☐	☐	☐
L12. Numbness or tingling in parts of your body	☐	☐	☐	☐	☐
L13. Feeling hopeless about the future	☐	☐	☐	☐	☐
L14. Feeling weak in parts of your body	☐	☐	☐	☐	☐
L15. Feeling tense or keyed up	☐	☐	☐	☐	☐
L16. Spells of terror or panic	☐	☐	☐	☐	☐
L17. Feeling so restless you couldn't sit still	☐	☐	☐	☐	☐
L18. Feelings of worthlessness	☐	☐	☐	☐	☐

L19. In general, would you say your health is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

L20. Do you currently have anxieties/fears as a result of your cancer, leukemia, tumor or similar illness, or its treatment?

- ☐ No anxiety/fears
- ☐ Small amount of anxiety/fears
- ☐ Medium amount of anxiety/fears
- ☐ A lot of anxiety/fears
- ☐ Very many, extreme anxiety/fears

L21. How much bodily pain have you had during the past 4 weeks?

- ☐ None → *Go to Question M1, next page.*
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

L22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- ☐ Not at all
- ☐ A little bit
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

L23. For pain that you have had during the past 4 weeks, where has this pain been located? *(Check all that apply)*

- ☐ Head
- ☐ Neck
- ☐ Chest
- ☐ Hands/Arms
- ☐ Abdomen
- ☐ Back
- ☐ Pelvis
- ☐ Legs/Feet
- ☐ Other

Specify

Please! Do not mark below this line

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MARITAL STATUS

M1. What is your current living arrangement? *(Mark all that apply)*

- ☐ Live with spouse/partner
- ☐ Live with parent(s)
- ☐ Live with roommate(s)
- ☐ Live with brother(s) and/or sister(s)
- ☐ Live with other relative(s) (not including minor children)
- ☐ Live alone
- ☐ Other

Specify

M2. Which of the following best describes your current marital status?

- ☐ Single, never married or never lived with partner as married → *Go to Question N1.*
- ☐ Married
- ☐ Living with partner as married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated or no longer living as married

M3. How many times have you been married or lived as married?

1	2	3	4	5	6	7	8	9+
☐	☐	☐	☐	☐	☐	☐	☐	☐

HEALTH HABITS

Alcohol

N1. In your entire life, have you ever had at least 2 drinks of any kind of alcoholic beverage?

- ☐ No → *Go to Question N7, next page.*
- ☐ Yes

N2. How old were you when you first started drinking alcohol?

☐☐ years old

N3. During the last 12 months, how many alcoholic drinks did you have on a typical day when you drank alcohol? *(If less than one per day, enter 0.)*

Wine (4 oz. glass):	Beer (12 oz. can):	Mixed drink (1 shot):
☐☐	☐☐	☐☐
Glasses a day	Cans a day	Drinks a day

N4. During the last 12 months, what is the largest number of drinks you had on any single day? Was it. . .

- ☐ 24+ drinks
- ☐ 12-23 drinks
- ☐ 8-11 drinks
- ☐ 5-7 drinks
- ☐ 4 drinks
- ☐ 3 drinks
- ☐ 2 drinks
- ☐ 1 drink

Please! Do not mark below this line

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N5. During the last 12 months, how often did you usually have any kind of drink containing alcohol?

- ☐ Every day
- ☐ 5 to 6 times a week
- ☐ 3 to 4 times a week
- ☐ twice a week
- ☐ once a week
- ☐ 2 to 3 times a month
- ☐ once a month
- ☐ 3 to 11 times in the past year
- ☐ 1 or 2 times in the past year
- ☐ Never in the past year

N6. During the last 12 months, how often did you have 5 or more (males) or 4 or more (females) drinks containing any kind of alcohol in a single day?

- ☐ Every day
- ☐ 5 to 6 days a week
- ☐ 3 to 4 days a week
- ☐ two days a week
- ☐ one day a week
- ☐ 2 to 3 days a month
- ☐ one day a month
- ☐ 3 to 11 days in the past year
- ☐ 1 or 2 days in the past year
- ☐ Never in the past year

Smoking

N7. Have you smoked at least 100 cigarettes in the previous two years?

- ☐ No → *Go to Question N13.*
- ☐ Yes

N8. If you started smoking since you last provided us this information on %fu2date%, how old were you when you started smoking?

☐☐

N9. Do you smoke cigarettes now?

- ☐ No
- ☐ Yes

N10. On average, how many cigarettes a day do/did you smoke?

☐☐

N11. How many years, in total, have you smoked?

☐☐

N12. If you currently smoke, how many times in the past 12 months have you tried to quit smoking and not smoked for at least 24 hours?

☐☐

N13. In the past year, have you ever used any of these tobacco products? *(Mark all that apply)*

	Never used	No longer use	Occasionally use	Regularly use
Chewing tobacco	☐	☐	☐	☐
Snuff tobacco	☐	☐	☐	☐
Pipes	☐	☐	☐	☐
Cigars	☐	☐	☐	☐

N14. For any of those that you have used or are currently using, how long have you used it?

	Less than 1 year	1 - 2 years	3 - 4 years	5 - 10 years	11+ years
Chewing tobacco	☐	☐	☐	☐	☐
Snuff tobacco	☐	☐	☐	☐	☐
Pipes	☐	☐	☐	☐	☐
Cigars	☐	☐	☐	☐	☐

Please! Do not mark below this line

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Physical Activity

The following questions are about exercise, recreation, or physical activities other than your regular job duties.

N15. During the past month, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?

☐ No

☐ Yes

We are interested in two types of physical activity: vigorous and moderate.
- **Vigorous activities cause large increases in breathing or heart rate.**
- **Moderate activities cause small increases in breathing or heart rate.**

N16. Now thinking about the vigorous physical activities you do in a usual week, do you do vigorous activities for at least 10 minutes at a time, such as running, aerobics, wheelchair basketball, heavy yard work, or anything else that causes large increases in breathing or heart rate?

☐ No → *Go to Question N19.*

☐ Yes

N17. How many days per week do you do these vigorous activities for at least 10 minutes at a time?

☐ Days per week

N18. On days when you do vigorous activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?

☐☐☐ Minutes per day

N19. Now, thinking about the moderate physical activities you do in a usual week, do you do moderate activities for at least 10 minutes at a time, such as brisk walking, bicycling, gardening, manual operation of a wheelchair, or anything else that causes small increases in breathing or heart rate?

☐ No → *Go to Question N22.*

☐ Yes

N20. How many days per week do you do these moderate activities for at least 10 minutes at a time?

☐ Days per week

N21. On days when you do moderate activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?

☐☐☐ Minutes per day

N22. Because of any impairment or health problems, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around your home?

☐ No

☐ Yes

N23. Because of any impairment or health problems, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?

☐ No

☐ Yes

N24. Does any impairment or health problem keep you from holding a job or attending school?

☐ No

☐ Yes

N25. Do you currently have a driver's license?

☐ No

☐ Yes

Please! Do not mark below this line

N26. Over the last 2 years, how long (if at all) has your health limited you in each of the following activities?

(Mark one box for each item.)	Limited for more than 3 months	Limited for 3 months or less	Not limited at all
a. The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports	☐	☐	☐
b. The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling	☐	☐	☐
c. Walking uphill or climbing a few flights of stairs	☐	☐	☐
d. Bending, lifting, or stooping	☐	☐	☐
e. Walking one block	☐	☐	☐
f. Eating, dressing, bathing, or using the toilet	☐	☐	☐

OTHER ISSUES

Please rate how concerned you are about the following:	Very concerned	Somewhat concerned	Concerned	Not very concerned	Not at all concerned
O1. Your future health	☐	☐	☐	☐	☐
O2. Your ability to have children	☐	☐	☐	☐	☐
O3. Developing a cancer	☐	☐	☐	☐	☐
O4. Your ability to get health insurance	☐	☐	☐	☐	☐
O5. Your ability to get life insurance	☐	☐	☐	☐	☐
O6. Any other issues	☐	☐	☐	☐	☐

Please specify.

CANCER, LEUKEMIA, OR TUMOR

P1. Have you been diagnosed with another cancer, leukemia, tumor, or a recurrence (relapse) since you last provided us information in %LastMo%, %LastYr%? (Please include skin cancers.)

☐ No → *Go to next page.*

☐ Yes

What was the name of this disease?

If this was a skin cancer, where was it located on your body? (Example: right upper arm, left ear)

Where was this diagnosed?

Doctor's name

Hospital or clinic

Address

City, State, Zipcode

Was this a:

☐ Recurrence of original diagnosis

☐ New cancer, leukemia, tumor, or similar illness

☐ Don't know

Date of Recurrence or New Diagnosis:

Month (mm) **Year (yyyy)**

Please use a separate sheet of paper for additional cancers

Please! Do not mark below this line

FAMILY HISTORY INFORMATION

Conditions or illnesses occurring in family members may be important clues in determining our genetic make-up. The following section of the questionnaire deals with cancer, conditions present at birth, and hereditary conditions that may be present in your children. Please use the list below to complete the following section.

Cancer

Any diagnosis of cancer or malignant tumor, such as:

- Leukemia
- Retinoblastoma
- Brain tumor
- Hodgkins disease
- Sarcoma
- Germ cell tumor
- Cancer - any other type, or location unknown
- Skin cancer - Please note if melanoma or non-melanoma
- Wilms tumor
- Lymphoma
- Teratoma
- Seminoma
- Neuroblastoma
- Carcinoma

Conditions Present at Birth

Any abnormality present at birth, such as:

- Blindness or difficulty seeing
- Crossed eyes (strabismus)
- Eyes different colors
- Hare lip (cleft lip)
- Hole in roof of mouth (cleft palate)
- Absent, fused or extra fingers or toes
- Hip displacement
- Diverted urinary stream (hypospadias)
- Undescended testicle (cryptorchism)
- Deafness or impaired hearing
- Shortened limbs
- Club foot
- Hole in the heart
- Other congenital heart defect
- Down Syndrome Trisomy 21
- Open spine (spina bifida)
- Exposed brain (anencephaly)
- Large or multiple birth marks
- Water on the brain (hydrocephalus)
- Macrocephaly (enlarged head)
- Microcephaly (small head)
- Hemihypertrophy (enlargement of one arm or leg)
- Deformed chest
- Other skeletal abnormality

Hereditary Conditions

Some of the more common conditions known to be hereditary:

- Achondroplasia
- Acrocephalosyndactyly
- Aniridia (missing an iris)
- Apert's syndrome
- Ataxia-telangiectasia
- Beckwith-Wiedemann syndrome
- Bilateral acoustic neurofibromatosis (type 2)
- Bloom's syndrome
- Congenital megacolon (Hirschsprung's disease)
- Cystic fibrosis
- Fanconi's anemia
- Klinefelter's syndrome
- Marfan's syndrome
- Multiple exostoses
- Multiple polyposis
- Myotonic dystrophy
- Neurofibromatosis (type 1)
- Nevoid basal cell carcinoma syndrome
- Osteogenesis imperfecta
- Polycystic disease of the kidney
- Polyposis coli (Gardner's syndrome)
- Tuberous sclerosis
- Turner's syndrome
- Von Hippel-Lindau syndrome
- Von Recklinghausen's disease
- Wiskott-Aldrich syndrome
- Xeroderma pigmentosum

Please! Do not mark below this line

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PREGNANCY AND OFFSPRING

Q1. Have you, or your partner, had any new pregnancies since you last provided us with this information on %fu2date%?

☐ No → *Go to Question R1 on page 25.*

☐ Yes

Q2. Are you, or your partner, currently pregnant?

☐ No

☐ Yes

Q3. Please write down the names of each of your children who have been born since %fu2date%.
Indicate whether each child has a history of cancer, a birth defect, and/or any hereditary conditions (refer to the list of conditions on the previous page). Please list twin births or multiple births as separate children.
Use a separate piece of paper if you need to record more pregnancies.

Full Name (First, Middle, Last)	Sex	Date of Birth (Mo/Day/Yr)	Status	Date of Death (Mo/Day/Yr)	Medical history of cancer, birth defect, hereditary condition Provide specific type.	Age of onset (yrs)
	☐ Male ☐ Female		☐ Alive ☐ Dead			
	☐ Male ☐ Female		☐ Alive ☐ Dead			
	☐ Male ☐ Female		☐ Alive ☐ Dead			
	☐ Male ☐ Female		☐ Alive ☐ Dead			

Q4. This question concerns the birth (biological) parents of your children listed above. Please list the other parent or parents of your children. ***Use a separate sheet of paper if you need to record additional parents.***

Full Name of other parent (First, Middle, Last)	Date of Birth (Mo/Day/Yr)	Status	Date of Death (Mo/Day/Yr)	Medical history of cancer, birth defect, hereditary condition Provide specific type.	Age of onset (yrs)
		☐ Alive ☐ Dead			
Please list the names of the biological children of this parent.					

Please! Do not mark below this line

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Q5. Since %fu2date%, please fill in the following information for each of your pregnancies, or each time a woman has become pregnant by you, regardless of the outcome.

Pregnancy outcome

	Live birth	Stillbirth	Miscarriage	Medical abortion	Your age at start of pregnancy	Partner's age at start of pregnancy	Weeks pregnancy lasted
Pregnancy 1	☐	☐	☐	☐	☐☐	☐☐	☐☐
Pregnancy 2	☐	☐	☐	☐	☐☐	☐☐	☐☐
Pregnancy 3	☐	☐	☐	☐	☐☐	☐☐	☐☐
Pregnancy 4	☐	☐	☐	☐	☐☐	☐☐	☐☐
Pregnancy 5	☐	☐	☐	☐	☐☐	☐☐	☐☐

Please attach a separate sheet of paper, if more than 5 pregnancies

Continue on next page.

OTHER TREATMENT

We are interested in whether you have had any radiation or chemotherapy for cancer or similar illness. Radiation is a treatment you would have received in a radiation therapy department and does not include CAT scans, MRI's, or diagnostic x-rays.

R1. Have you received any radiation treatment since %fu1date%?

- ☐ No → *Go to Question R2.*
- ☐ Yes
- ☐ Not sure

If yes, please indicate the date of any (additional) radiation treatment you received for a recurrence or a new cancer.

Date of Treatment

☐☐ ☐☐☐☐

Month (mm) **Year (yyyy)**

Please indicate the reason for radiation.

Where was the radiation performed?

Hospital or clinic
Address
City, State, Zipcode
Doctor's name

R2. Have you received any chemotherapy treatment since %fu1date%?

- ☐ No → *Go to next page.*
- ☐ Yes
- ☐ Not sure

If yes, please indicate the date of any (additional) chemotherapy treatment you received for a recurrence or a new cancer.

Date of Treatment

☐☐ ☐☐☐☐

Month (mm) **Year (yyyy)**

Please indicate the reason for chemotherapy.

Where was the chemotherapy performed?

Hospital or clinic
Address
City, State, Zipcode
Doctor's name

Continue on next page.

Please! Do not mark below this line

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This form is a medical release that we would like you to sign. It will give us permission to obtain copies of parts of your medical records that we may need to review, such as treatment history for your cancer or similar illness, or pathology reports for a subsequent cancer. You may have already signed a similar release when you filled out a previous questionnaire; however, since that release may have expired we need to ensure that your permission is kept current.

LONG-TERM FOLLOW-UP STUDY
HIPAA[1] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH

1. Purpose. As a research participant, I authorize Leslie L. Robison, Ph.D. and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research project entitled Long-Term Follow-Up (LTFU) Study.

2. Individual Health Information to be Used or Disclosed. My individual health information that may be used or disclosed to conduct this research includes medical records since the diagnosis of a serious illness such as a cardiac condition or a cancer or similar illness.

3. Parties Who May Disclose My Individual Health Information. The researcher and the researcher's staff may obtain my individual health information from:

Hospitals: _____
Clinics: _____
Other Providers: _____
Health Plan: _____,
and from hospitals, clinics, health care providers and health plans that provide my health care during the study.

4. Parties Who May Receive or Use My Individual Health Information. The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by Leslie L. Robison, Ph.D., the researcher's staff, LTFU collaborators, the LTFU Biopathology Center (Columbus, OH), the LTFU Molecular Center (Cincinnati, OH), the LTFU Radiation Physics Center (Houston, TX), and the LTFU Statistical Center (Seattle, WA).

5. Right to Refuse to Sign this Authorization. I do not have to sign this Authorization. If I decide not to sign the Authorization, I may not be allowed to participate in this study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke. I can change my mind and withdraw this authorization at any time by sending a written notice to Dr. Leslie L. Robison, St. Jude Children's Research Hospital, Department of Epidemiology and Cancer Control, 262 Danny Thomas Place, Mail Stop 735, Memphis, TN 38105 to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

7. Potential for Re-disclosure. Once my health information is disclosed under this authorization, there is a potential that it will be re-disclosed outside this study and no longer covered by this authorization. However, the research team and the St. Jude Institutional Review Board (the committee that reviews studies to be sure that the rights and safety of study participants are protected) are very careful to protect your privacy and limit the disclosure of identifying information about you.

7A. Also, there are other laws that may require my individual health information to be disclosed for public purposes. Examples include potential disclosures if required for mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

This authorization does not have an expiration date.

I am the research participant or personal representative authorized to act on behalf of the participant.

I have read this information, and I will receive a copy of this authorization form after it is signed.

Sign Here

_____ Printed name of research participant

_____ Signature of research participant or research Participant's personal representative

_____ Date of birth

_____ Today's Date

Fill in Date

_____ Printed name of research participant's personal representative

_____ Description of personal representative's authority to act on behalf of the research participant

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

Please! Do not mark below this line

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We have your current address and phone as:

Is this information correct, or are you planning on moving in the next 6 months?

☐ Correct ☐ Not correct ☐ Moving

If this information is not correct, please give us your correct address or location:

Address	
City	State
Zip Code	Phone Number

Please provide the name and address of someone who could give us your new address should you move. We will contact this person only if we are unable to reach you at your home address.

Name	
Address	Relationship to you
City	State
Zip Code	Phone Number

Do you have an email address we could use to contact you?

☐ No ☐ Yes → Your Email Address

On average, how many times per week do you use the internet?

☐ Never ☐ 1-10 times ☐ 11 or more times

Please! Do not mark below this line

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We are always interested in your input in the follow-up study.
Use this space for any additional comments you may have:

When you have completed this questionnaire please return it to us in the enclosed envelope.

Mail to:

LONG-TERM FOLLOW-UP STUDY
St. Jude Children's Research Hospital
Department of Epidemiology
Mail Stop 735
262 Danny Thomas Place
Memphis, TN 38105-3678

Thank you!

Please! Do not mark below this line

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