STUDY TITLE

Estimating the direct and indirect effects of anthracycline exposure on late cardiac outcomes among childhood cancer survivors

WORKING GROUPS

Biostatistics/Epidemiology (Primary)
Cancer Control (Secondary)
Chronic Disease (Secondary)

INVESTIGATORS

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BACKGROUND AND RATIONALE

The introduction of new therapeutic strategies over the past few decades have resulted in significantly improved survival among children and adolescents with cancer.[1] However, numerous studies have reported late effects of chemotherapy and radiotherapy among this growing population.[2] Mertens, et al. demonstrated an 8.4-fold excess in all cause mortality and a 7.0-fold excess risk of death related to cardiac events in a cohort of 20,483 5-year survivors in the Childhood Cancer Survivor Study.[3]

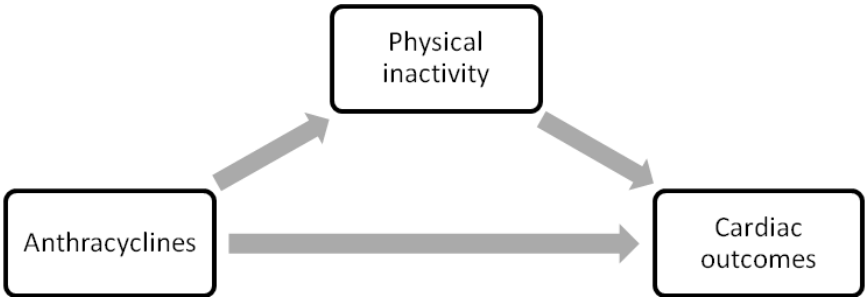
Although anthracyclines are some of the most effective chemotherapeutic agents in use, they are the most common chemotherapeutic agents associated with cardiotoxicity.[4] Although many survivors appear asymptomatic, during times of increased metabolic demands, many childhood cancer survivors with anthracycline cardiotoxicity will experience acute cardiac failure.[5-7]

Additionally, long-term survivors of childhood cancer may be at increased risk of developing heart failure due to increases in the prevalence of cardiovascular disease risk factors. Numerous studies have reported an increase in the prevalence of obesity following cancer treatment in the pediatric population.[8-13] _ENREF_9 Additionally, childhood cancer survivors are more likely than their siblings to report taking medications for dyslipidemia, hypertension, or diabetes[14] and have higher fasting plasma glucose and insulin levels than age matched controls.[15]

Furthermore, long-term childhood cancer survivors are less likely to meet federal recommendation for physical activity than sibling controls[16] and they exhibit impaired exercise capacity,[17] further increasing their risk of cardiovascular disease long after remission. Despite evidence and recommendations that regular moderate exercise and fitness among this population is beneficial,[18-21] parents and physicians may not emphasize the importance of physical activity because of fear that physical activity may exacerbate existing cardiac damage due to their treatment.[21] This protective approach, however, may lead to a sedentary life style with an increased risk of cardiovascular disease, secondary to that associated with anthracyclines, or other cardiotoxic therapies.

We are interested in determining 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 will decompose the total, direct, and indirect effects of anthracycline use on cardiac outcomes among long-term childhood cancer survivors. This concept is illustrated in Figure 1. Within this framework, the cardiotoxicity of anthracyclines produces the direct effect. By contrast, the indirect effect is explained by physical inactivity following cancer diagnosis and chemotherapy. The indirect and direct effects together form the total effect of anthracycline exposure on the outcome.

Figure 1: Simplified diagram depicting the relation of anthracyclines to physical inactivity and cardiac outcomes



SPECIFIC AIM

We will utilize CCSS data in a newly developed path analysis to estimate the relative contributions of drug-induced cardiotoxicity and physical inactivity to the total effect of anthracyclines on cardiac outcomes. This analysis will allow us to determine the potential importance of exercise interventions following anthracycline therapy.

ANALYSIS FRAMEWORK

Eligibility: The CCSS participants eligible for this analysis will be childhood cancer survivors who responded to both the 2003 and 2007 CCSS surveys and reported no cardiac outcomes of interest prior to 2003 (as reported on the 2007 CCSS survey). Many cancer survivors who received anthracyclines also received potentially cardiotoxic radiotherapy. While our primary

objective is to determine the effect of anthracyclines alone, we will explore potential effect modification by radiotherapy to the heart as a secondary objective. A summary table of all variables to be examined in this analysis can be found in Appendix I.

Outcome: The outcome of interest in this analysis is myocardial dysfunction diagnosed after 2003. During the 2007 follow-up survey, participants were asked a series of questions related to their cardiac health and medications, and the timing of the reported events. To conform to previous scales developed for examining late effects of cancer treatment, we will define our outcome using the *Categories of Myocardial Dysfunction by Severity* (Table 1). We will examine Grades 2-4 and Grades 3-4 separately in the analysis. We will use the timing of these self-reported events to exclude anyone with myocardial dysfunction reported prior to 2003. Results of the preliminary summary of the reported number of individual outcomes reported between 2003 and 2007 among the respondents (with no history of these outcomes prior to 2003) can be found in Appendix II.

Table 1: Categories of Myocardial Dysfunction by Severity

Variable	Grade and Severity
Congestive heart failure, not requiring medication	Grade 2, moderate
Congestive heart failure, requiring medication	Grade 3, severe
Heart transplant	Grade 4, life-threatening or disabling

Exposure Variable(s): The medical record abstraction data will be used to determine exposure to anthracyclines. We will examine anthracycline exposure as a continuous, categorical and dichotomous variable to determine and report the most parsimonious and clinically-relevant format. The Meacham et al article (2010) on cardiovascular risk factors used categorization for anthracyclines as: none, <100 mg/m^2, 100-299 mg/m^2, and >300 mg/m^2. To be consistent with this analysis, we will use these categorical cut-offs.

Physical activity, the other exposure variable of interest, will be ascertained from questionnaires. 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. As with the anthracycline variable, we will also explore various ways of categorizing physical activity in this analysis. We will consider three levels of physical activity as categorized in previous CCSS manuscripts (no activity, some activity, but did not meet CDC guidelines and met CDC guidelines),[23] and as a continuous variable by converting questionnaire responses into metabolic equivalents per week. This variable will be graphed and evaluated, and perhaps divided into categories depending on its distribution.

Covariates/Potential Confounders: We will investigate the potential for confounding by considering patient characteristics including sex, age, highest level of education completed, current income, health insurance status and employment status and clinical factors such as cancer type and timing as well as other chemotherapeutic agents and radiation received. We will categorize radiation exposure to be consistent with the Mulrooney et al (2009) analysis: no cardiac radiation, <500 cGy, 500 to <1500 cGy, 1500 to <3500 cGy, and ≥3500 cGy. This variable will also be closely examined in our models for interaction with anthracycline therapy.

We will also examine other cardiovascular risk factors including current body mass index (e.g., obesity), diabetes, hypertension, dyslipidemia, family history of cardiovascular disease, smoking status and general health status. Additionally, we will explore the necessity of controlling for the presence of a Cardiovascular Risk Factor Cluster (CVRFC), a variable defined previously by Meacham et al. as a surrogate for metabolic syndrome in the CCSS.[14] Finally, restrictions on physical activity levels among some of the cancer survivors receiving certain lower extremity or amputation surgeries may confound the relationships of interest. We will explore this potential by controlling for history of these treatments in the analysis.

Statistical Analysis: We will examine the direct, indirect, and total effects of anthracycline exposure on cardiac outcomes using a method developed by Erikson et al.,[24] and generalized for a logistic model by Buis.[25] The parameter estimates will be calculated as follows in Stata *(note that the models presented are examples of a subset of models that will be explored)*:

1. Construct a logistic regression model that includes anthracycline, physical inactivity, and the interaction between these two exposures (if statistically significant at α=0.05):

$$\text{Cardiac Outcome} = \beta_0 + \beta_1(\text{Anth}) + \beta_2(\text{Inactive}) + \delta_1(\text{Anth*Inactive}) + \sum_{i=1}^{p} \gamma_i(\text{Covariates}) + E$$

where:

Anth= anthracycline exposure
Inactive=physical inactivity
Covariates=***p*** covariates identified for appropriate confounding control

2. Predict, for each individual in our dataset, the log odds of a cardiac outcome.
3. Transform these 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 to log odds.
    c. The difference in the average predicted log odds between anthracycline exposed and unexposed (with their own physical activity distributions) represents the ***total effect***.

$$\text{Total Effect} = \ln\left(\text{Odds}_{\text{anth=1, inactive|anth=1}}\right) - \ln\left(\text{Odds}_{\text{anth=0, inactive|anth=0}}\right)$$

5. Create a counterfactual scenario by predicting the log odds of a cardiac outcome among anthracycline unexposed, assuming they were exposed to anthracyclines.

6. Transform the individual counterfactual log odds to probabilities, fixing the value of all covariates in the model to the sample mean.
7. 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.
8. Transform the counterfactual probability to the log odds.
9. Compute the difference in the log odds of a cardiac outcome among the anthracycline exposed 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, that is, the ***indirect effect***.

$$\text{Indirect Effect} = \ln\left(\text{Odds}_{\text{anth=1, inactive|anth=1}}\right) - \ln\left(\text{Odds}_{\text{anth=1, inactive|anth=0}}\right)$$

10. Compute the difference in the log odds of a cardiac outcome among the anthracycline unexposed 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. Therefore, this difference gives the effect of anthracycline exposure while controlling for the distribution of physical activity, or the ***direct effect***.

$$\text{Direct Effect} = \ln\left(\text{Odds}_{\text{anth=0, inactive|anth=0}}\right) - \ln\left(\text{Odds}_{\text{anth=1, inactive|anth=0}}\right)$$

11. If desired, the same calculations can be presented in terms of odds ratios.

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

$$\ln\left(O_{x=1,z|x=1}\right) - \ln\left(O_{x=0,z|x=0}\right) = \left[\ln\left(O_{x=1,z|x=1}\right) - \ln\left(O_{x=1,z|x=0}\right)\right] + \left[\ln\left(O_{x=0,z|x=0}\right) - \ln\left(O_{x=1,z|x=0}\right)\right] \rightarrow$$

$$ln\left(\frac{O_{(x=1,z|x=1)}}{O_{(x=0,z|x=0)}}\right) = ln\left(\frac{O_{x=1,z|x=1}}{O_{x=1,z|x=0}}\right) + ln\left(\frac{O_{x=0,z|x=0}}{O_{x=1,z|x=0}}\right) \rightarrow$$

$$\frac{O_{(x=1,z|x=1)}}{O_{(x=0,z|x=0)}} = \frac{O_{x=1,z|x=1}}{O_{x=1,z|x=0}} \times \frac{O_{x=0,z|x=0}}{O_{x=1,z|x=0}}$$

where:

O=odds
x=anthracycline exposure
z=physical inactivity

12. Compute standard errors and accompanying confidence intervals using the bootstrap.[26]

Proposed Working Table Shells *(note that tables will change depending on how each variable is defined in the final analysis)*

Table 1: Characteristics of childhood cancer survivors treated with and without anthracyclines

	Anthracyclines (n=)	No Anthracyclines (n=)	p-value
Age at interview			
18-24 years			
25-34 years			
≥ 35 years			
Sex			
Male			
Female			
Race/Ethnicity			
White, Non-Hispanic			
Black, Non-Hispanic			
Other, Non-Hispanic			
Hispanic/Latino			
Current Employment Status			
Employed or not seeking paid work			
Unemployed			
Household income (US$)			
<20,000			
≥20,000			
Education level			
Did not graduate HS			
Graduated from HS			
Some college or technical school			
Graduated from college or technical school			
Ever smoker			
Current smoker			
Body mass index			
Not overweight or obese (<25 kg/m^2)			
Overweight (25 to <30 kg/m^2)			
Obese (≥30 kg/m^2)			
General health status			
Excellent			
Very good			
Good			
Fair			
Poor			
Meet CDC physical activity guidelines			

US=United States; HS=high school; CDC=Centers for Disease Control and Prevention

Table 2: Cardiac diagnoses, medication and screening utilization among childhood cancer survivors treated with and without anthracyclines

	Anthracyclines (n=)	No Anthracyclines (n=)	p-value
Ever had an echocardiogram or MUGA Scan			
Currently† taking medication for:			
Diabetes			
Hypertension			
Cholesterol			
Heart‡			
Ever diagnosed with diabetes			
Ever diagnosed with hypertension			
Ever diagnosed with any heart or circulatory problems			
Cardiomyopathy/CHF			
Myocardial infarction			
Arrhythmia requiring follow-up/medication			
Coronary heart disease			
Hypertension			
Angina pectoris			
Pericarditis			
Pericardial constriction			
Stiff/leaking heart valves			
Blood clot			
High cholesterol			
Other			
Current cardiac/pulmonary symptoms with exercise			
Immediate family history of MI <55 years of age			
Ever have any heart related surgery			
Coronary artery bypass			
Pericardiectomy			
Heart catheterization			
Angioplasty			
Heart valve replacement			
Pacemaker			
Other			
Ever have a heart transplant			

†Current medications taken consistently for 30 or more days in a year during the two-year period prior to survey.

‡Medications for heart conditions, including angina, coronary artery disease, congestive heart failure, or irregular heart beat.

CHF=chronic heart failure; MI=myocardial infarction

Table 3: Association between various patient characteristics and cardiac outcomes stratified on physical activity status based on CDC guidelines*

	Physically active OR (95% CI)	Physically inactive OR (95% CI)
Anthracycline exposure		
Age at interview (18-24 years, referent)		
25-34 years		
≥ 35 years		
Male		
Race/Ethnicity (White, Non-Hispanic, referent)		
Black, Non-Hispanic		
Other, Non-Hispanic		
Hispanic/Latino		
Unemployed		
Household income <$20,000		
Education level (college graduate, referent)		
Did not graduate HS		
Graduated from HS		
Some college or technical school		
Ever smoke		
Current smoker		
Body mass index (BMI<25 kg/m^2, referent)		
Overweight (25 to <30 kg/m^2)		
Obese (≥30 kg/m^2)		
General health status (excellent, referent)		
Very good		
Good		
Fair		
Poor		
Ever had an echocardiogram or MUGA Scan		
Diagnosed or medicated for diabetes		
Immediate family history of MI <55 years of age		

*p-value for interaction term = (if it is not significant at α=0.05, then we will report a single, combined odds ratio in this table, not stratified by physical activity)

CCSS=Childhood Cancer Survivor Study; CDC=Centers for Disease Control and Prevention; OR=odds ratio; HS=high school; BMI=body mass index; MUGA=multi gated acquisition scan; MI=myocardial infarction

Table 4: Decomposition of the effect of anthracycline exposure and physical activity on cardiac outcomes [note: this table will be modified/repeated for any cardiac outcome (combined) and for each outcome separately]

	Observed Coefficient	Odds Ratio (CI)*	Bootstrap SE	z	P>|z|
Total	(1)				
Indirect	(2)				
Direct	(3)				

*when the effects are presented as odds ratios, the total effects is the product of the direct and indirect effects.

(1) Overall, the odds of a cardiac outcome for survivors not exposed to anthracycline is [exp(1)] times as small as the odds for those exposed to anthracyclines (the total effect).

(2) Survivors exposed to anthracyclines would have [exp(2)] times lower odds of a cardiac outcome if they had the same physical activity levels as survivors not exposed to anthracyclines (the indirect effect)

(3) The survivors not exposed to anthracyclines would have [exp(3)] times lower odds than the survivors exposed to anthracyclines, holding the physical activity levels constant at the unexposed survivor's levels (direct effect).

To get an idea of the relative importance of the indirect effect compared with the total effect, we can divide (2)/(1) = %.Think of this as the size of the indirect effect relative to the size of the total effect since because the coefficients can have different signs, this calculation can result in percentages larger than 100%, negative or both.

DISCUSSION

Strengths and Limitations: While the CCSS is the largest and most comprehensive and diverse cohort of cancer survivors in North America, the dataset and this analysis may be subject to a number of limitations. First, not all eligible survivors participate in these surveys. However, among those eligible, 69% were successfully located and responded to the baseline questionnaire and the demographic data between participants and non-participants was not significantly different.[27] Similarly, selection bias may occur because of the selective availability of information only on participants surviving until the 2007 survey. Although we can obtain vital statistics data, including cause of death information, on anyone that dies between 2003 and 2007, we will be unable to categorize their eligibility for inclusion in the study because we will not have their outcome data prior to 2003 (to determine if they are "disease free"). However, we will obtain the death record data for these individuals to review the potential impact of this bias.

Second, both the cardiac outcomes and physical activity levels are assessed using self reports, which may be subject to error. A study by Strath et al.,[28] compared results obtained from physical activity questions to those ascertained using heart rate motion sensors. This study showed that under-reporting and over-reporting were only apparent for moderate intensity activities, and these cancelled each other out such that there were no mean differences between the self reported data and the objective physical activity groups. Sensitivity for

meeting CDC recommendations was 91% with a specificity of 71%. Similarly, because cardiac conditions are assessed only by self report, there is the potential for outcome misclassification. Since the questionnaires ascertain only diagnosed conditions, we are unable to assess subclinical cardiomyopathy in this population. This may introduce differential misclassification between those exposed and not exposed to anthracyclines as those exposed receive recommendations for routine surveillance and may be more likely to know of their subclinical diagnosis. To address this issue we will conduct a series of sensitivity analyses. First, we will exclude participants who have not had a recent echocardiogram or MUGA scan. Individuals with a recent exam will be more likely to be aware of abnormal findings, minimizing potential disease misclassification. Another possible sensitivity analysis would be to retain all the subjects in the analysis, though we would assume anyone who did not have a recent screening or diagnostic exam had the event. We will then examine how large the difference in results would be under the most extreme of assumptions, thus determining the maximum impact that under-diagnosis could have on the results. If we detect any meaningful differences between the model outcomes of the original analysis and these two sub-analyses, we will explore possible methods of adjustment.

Third, the causal diagram depicted in Figure 1 ignores the possible bidirectional relationship between cardiac outcomes and physical activity levels. It is possible that as people develop subclinical cardiac dysfunction, they decrease their activity levels (Figure 2). We will explore the potential of this reverse causation through a sensitivity analysis using information only from those who report having had an echocardiogram or MUGA scan prior to the start of our follow-up period. This will presumably allow us to compare our results to those excluding participants with known subclinical disease prior to follow-up.

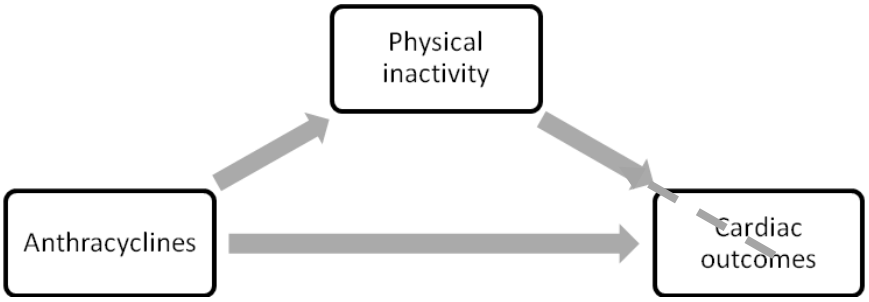


Figure 2: Simplified diagram depicting the relation of anthracyclines to physical inactivity and cardiac outcomes

Lastly, the proposed statistical analysis is based on a relatively new methodology and is not the only way of attaining estimates of direct and indirect effects. For instance, methods proposed by Gomulka and Stern,[29] Even and Macpherson,[30] Yun,[31] and Bauer and Sinning[32] are alternatives to the present analysis and h_ENREF_29_ENREF_29ow these alternatives compare with the method used here has not yet been explored.

Contributions: Results of this study will quantify the relative contributions of direct and indirect mechanisms by which anthracycline exposure may produce cardiac outcomes in cancer survivors. This research may be used to better understand the possible role of exercise interventions in the prevention of clinical manifestations of cardiotoxicity among childhood cancer survivors treated with anthracyclines. If successful, this project may contribute to finding new approaches towards decreasing the morbidity and mortality related to cancer therapy.

SPECIAL CONSIDERATIONS

The proposed analysis is part of Blythe Ryerson's epidemiology PhD dissertation entitled "Determinants and Early Detection of Late Cardiotoxic Effects of Anthracyclines in Childhood Cancer Survivors." Mrs. Ryerson has an MPH in epidemiology from Emory University and has worked as an epidemiologist at the Centers for Disease Control, Division of Cancer Prevention and Control for more than 8 years. She has extensive experience analyzing complex data and publishing original research in peer-reviewed journals. She would like to obtain the data to complete the analysis herself, under direct supervision of her dissertation chair, Ann Mertens, PhD. Additionally she will be collaborating with Harland Austin, a Senior epidemiologist at Emory University with extensive biostatistics and methodology experience and William Border, MBChB, MPH, a pediatric cardiologist and Director of Noninvasive Imaging at the Sibley Heart Center at Children's Healthcare of Atlanta. Although Mrs. Ryerson would like to complete the analysis herself, we understand that CCSS biostatisticians will have an opportunity to review the analysis prior to publication.

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APPENDIX I

Variables collected on each survey (or data source) to be explored in this analysis

	Baseline	Treatment Data	2000 Questionnaire	2003 Questionnaire	2007 Questionnaire	Vital Stats
Outcome					G1. Ever congestive heart failure (age) G2. Ever MI (age) G3. Ever irregular heart beat (age) G4. Ever coronary heart disease (age) G6. Ever angina pectoris (age) G7. Ever pericarditis (age) G8. Ever pericardial constriction (age) G9. Ever stiff or leaking heart valves (age) G10. Ever blood clots (age) G11. Severe chest pain during exercise (age) G13. Ever any other heart or circulatory problems (type, and age)? C87. Heart meds in past 2 years(age)	Cause of death
Anthracyclines		For each cancer diagnosis (including all relapses): ***Chemotherapy*** information (type, route, date started, date of last dose, cumulative dose, BSA, weight)				
Exercise				D1.Any physical activity D2.Any vigorous activity D3.Frequency of vigorous activity D4.Time per day of vigorous activity D5.Any moderate activity D6.Frequency of moderate activity D7.time per day of moderate activity		

Variables collected on each survey (or data source) to be used in this analysis *(continued)*						
	Baseline	**Treatment Data**	**2000 Questionnaire**	**2003 Questionnaire**	**2007 Questionnaire**	**Vital Stats**
c	A1. Date of birth					

	A2. Sex A4. Race A4a. Ethnicity	***Radiation*** information (date Rx start, date Rx end, fields, dose) ***Surgery*** information (date, type)	4e. Down's syndrome 5l. Congenital heart defect	1. Education 2. Marital status 3. Current living arrangement 4. Current employment status 6. Activity level at work E1. General health status M1. Health insurance M1a. Type of health insurance S1. Household income S2. Number in household S3. Personal income 7. Current height 8. Current weight B1. Last echocardiogram L1. Ever smoke, and age at start L2. Current smoking status L3. Cigarettes per day L4. Smoking years L5. Number of times tried to quit smoking L6. Other tobacco products in past year	G14. Family history of early heart attack Q1. New pregnancies since last survey Q2. Currently pregnant Q5. Pregnancy info (outcome, your age at start, length) C84. Diabetes meds in past 2 years (and age of first use) F5/F6/F7. Ever diagnosed with diabetes (and age of first occurrence) G5. Ever hypertension (age) G12. Ever high cholesterol (age) C85. High blood pressure meds in past 2 years (age) C86. Cholesterol meds in past 2 years (age) A1. Current height A2. Current weight C1. Last echocardiogram N7. Smoke in past 2 years N8. Age started smoking N9. Current smoking status N10. Cigarettes per day N11. Smoking years N12. Number of times tried to quit smoking N13. Other tobacco products in past year N14. How long used other tobacco products	

APPENDIX II

CCSS survivors completing FU2003 and FU2007
Cardiac conditions diagnosed after FU2003 completion
Any with heart problems indication at baseline/FU2000 or age at onset before 2003 have been removed

	Survivors			
Cardiac condition	**Both chest radiation and anthracyclines**	**Chest radiation, no anthracyclines**	**No chest radiation, some anthracyclines**	**No chest radiation, no anthracyclines**
Cardiomyopathy/CHF	13	9	18	3
Heart transplant	1	0	1	0