CCSS Analysis Concept Proposal

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TITLE: Vigorous Physical Activity in Adult Survivors of Adolescent and Young Adult Cancers: Description, Predictors, and Associations with Cardiovascular Outcomes.

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1. TITLE: Vigorous Physical Activity in Adult Survivors of Adolescent and Young Adult Cancers: Description, Predictors, and Associations with Cardiovascular Outcomes.

2. WORKING GROUP AND INVESTIGATORS:

Primary: Chronic Disease

Secondary: Cancer Control

3. BACKGROUND/RATIONALE:

The 5-year overall survival rate for Adult Survivors of Adolescent and Young Adult (AYA) cancers has increased from ~70% in 1975 to >80% in recent years, resulting in approximately 633,000 survivors currently living in the United States and this number is expected to grow.[1] These patients are susceptible to an elevated risk of mortality and chronic noncancer health conditions, including cardiovascular disease (CVD), compared to the general population.[2] Research has shown a correlation between participation in physical activity and improved health conditions (e.g. improved body mass index, reduction of fatigue, reduction of mortality, improved cardiovascular health) for persons living past a cancer diagnosis.[3] American Cancer Society, American College of Sports Medicine and Center for Disease Control and Prevention state that physical activity is safe and recommended for persons living past a cancer diagnosis.[4,5] The current recommendations are for 150-300 minutes/week of moderate physical activity, 75-150 minutes/week of vigorous activity, or a combination of the two.[4,5] Despite this overwhelming body of research supporting physical activity participation and current recommendations, people living past a cancer diagnosis continue to have low levels of participation.[6,7] Reports have shown that social inequities (e.g., income, education), as well as current health behaviors (e.g., smoking, current PA participation), have been linked to participation in PA.[33] Understanding if there are predictors of change in participation in physical activity (PA) and what these predictors are, is an area in which more research is needed. This study will explore predictors of changes in physical activity for adult survivors of AYA cancers.

In childhood and adult-onset cancers, excess cardiovascular disease-related morbidity and mortality is likely driven by the direct adverse cardiovascular effects of cancer treatment in conjunction with lifestyle behaviors (e.g., physical inactivity, weight gain) that synergistically predispose patients to CVD risk factors (CVRF; hypertension, dyslipidemia, diabetes) and the potential increased risk of CVD events (heart failure, valvular heart disease, ischemic heart disease/myocardial infarction, stroke).[8,9] It is known that exposure to cardiotoxic treatments such as chemotherapy [anthracyclines, alkylating agents, 5-flurouracil, monoclonal antibodies, and topoisomerase inhibitors (See Appendix 1)] and/or chest or neck radiation increases the risk of CVRF and CVD compared to non-cardiotoxic exposed survivors of cancer. However, risk stratification by cardiotoxic treatment verses non-cardiotoxic treatment within those diagnosed as AYA has been underutilized in clinical care.[10-12] Several studies have examined PA using the CCSS data, however, none have specifically examined PA in those diagnosed with cancer as AYAs.[9,14,20,30] This is a unique group due to differences present for AYAs as compared to the pediatric and adult cancer survivor groups. These differences include more prevalent cancer types specific to AYAs (e.g., germ cell tumors), developmental status at diagnosis (e.g., psychosocial needs), potential for different treatments based on tumor genetics and biology, and

there has been little focus on the lasting impacts specific to this age group thus far.[34] This study will specifically characterize the incidence of CVRF and CVD events among adult survivors of AYA cancers (age 15 to 20 at diagnosis) who were exposed to cardiotoxic treatment compared to non-cardiotoxic exposed survivors.

Cancer survivors, including AYA's, often have a disrupted life path due to their diagnosis and treatment which can lead to persistent fatigue and sedentary lifestyle behaviors.[3,13-15] In the general population, physical activity is associated with substantial reductions in the risk of CVRF and CVD events.[16,17] Moreover, there is a growing body of observational work from our group,[18-20] as well as others,[21-23] showing that exercise (i.e., physical activity that is planned, structured, repetitive and done with intention to improve physical fitness[24]) is associated with lower incidence, and risk of relapse and mortality (both cancer and other). Whether the protective impact of physical activity (defined by METs or metabolic equivalents) extends to AYA cancer survivors exposed to cardiotoxic treatment compared to AYA survivors not exposed to cardiotoxic treatment is not known.

Accordingly, we proposed to investigate predictors associated with change in vigorous physical activity (VPA) in adult survivors of AYA cancers. Additionally, we proposed to explore the incidence of CVRF and CVD events among adult survivors of AYA cancers (age 15 to 20 at diagnosis) who were exposed to cardiotoxic treatment and compare them to non-cardiotoxic exposed AYA survivors. A secondary objective is to examine the association of physical activity with CVRF and CVD events in cardiotoxic treatment exposed and non-exposed AYA survivors. If an association is found, the results will guide future physical activity interventions in AYA survivors at high risk of CVRF and CVD. [4,25,26]

4. OBJECTIVES/RESEARCH HYPOTHESIS:

Primary AIM:

1) **To characterize vigorous physical activity (VPA) change over time across three time points: T1 (baseline), T2 (2014), and T3 (2020); and identify factors associated with VPA change in adult survivors of AYA cancers.**

   Hypothesis 1: The distribution of change in VPA will be skewed toward no change and decrease in VPA. We expect to see the mean change to be negative reflecting decline over time.

   Hypothesis 2: The following baseline factors will be associated with negative VPA change: lower level of education, lack of employment, lack of insurance, specific cancer treatments, less time since diagnosis, presence of comorbid conditions, and smoking.

Secondary AIMs:

1) **Compare the incidence of (a) cardiovascular risk factors (CVRF) and (b) cardiovascular disease (CVD) across T1 (baseline) and T3 (2020 follow up) between adult survivors of AYA cancers who were exposed and those not exposed to cardiotoxic treatments, controlling for other variables.**

Hypothesis: CVRF and CVD incidence will be higher at T1 and T3 in those who received cardiotoxic treatments, compared to those who did not, controlling for other variables.

2) Examine the association between vigorous physical activity (VPA) at T1 (baseline) with (a) cardiovascular risk factors (CVRF) and (b) cardiovascular disease (CVD) at T3 (2020 follow up) in adult survivors of AYA cancers who were exposed and not exposed cardiotoxic treatments, controlling for other variables.

Hypothesis: Increased participation in VPA at T1 (baseline) will be associated with decreased CVRF and CVD outcomes at T3, controlling for other variables.

5. ANALYSIS FRAMEWORK

Primary AIM:

Study Population: Cancer survivors from the Childhood Cancer Survivor Study (CCSS) database who were diagnosed between the ages of 15 and 20 years old and survived five years after diagnosis who have completed a baseline questionnaire in 1999 for the original cohort or in 2007 for the expansion cohort, a follow up questionnaire from FU5 and a follow up questionnaire from FU7. All variables are self-reported except those explicitly identified.

Time points include: T1 (baseline)= 1999 original cohort, 2007 (FU4) variables from the original cohort, and baseline from the expansion cohort. T2 = full cohort 2014 (FU5) T3 = full cohort 2020 (FU7). (See figure 1)

Figure 1. Baseline and follow-up surveys to be used in proposed analyses.

	T1	T2	T3
	Year of Survey Collection		
Cohort			
Original	1999 Baseline	2014 follow up survey (FU5)	2020 follow up survey (FU7)
Expansion	2007 Baseline		

Note: T1 = original cohort 1999 baseline survey and expansion cohort 2007 baseline survey; T2 = original cohort and expansion cohort 2014 follow up survey; T3 = original cohort and expansion cohort 2020 follow up survey.

Description and categorization of vigorous physical activity: Vigorous physical activity (VPA) is defined from the CCSS at baseline and in follow up surveys. (Baseline survey "*On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breath hard (e.g., dancing, jogging, basketball, etc.)?"* Follow up surveys: *"Now thinking about vigorous physical activity 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?," "How many days per week do you do these vigorous activities for at least 10 minutes at a time?," "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?").*[27-29]

VPA questions will be used to determine average MET hrs/wk. To calculate the total VPA, the number of physical activity sessions (frequency) per week is multiplied by the session duration (i.e., 20 minutes or as specified in the questionnaire), weighted by the standardized classification of energy expenditure for vigorous physical activity (i.e., 9 metabolic equivalent tasks)[20,30] at T1 and T2. (Calculation: frequency X duration X 9 = MET minutes/week→ MET minutes/week divided by 60 minutes = MET hr/week). Using this approach, the range of VPA will be from 0 MET hrs/wk to 21 MET hrs/wk and will be a continuous variable. Changes in physical activity will be defined as (1) positive, (2) negative, or (3) no change in weekly METs between T1 and T2, and between T1 and T3. The increase or decrease is defined as one full MET hr/week change.

Predictors of change in VPA include: Demographics, Cancer Variables, Comorbid Conditions, and Health Behaviors (table 1a, 1b, 1c). Time points to be used are listed after each variable.

Demographics: (self-reported): current age (T3), biological sex (T1), race/ethnicity (T1), education*(T3), employment*(T3), household income*(T1, T3), insurance (T1, T2, T3)*, marital status (T1, T3)*, and zip code (T1, T2, T3)* [*associated with social determinants of health].[31]

Health Behaviors: Health behaviors reported as having an impact on VPA will be considered as potential factors associated with change in VPA and include smoking (T3) (current, past, never) and alcohol consumption (T3) (current, past, never).

Cancer Variables:

Diagnosis: (abstracted from the medical record) Leukemia (Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Other Leukemia), Central Nervous System tumors (Astrocytoma, Medulloblastoma/PNET, Other CNS), Hodgkin lymphoma, non-Hodgkin lymphoma, Kidney Tumor (Wilms), Neuroblastoma, Soft Tissue Sarcomas, and Bone Sarcomas (Ewings, Osteosarcoma, Other Bone) (T1).

Treatment: (abstracted from the medical record) As categorized in CCSS publicly available data tables and previous CCSS publications.[20,30,32]

Tx modality: no treatment, Chemo + RT + surgery, Chemo + RT, Chemo + Surgery, RT + surgery, RT only, Surgery only, Chemo only, medical data not available (T1).

Tx variables/measure groups:

Anthracycline (doxorubicin equivalent dose): no exposure; 0 - < 250 mg/m2; >= 250 mg/m2

Alkylating agent (cyclophosphamide equivalent dose): no exposure; 0 - < 4000 mg/m2; >= 4000 - < 8000 mg/m2; >= 8000 mg/m2

Platinum based exposure: no exposure, yes exposure

Antimetabolites exposure: no exposure, yes exposure

Topoisomerase inhibitors exposure: no exposure, yes exposure

Brain RT: no exposure; 0 - <20 Gy; 20- <30 Gy; 30 - <40 Gy; 40 - <50 Gy; 50+Gy

Chest RT: no exposure; 0 - <20 Gy; 20- <30 Gy; 30 - <40 Gy; 40 - <50 Gy; 50+Gy

Neck RT exposure: no exposure, yes exposure

Spine RT exposure: no exposure, yes exposure

Abdomen RT exposure: no exposure, yes exposure

Pelvis RT exposure: no exposure, yes exposure

Limb (arm/leg) RT exposure: no exposure, yes exposure

Total body RT exposure: no exposure, yes exposure

Time Since Diagnosis: (abstracted from the medical record) 10-15 years, 15-20 years, 20-25 years, 23-30 years, 30-35 years, 35-40 years, 40-45 years, and 45+ years (T1, T2, T3).

Comorbid Conditions potentially affecting participation in VPA: Using the Chronic Disease Matrix, based upon the Common Terminology Criteria for Adverse Events (CTCAE, v4.03), conditions to be included as potential predictors of change in VPA are divided into 2 categories:

Conditions NOT graded 3 or 4: seizure (T3), epilepsy (T3), osteoporosis (T3), pain (T1, T2, T3), depression (T1, T2, T3), asthma (T1, T2, T3), tremors (T3), weakness in legs (T3), weakness in arms (T3), and neuropathy (T3).

Conditions graded as 3 or 4: cataracts (T1, T2, T3), blindness (T3), thyroid nodules (T1, T2, T3), diabetes (T1, T2, T3), emphysema (T3), lung fibrosis (T3), heart attack (T1, T2, T3), congestive heart failure (T1, T2, T3), arrhythmias (T1, T2, T3), hypertension (T1, T2 T3), valvular disease (T1, T2, T3), stroke (T1, T2, T3), pericardial diagnosis (T1, T2, T3), blood clot (T1, T2, T3), blood disease (T3), surgery for intestinal obstruction (T3), dialysis (T1, T2, T3), urinary incontinence (T3), amputation (T3), joint replacement (T3), balance (T3), paralysis (T3), loss of hearing (T3).

Cumulative count of multiple conditions: multiple comorbid conditions: $\geq$ 2 grade 3 or 4 conditions (T1, T2, T3).

Analyses (Primary AIM): A longitudinal mixed effects linear regression analysis will be conducted to assess whether the explanatory variables (described above) are associated with the response variable of change in VPA between T2 and T1 and a change in VPA between T3 and T1.

We will enter all explanatory variables into the model.

The interaction of each of the following explanatory variables will be tested in pairwise fashion, and if determined to be statistically significant at the 0.05 level, that term will be added to the model accordingly. The candidate explanatory variables for interaction testing with visit include [Demographics]: current age, biological sex, race/ethnicity, education, employment, household income, marital status, zip code, [Health behaviors]: smoking status, alcohol consumption, [Cancer variables]: diagnosis, treatment, treatment decade, time since diagnosis, and presence of listed comorbid conditions.

Secondary AIM:

Study Population: (Same as Primary Aim)

Time points include: (Same as Primary Aim)

Secondary AIM 1 Dependent Variables: Cardiovascular Risk Factors (CVRF) and Cardiovascular Disease (CVD)

Cardiovascular Risk Factors (CVRF): Hypertension, Dyslipidemia, Diabetes, Overweight (BMI = 25-30), Obese (BMI ≥ 30).

Cardiovascular Disease (CVD): Congestive Heart Failure, Valvular Heart Disease, Myocardial Infarction, Coronary Heart Disease, Blood Clot, Stroke, Pericardial Disease, Arrhythmias.

Cumulative count of multiple conditions: multiple CVRF/CVD conditions: ≥ 2 CVRF/CVD

Secondary AIM 1 Independent Variable: Cardiotoxic treatment

Cardiotoxic treatment: (same as Primary Aim)

Secondary AIM 1 Control Variables: Demographics, Cancer Variables (Diagnosis, Time), Comorbid Conditions, and Physical Activity (see table 2 for list of variables and survey time points).

Demographics: (same as primary aim)

Cancer Variables:

Diagnosis: (same as primary aim)

Time Since Diagnosis: (same as primary aim)

Comorbid Conditions to be controlled for: (same as primary aim).

Vigorous Physical Activity (VPA): (Same as primary aim)

Secondary AIM 2 Variables:

Vigorous Physical Activity (VPA): (Same as primary aim)

Cardiovascular Risk Factors (CVRF): (Same as secondary Aim 1)

Cardiovascular Disease (CVD): (Same as secondary Aim 1)

Secondary AIM 2 Independent Variable: Cardiotoxic treatment

Cardiotoxic treatment: (abstracted from the medical record) As categorized in CCSS publicly available data tables and previous CCSS publications.[20,30,32]

Treatment Modalities:

Model A: (focus of this model is to compare no treatment/surgery only to combination treatments)

Group A1: no treatment, surgery only;

Group A2 (combination treatment): Chemo + RT + surgery, Chemo + RT, Chemo + surgery, RT + surgery;

Model B: (focus of this model to compare within the chemo groups)

Group B1: Any non-CT Chemo;

Group B2 (CT chemo commonly used): treatment yes/no with EXACTLY ONE of the following known cardiotoxic treatments: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2), Anthracycline exposure (doxorubicin dose >= 250 mg/m2), Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2).

Group B3: (CT chemo less commonly used): Platinum based exposure, Antimetabolites, Topoisomerase inhibitors

Group B4: More than one CT chemo from Group B2/B3.

Group B5: Commonly used combination CT chemo treatments.

Group B5: All other treatments

Model C: (focus of this model is to compare within RT treatment groups)

Group C1: Any RT, total body RT;

Group C2: treatment yes/no with EXACTLY ONE of the following: brain RT <20 Gy, brain RT 20- <30 Gy, brain RT 30 - <40 Gy, brain RT 40 - <50 Gy, brain RT 50+Gy, chest RT <20 Gy, chest RT 20- <30 Gy, chest RT 30 - <40 Gy, chest RT 40 - <50 Gy, chest RT 50+Gy, neck RT, spine RT, abdomen RT

Group C3: Treatment with more than one RT treatments from Group C2

Group C4: All other treatments

Secondary AIM 2 Control Variables: Demographics, Cancer Variables (Diagnosis, Time), Comorbid Conditions (see table 2 for list of variables and survey time points).

Demographics: (Same as primary aim)

Cancer Variables:

Diagnosis: (Same as primary aim)

Time: (same as primary aim)

Comorbid Conditions to be controlled for: (Same as primary aim)

Analyses (Secondary AIM 1): Participants with prevalent diagnosis of CVRF/CVD at CCSS cohort entry will be excluded from incidence analyses. Cumulative incidence curves will be used to visualize the incidence of CVRF/CVD (individual conditions and a composite of any condition) between exposure groups (see above); and compared using Gray's K-sample test. The outcome is time to first occurrence of CVRF/CVD. Person-time will be accrued from the cohort entry until CVRF/CVD occurrence or censoring at end of the last follow-up questionnaire completed; death, second malignant neoplasms, and late recurrence will be competing events. We will use multivariable Cox regression models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for first occurrence of CVRF/CVD will consider each condition separately and accounting for the others as competing risks. Multivariable model adjustment will include time-fixed variables for biological sex, race/ethnicity; and time-varying exposures for current smoking status (1999, 2007, 2014), and education (1999, 2007, 2014). The primary exposure will be receipt of cardiotoxic cancer therapy (yes/no) as well as the categorical variable of types of cardiotoxic therapies received previously described. All covariates will be tested for collinearity; if collinearity is present then select variables will be removed.

Analyses (Secondary AIM 2): Participants with a prevalent diagnosis of diabetes, hypertension, dyslipidemia, overweight (BMI>25-29), obesity (BMI>30), heart failure, valvular heart disease, ischemic heart disease, myocardial infarction or stroke at CCSS enrollment will be excluded from incidence analyses. Exercise exposure in METs will be

calculated for vigorous exercise as described previously. The standard MET measurement for vigorous intensity exercise is >9 MET hours/week.[55] Categories of total vigorous exercise will be defined as 0, 3-6, 6-9, 9-12, 15- 21 MET hours/week to encompass standards for vigorous intensity activity. Cumulative incidence curves will be used to visualize the time to onset and incidence of first CVRF or CVD among exposure groups (0, 3-6, 6-9, 9-12,15-21 MET hours/week); and compared using Gray's K-sample test. Person-time will be accrued from the enrollment questionnaire in 1999 until the event of interest (development of first CVRF or CVD event) or censoring at end of study (2014) or loss to follow-up; death, second malignant neoplasms, and recurrence will be analyzed as competing events. We will use multivariable Cox regression models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for first occurrence of CVRF or CVD by vigorous exercise group. The primary exposure will be categorical total vigorous exercise (METs/week) defined in 1999 and updated in 2007 and 2014. Multivariable model adjustment will include time-fixed variables for biological sex, race, ethnicity, and receipt of cardiotoxic cancer therapy at enrollment; and time-varying exposures for attained age, smoking status (1999, 2007, 2014), and education (1999, 2007, 2014). All covariates will be tested for collinearity; if collinearity is present then select variables will be removed.

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Table 1a: Predictors of Change in Vigorous Physical Activity: Demographic Characteristics (mean/sd OR No. %)			
	T1 (baseline) 1999/2007/2008	**T2 FU5 (2014)**	**T3 FU7 (2020)**
Age			
20-29			
30-39			
40-49			
50-59			
60-69			
70+			
Biological sex			
Male			
Female			
Race			
White			
Black			
American Indian/Alaska Native			
Asian/Pacific Islander			
Other			
Unknown			
Ethnicity			
Hispanic			
Non-Hispanic			
Unknown			
Education			
HS graduate or less			
Some college/vocational school			
College graduate			
Post college education			

Employment			
Not currently working			
Full time			
Part time			
Caring for home/family			
Unemployed			
Unable to work due to illness/disability			
Retired			
Student			
Household Income			
$0-19,999			
$20,000-39,000			
$40,000-59,000			
$60,000-79,000			
$80,000-99,999			
$100,000+			
Insurance			
Private			
Federal			
None			
Marital Status			
Living with spouse/partner			
Living with parents			
Living with roommate			
Living with brother/sister			
Living with other family (other than minor children)			
Living alone			
Zip Code			
Rural			

Urban			
Health Behaviors			
Smoking Status			
Current			
Past			
Present			
Alcohol Consumption			
Current			
Past			
Present			

Table 1b: Predictors of Change in Vigorous Physical Activity: Cancer Variables Characteristics (mean /sd OR No/%)			
	T1 (baseline) 1999/2007/2008	**T2 FU5 (2014)**	**T3 FU7 (2020)**
Cancer Diagnosis			
Leukemia (Total)			
Acute Lymphocytic Leukemia			
Acute Myeloid Leukemia			
Other Leukemias			
Central Nervous System (CNS) Tumors			
Astrocytoma			
Medulloblastoma/PNET			
Other CNS malignancy			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Kidney tumors (Wilms)			
Neuroblastoma			
Soft tissue sarcoma			
Bone malignancy			
Ewings sarcoma			
Osteosarcoma			
Other bone malignancy			
Cancer Treatment Modality			
No treatment			
Chemo + RT + surgery			
Chemo + RT			
Chemo + surgery			
Chemo only			
RT + surgery			
RT only			
Surgery only			
No medical data			

Treatment Decade			
1970-1979			
1980-1989			
1990-1999			
Time Since Diagnosis			
10-15 years			
15-20 years			
20-25 years			
25-30 years			
30-35 years			
35-40 years			
40-45 years			
45 + years			

Table 1c: Predictors of Change in Vigorous Physical Activity: Comorbid Conditions Characteristics (mean/sd OR No/%)			
	T1 (baseline) 1999/2007/2008	**T2 FU5 (2014)**	**T3 FU7 (2020)**
Comorbid Conditions (NOT grade 3 or 4)			
Seizure			
Epilepsy			
Osteoporosis			
Pain Diagnosis			
Depression			
Asthma			
Tremors			
Weakness Legs			
Weakness Arms			
Neuropathy			
Comorbid Conditions (Grade 3 or 4)			
Cataracts (grade 3)			
Blindness (3,4)			
Thyroid Nodules (3)			
Diabetes (3)			
Emphysema (3)			
Lung Fibrosis (3)			
Heart Attack (3,4)			
Congestive Heart Failure (3,4)			
Arrhythmias (3)			
Hypertension (3)			
Valvular disease (4)			
Stroke (3,4)			
Pericardial Diagnosis (3)			
Blood Clot (3)			
Blood Disease (3)			

Surgery for Intestinal Obstruction (3)			
Dialysis (3,4)			
Urinary Incontinence (3)			
Amputation (3)			
Joint Replacement (3)			
Balance (3,4)			
Paralysis (4)			
Loss of Hearing (3,4)			
≥ 2 grade 3 and/or 4 conditions			

Table 2a: Predictors of Change in Vigorous Physical Activity: Longitudinal Regression					
	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig.
Age					
20-29					
30-39					
40-49					
50-59					
60-69					
70+					
Biological sex					
Male					
Female					
Race					
White					
Black					
American Indian/Alaska Native					
Asian/Pacific Islander					
Other					
Unknown					
Ethnicity					
Hispanic					
Non-Hispanic					
Unknown					
Education					
HS graduate or less					

Some college/vocational school					
College graduate					
Post college education					
Employment					
Not currently working					
Full time					
Part time					
Caring for home/family					
Unemployed					
Unable to work due to illness/disability					
Retired					
Student					
Household Income					
$0-19,999					
$20,000-39,000					
$40,000-59,000					
$60,000-79,000					
$80,000-99,999					
$100,000+					
Insurance					
Private					
Federal					
None					
Marital Status					
Living with spouse/partner					
Living with parents					

Living with roommate					
Living with brother/sister					
Living with other family (other than minor children)					
Living alone					
Zip Code					
Rural					
Urban					
Health Behaviors					
Smoking Status					
Current					
Past					
Present					
Alcohol Consumption					
Current					
Past					
Present					

*Interactions will be tested for the predictor variables, if determined they are statistically significant, adjustments will be made to the model.

Table 2b: Predictors of Change in Vigorous Physical Activity: Cancer Variables Longitudinal Regression					
	Unstandardized Coefficients		**Standardized Coefficients**		
	B	**Std. Error**	**Beta**	**t**	**Sig.**
Cancer Diagnosis					
Leukemia (Total)					
Acute Lymphocytic Leukemia					
Acute Myeloid Leukemia					
Other Leukemias					
Central Nervous System (CNS) Tumors					
Astrocytoma					
Medulloblastoma/PNET					
Other CNS malignancy					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Kidney tumors (Wilms)					
Neuroblastoma					
Soft tissue sarcoma					
Bone malignancy					
Ewings sarcoma					
Osteosarcoma					
Other bone malignancy					
Cancer Treatment Modality					
No treatment					
Chemo + RT + surgery					
Chemo + RT					
Chemo + surgery					
Chemo only					
RT + surgery					
RT only					

Surgery only					
No medical data					
Treatment Decade					
1970-1979					
1980-1989					
1990-1999					
Time Since Diagnosis					
10-15 years					
15-20 years					
20-25 years					
25-30 years					
30-35 years					
35-40 years					
40-45 years					
45 + years					

*Interactions will be tested for the predictor variables, if determined they are statistically significant, adjustments will be made to the model.

Table 2c: Predictors of Change in Vigorous Physical Activity: Comorbid Conditions					
	Unstandardized Coefficients		**Standardized Coefficients**		
	B	**Std. Error**	**Beta**	**t**	**Sig.**
Comorbid Conditions (Not grade 3 or 4)					
Seizure					
Epilepsy					
Osteoporosis					
Pain Diagnosis					
Depression					
Asthma					
Tremors					
Weakness Legs					
Weakness Arms					
Neuropathy					
Comorbid Conditions (Grade 3 or 4)					
Cataracts (grade 3)					
Blindness (3,4)					
Thyroid Nodules (3)					
Diabetes (3)					
Emphysema (3)					
Lung Fibrosis (3)					
Heart Attack (3,4)					
Congestive Heart Failure (3,4)					
Arrhythmias (3)					
Hypertension (3)					
Valvular disease (4)					
Stroke (3,4)					
Pericardial Diagnosis (3)					

Blood Clot (3)					
Blood Disease (3)					
Surgery for Intestinal Obstruction (3)					
Dialysis (3,4)					
Urinary Incontinence (3)					
Amputation (3)					
Joint Replacement (3)					
Balance (3,4)					
Paralysis (4)					
Loss of Hearing (3,4)					
$\geq$ 2 grade 3 and/or 4 conditions					

*Interactions will be tested for the predictor variables, if determined they are statistically significant, adjustments will be made to the model.

Table 3a: Categories of VPA change by predictor variables (Demographics)				
	Overall Change (mean, sd)	**Positive Change (means, sd)**	**No Change (mean, sd)**	**Negative Change (mean, sd)**
Age				
20-29				
30-39				
40-49				
50-59				
60-69				
70+				
Biological sex				
Male				
Female				
Race				
White				
Black				
American Indian/Alaska Native				
Asian/Pacific Islander				
Other				
Unknown				
Ethnicity				
Hispanic				
Non-Hispanic				
Unknown				
Education				
HS graduate or less				

Some college/vocational school				
College graduate				
Post college education				
Employment				
Not currently working				
Full time				
Part time				
Caring for home/family				
Unemployed				
Unable to work due to illness/disability				
Retired				
Student				
Household Income				
$0-19,999				
$20,000-39,000				
$40,000-59,000				
$60,000-79,000				
$80,000-99,999				
$100,000+				
Insurance				
Private				
Federal				
None				
Marital Status				
Living with spouse/partner				

Living with parents				
Living with roommate				
Living with brother/sister				
Living with other family (other than minor children)				
Living alone				
Zip Code				
Rural				
Urban				
Health Behaviors				
Smoking Status				
Current				
Past				
Present				
Alcohol Consumption				
Current				
Past				
Present				

Table 3b: Categories of VPA change by predictor variables (Cancer Variables)				
	Overall Change (mean, sd)	**Positive Change (means, sd)**	**No Change (mean, sd)**	**Negative Change (mean, sd)**
Cancer Diagnosis				
Leukemia (Total)				
Acute Lymphocytic Leukemia				
Acute Myeloid Leukemia				
Other Leukemias				
Central Nervous System (CNS) Tumors				
Astrocytoma				
Medulloblastoma/PNET				
Other CNS malignancy				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Kidney tumors (Wilms)				
Neuroblastoma				
Soft tissue sarcoma				
Bone malignancy				
Ewings sarcoma				
Osteosarcoma				
Other bone malignancy				
Cancer Treatment Modality				
No treatment				
Chemo + RT + surgery				
Chemo + RT				
Chemo + surgery				
Chemo only				
RT + surgery				

RT only				
Surgery only				
No medical data				
Treatment Decade				
1970-1979				
1980-1989				
1990-1999				
Time Since Diagnosis				
10-15 years				
15-20 years				
20-25 years				
25-30 years				
30-35 years				
35-40 years				
40-45 years				
45 + years				

Table 3c: Categories of VPA change by predictor variables (Comorbid Conditions)				
	Overall Change (mean, sd)	**Positive Change (means, sd)**	**No Change (mean, sd)**	**Negative Change (mean, sd)**
Comorbid Conditions (NOT grade 3 or 4)				
Seizure				
Epilepsy				
Osteoporosis				
Pain Diagnosis				
Depression				
Asthma				
Tremors				
Weakness Legs				
Weakness Arms				
Neuropathy				
Comorbid Conditions (Grade 3 or 4)				
Cataracts (grade 3)				
Blindness (3,4)				
Thyroid Nodules (3)				
Diabetes (3)				
Emphysema (3)				
Lung Fibrosis (3)				
Heart Attack (3,4)				
Congestive Heart Failure (3,4)				
Arrhythmias (3)				
Hypertension (3)				
Valvular disease (4)				
Stroke (3,4)				
Pericardial Diagnosis (3)				
Blood Clot (3)				
Blood Disease (3)				

Surgery for Intestinal Obstruction (3)				
Dialysis (3,4)				
Urinary Incontinence (3)				
Amputation (3)				
Joint Replacement (3)				
Balance (3,4)				
Paralysis (4)				
Loss of Hearing (3,4)				
≥ 2 grade 3 and/or 4 conditions				

Table 4a: Demographics AIM 2			
	Total N of AYA (No, %)	**Exposed to CT treatment (No, %)**	**Not Exposed to CT treatment (No, %)**
Age			
20-29			
30-39			
40-49			
50-59			
60-69			
70+			
Biological sex			
Male			
Female			
Race			
White			
Black			
American Indian/Alaska Native			
Asian/Pacific Islander			
Other			
Unknown			
Ethnicity			
Hispanic			
Non-Hispanic			
Unknown			
Education			
HS graduate or less			

Some college/vocational school			
College graduate			
Post college education			
Employment			
Not currently working			
Full time			
Part time			
Caring for home/family			
Unemployed			
Unable to work due to illness/disability			
Retired			
Student			
Household Income			
$0-19,999			
$20,000-39,000			
$40,000-59,000			
$60,000-79,000			
$80,000-99,999			
$100,000+			
Insurance			
Private			
Federal			
None			
Marital Status			
Living with spouse/partner			

Living with parents			
Living with roommate			
Living with brother/sister			
Living with other family (other than minor children)			
Living alone			
Zip Code			
Rural			
Urban			

Table 4b: Demographics AIM 2: Cancer Variables			
	Total N AYA (No, %)	**Exposed to CT treatment (No, %)**	**Not Exposed to CT treatment (No, %)**
Cancer Diagnosis			
Leukemia (Total)			
Acute Lymphocytic Leukemia			
Acute Myeloid Leukemia			
Other Leukemias			
Central Nervous System (CNS) Tumors			
Astrocytoma			
Medulloblastoma/PNET			
Other CNS malignancy			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Kidney tumors (Wilms)			
Neuroblastoma			
Soft tissue sarcoma			
Bone malignancy			
Ewings sarcoma			
Osteosarcoma			
Other bone malignancy			
Cancer Treatment Modality			
No treatment			
Chemo + RT + surgery			
Chemo + RT			
Chemo + surgery			
Chemo only			
RT + surgery			

RT only			
Surgery only			
Treatment Decade			
1970-1979			
1980-1989			
1990-1999			
Time Since Diagnosis			
10-15 years			
15-20 years			
20-25 years			
25-30 years			
30-35 years			
35-40 years			
40-45 years			
45 + years			

Table 4c: Demographics AIM 2: Comorbid Conditions			
	Total N AYA (No, %)	**Exposed to CT treatment (No, %)**	**Not Exposed to CT treatment (No, %)**
Comorbid Conditions (Not grade 3 or 4)			
Seizure			
Epilepsy			
Osteoporosis			
Pain Diagnosis			
Depression			
Asthma			
Tremors			
Weakness Legs			
Weakness Arms			
Neuropathy			
Comorbid Conditions (Grade 3 or 4)			
Cataracts (grade 3)			
Blindness (3,4)			
Thyroid Nodules (3)			
Diabetes (3)			
Emphysema (3)			
Lung Fibrosis (3)			
Heart Attack (3,4)			
Congestive Heart Failure (3,4)			
Arrhythmias (3)			
Hypertension (3)			
Valvular disease (4)			
Stroke (3,4)			
Pericardial Diagnosis (3)			

Blood Clot (3)			
Blood Disease (3)			
Surgery for Intestinal Obstruction (3)			
Dialysis (3,4)			
Urinary Incontinence (3)			
Amputation (3)			
Joint Replacement (3)			
Balance (3,4)			
Paralysis (4)			
Loss of Hearing (3,4)			
≥ 2 grade 3 and/or 4 conditions			

Table 5. Cumulative Incidence and RR for CVRF Events Among 15-20-year-olds by Treatment Factors											
		Model A		Model B				Model C			
Characteristic	N= Total AYA	Group A1	Group A2	Group B1	Group B2	Group B3	Group B4	Group C1	Group C2	Group C3	Group C4
Any CVRF											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Hypertension											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Diabetes											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Dyslipidemia											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Overweight (BMI>25-29)											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Obesity (BMI >30)											
Cumulative Incidence											

Adjusted relative risk		**REF**		**REF**							
P value											

BMI=body mass index.

Treatment Groups:

Model A: Group A1: no treatment, surgery only; Group A2 (combination treatment): Chemo + RT + surgery, Chemo + RT, Chemo + surgery, RT + surgery;

Model B: Group B1: Any non-CT Chemo; Group B2 (CT chemo): treatment yes/no with EXACTLY ONE of the following known cardiotoxic treatments: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2), Anthracycline exposure (doxorubicin dose >= 250 mg/m2), Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2), Platinum based exposure, Antimetabolites, Topoisomerase inhibitors; Group B3: More than one CT chemo from Group B2; Group B4: All other treatments

Model C: Group C1: Any RT, total body RT; Group C2: treatment yes/no with EXACTLY ONE of the following: brain RT <20 Gy, brain RT 20- <30 Gy, brain RT 30 - <40 Gy, brain RT 40 - <50 Gy, brain RT 50+Gy, chest RT <20 Gy, chest RT 20- <30 Gy, chest RT 30 - <40 Gy, chest RT 40 - <50 Gy, chest RT 50+Gy, neck RT, spine RT, abdomen RT; Group C3: Treatment with more than one RT treatments from Group C2; Group C4: All other treatments

List of Cardiotoxic Chemotherapies: Anthracyclines (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, and Mitoxantrone), **Alkylating agents and Platinum based (**Busulfan, Carboplatin, Carmustine (BCNU), Chlorambucil, Cisplatin, Cyclophosphamide-All Routes, Cyclophosphamide-IV/IM, Cyclophosphamide-PO, Dacarbazine (DTIC), Ifosfamide, Lomustine (CCNU), Mechlorethamine (N. Mustard), Melphalan-All Routes, Melphalan-IV/IM, Melphalan-PO, Procarbazine, Thiotepa-All Routes, Thiotepa-IT, Thiotepa-IV/IM;) **Antimetabolites** (fluorouracil (5-FU)); **Topoisomerase inhibitors** (etoposide (VP-16)-all routes, etoposide (VP-16)-IV/IM, etoposide (VP-16)-PO,); or any combination of these treatments.

Table 6. Cumulative Incidence and RR for CVD Events Among 15-20-year-olds by Treatment Factors											
		Model A		Model B				Model C			
Characteristic	**N= Total AYA**	**Group A1**	**Group A2**	**Group B1**	**Group B2**	**Group B3**	**Group B4**	**Group C1**	**Group C2**	**Group C3**	**Group C4**
Any CVD											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Congestive Heart Failure											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Valvular Heart Disease											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Ischemic Heart Disease/Myocardial infarction											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											

Coronary Heart Disease											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Blood Clot											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Stroke											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Pericardial Disease											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											
Arrhythmias											
Cumulative Incidence											
Adjusted relative risk		**REF**		**REF**				**REF**			
P value											

Treatment Groups:

Model A: Group A1: no treatment, surgery only; Group A2 (combination treatment): Chemo + RT + surgery, Chemo + RT, Chemo + surgery, RT + surgery;

Model B: Group B1: Any non-CT Chemo; Group B2 (CT chemo): treatment yes/no with EXACTLY ONE of the following known cardiotoxic treatments: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2), Anthracycline exposure (doxorubicin dose >= 250 mg/m2), Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2), Platinum based exposure, Antimetabolites, Topoisomerase inhibitors; Group B3: More than one CT chemo from Group B2; Group B4: All other treatments

Model C: Group C1: Any RT, total body RT; Group C2: treatment yes/no with EXACTLY ONE of the following: brain RT <20 Gy, brain RT 20- <30 Gy, brain RT 30 - <40 Gy, brain RT 40 - <50 Gy, brain RT 50+Gy, chest RT <20 Gy, chest RT 20- <30 Gy, chest RT 30 - <40 Gy, chest RT 40 - <50 Gy, chest RT 50+Gy, neck RT, spine RT, abdomen RT; Group C3: Treatment with more than one RT treatments from Group C2; Group C4: All other treatments

List of Cardiotoxic Chemotherapies: Anthracyclines (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, and Mitoxantrone), **Alkylating agents and Platinum based (**Busulfan, Carboplatin, Carmustine (BCNU), Chlorambucil, Cisplatin, Cyclophosphamide-All Routes, Cyclophosphamide-IV/IM, Cyclophosphamide-PO, Dacarbazine (DTIC), Ifosfamide, Lomustine (CCNU), Mechlorethamine (N. Mustard), Melphalan-All Routes, Melphalan-IV/IM, Melphalan-PO, Procarbazine, Thiotepa-All Routes, Thiotepa-IT, Thiotepa-IV/IM;) **Antimetabolites** (fluorouracil (5-FU)); **Topoisomerase inhibitors** (etoposide (VP-16)-all routes, etoposide (VP-16)-IV/IM, etoposide (VP-16)-PO,); or any combination of these treatments.

Table 7a: Cumulative Incidence and RR for CVRF Among 15-20-year-olds by Vigorous Weekly MET groups Model A (no treatment verses combination treatment)					
Characteristic	**N= Total AYA**	**Group1/active**	**Group 1/inactive**	**Group 2/active**	**Group 2/inactive**
Any CVRF					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Hypertension					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Diabetes					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Dyslipidemia					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Overweight (BMI>25-29)					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Obesity (BMI >30)					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					

CVRF: cardiovascular risk factor, **MET:** metabolic equivalent tasks,

Treatment Groups: Group 1: no treatment, surgery only; Group 2 (combination treatment): Chemo + RT + surgery, Chemo + RT, Chemo + surgery, RT + surgery;

Treatment-by-Exercise Groups: Group 1 and meeting exercise guidelines (> 9 METs), Group 1 and not meeting exercise guidelines (< 9 METs), Group 2 and meeting exercise guidelines (> 9 METs), Group 2 and not meeting exercise guidelines (< 9 METs).

Table 7b: Cumulative Incidence and RR for CVRF Among 15-20-year-olds by Vigorous Weekly MET groups for Model B (focus on chemo treatment groups)									
Characteristic	**N= Total AYA**	**Group 3/ active**	**Group 3 /inactive**	**Group 4/ active**	**Group 4 /inactive**	**Group 5/ active**	**Group 5 /inactive**	**Group 6 /active**	**Group 6 /inactive**
Any CVRF									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Hypertension									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Diabetes									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Dyslipidemia									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Overweight (BMI>25-29)									

Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Obesity (BMI >30)									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									

CVRF: cardiovascular risk factor, **MET:** metabolic equivalent tasks,

Treatment Groups: Group 3: Any non-CT Chemo; Group 4 (CT chemo): treatment yes/no with ONE of the following known cardiotoxic treatments: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2), Anthracycline exposure (doxorubicin dose >= 250 mg/m2), Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2), Platinum based exposure, Antimetabolites, Topoisomerase inhibitors; Group 5: More than one CT chemo from group 4; Group 6: All other treatments

Exercise Groups: Group 3 and meeting exercise guidelines (> 9 METs), Group 3and not meeting exercise guidelines (< 9 METs), Group 4 and meeting exercise guidelines (> 9 METs), Group 4 and not meeting exercise guidelines (< 9 METs), Group 5 and meeting exercise guidelines (> 9 METs), Group 5 and not meeting exercise guidelines (< 9 METs), Group 6 and meeting exercise guidelines (> 9 METs), Group 6 and not meeting exercise guidelines (< 9 METs).

Table 7c: Cumulative Incidence and RR for CVRF Among 15-20-year-olds by Vigorous Weekly MET groups for Model C (focus on RT treatment groups)									
Characteristic	**N= Total AYA**	**Group 7/ active**	**Group 7 /inactive**	**Group 8/ active**	**Group 8 /inactive**	**Group 9/ active**	**Group 9/ inactive**	**Group 10/active**	**Group 10/inactive**
Any CVRF									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Hypertension									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Diabetes									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Dyslipidemia									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Overweight (BMI>25-29)									

Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Obesity (BMI >30)									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									

CVRF: cardiovascular risk factor, **MET:** metabolic equivalent tasks,

Treatment Groups: Group 7: Any RT, total body RT; Group 8: treatment yes/no with ONE of the following: brain RT <20 Gy, brain RT 20- <30 Gy, brain RT 30 - <40 Gy, brain RT 40 - <50 Gy, brain RT 50+Gy, chest RT <20 Gy, chest RT 20- <30 Gy, chest RT 30 - <40 Gy, chest RT 40 - <50 Gy, chest RT 50+Gy, neck RT, spine RT, abdomen RT; Group 9: Treatment with more than one RT treatments from group 8; Group 10: All other treatments

Exercise Groups: Group 7 and meeting exercise guidelines (> 9 METs), Group 7 and not meeting exercise guidelines (< 9 METs), Group 8 and meeting exercise guidelines (> 9 METs), Group 8 and not meeting exercise guidelines (< 9 METs), Group 9 and meeting exercise guidelines (> 9 METs), Group 9 and not meeting exercise guidelines (< 9 METs), Group 10 and meeting exercise guidelines (> 9 METs), Group 10 and not meeting exercise guidelines (< 9 METs).

Table 8a: Cumulative Incidence and RR for CVD Among 15-20-year-olds by Vigorous Weekly MET for Model A (no treatment verses combination treatment)					
Characteristic	**N= Total AYA**	**Group 1/active**	**Group 1/inactive**	**Group 2/ active**	**Group 2 /inactive**
Any CVD					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Congestive Heart Failure					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Valvular Heart Disease					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Ischemic Heart Disease/ Myocardial Infarction					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Coronary Heart Disease					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Blood Clot					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Stroke					
Cumulative Incidence					
Adjusted relative risk			**REF**		

P value					
Pericardial Disease					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					
Arrhythmias					
Cumulative Incidence					
Adjusted relative risk			**REF**		
P value					

CVD: cardiovascular disease, **MET**: metabolic equivalent tasks,

Treatment Groups: Group 1: no treatment, surgery only; Group 2 (combination treatment): Chemo + RT + surgery, Chemo + RT, Chemo + surgery, RT + surgery;

Exercise Groups: Group 1 and meeting exercise guidelines (> 9 METs), Group 1 and not meeting exercise guidelines (< 9 METs), Group 2 and meeting exercise guidelines (> 9 METs), Group 2 and not meeting exercise guidelines (< 9 METs).

Table 8b: Cumulative Incidence and RR for CVD Among 15-20-year-olds by Vigorous Weekly MET groups for Model B (focus on chemo treatment groups)									
Characteristic	**N= Total AYA**	**Group 3/ active**	**Group 3 /inactive**	**Group 4/ active**	**Group 4 /inactive**	**Group 5/ active**	**Group 5 /inactive**	**Group 6 /active**	**Group 6 /inactive**
Any CVD									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Congestive Heart Failure									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Valvular Heart Disease									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Ischemic Heart Disease/ Myocardial Infarction									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Coronary Heart Disease									

Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Blood Clot									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Stroke									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Pericardial Disease									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Arrhythmias									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									

CVD: cardiovascular disease, **MET**: metabolic equivalent tasks,

Treatment Groups: Group 3: Any non-CT Chemo; Group 4 (CT chemo): treatment yes/no with ONE of the following known cardiotoxic treatments: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2), Anthracycline exposure (doxorubicin dose >=

250 mg/m2), Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2), Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2), Platinum based exposure, Antimetabolites, Topoisomerase inhibitors; Group 5: More than one CT chemo from group 4; Group 6: All other treatments

Exercise Groups: Group 3 and meeting exercise guidelines (> 9 METs), Group 3and not meeting exercise guidelines (< 9 METs), Group 4 and meeting exercise guidelines (> 9 METs), Group 4 and not meeting exercise guidelines (< 9 METs), Group 5 and meeting exercise guidelines (> 9 METs), Group 5 and not meeting exercise guidelines (< 9 METs), Group 6 and meeting exercise guidelines (> 9 METs), Group 6 and not meeting exercise guidelines (< 9 METs).

Table 8c: Cumulative Incidence and RR for CVD Among 15-20-year-olds by Vigorous Weekly MET groups for Model C (focus on RT treatment groups)									
Characteristic	**N= Total AYA**	**Group 7/ active**	**Group 7 /inactive**	**Group 8/ active**	**Group 8 /inactive**	**Group 9/ active**	**Group 9/ inactive**	**Group 10/active**	**Group 10/inactive**
Any CVD									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Congestive Heart Failure									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Valvular Heart Disease									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Ischemic Heart Disease/ Myocardial Infarction									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Coronary Heart Disease									

Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Blood Clot									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Stroke									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Pericardial Disease									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									
Arrhythmias									
Cumulative Incidence									
Adjusted relative risk			**REF**						
P value									

CVD: cardiovascular disease, **MET**: metabolic equivalent tasks,

Treatment Groups: Group 7: Any RT, total body RT; Group 8: treatment yes/no with ONE of the following: brain RT <20 Gy, brain RT 20- <30 Gy, brain RT 30 - <40 Gy, brain RT 40 - <50 Gy, brain RT 50+Gy, chest RT <20 Gy, chest RT 20- <30 Gy, chest RT 30 - <40 Gy, chest RT 40 - <50 Gy, chest RT 50+Gy, neck RT, spine RT, abdomen RT; Group 9: Treatment with more than one RT treatments from group 8; Group 10: All other treatments

Exercise Groups: Group 7 and meeting exercise guidelines (> 9 METs), Group 7 and not meeting exercise guidelines (< 9 METs), Group 8 and meeting exercise guidelines (> 9 METs), Group 8 and not meeting exercise guidelines (< 9 METs), Group 9 and meeting exercise guidelines (> 9 METs), Group 9 and not meeting exercise guidelines (< 9 METs), Group 10 and meeting exercise guidelines (> 9 METs), Group 10 and not meeting exercise guidelines (< 9 METs).

We propose to generate additional FIGURES as part of this analysis:

- Figure 1 a-c: Trajectory over time of change in VPA for different predictor variable categories for AYA cancer survivors. Categories would be demographics, cancer variables, and comorbid conditions. With the ability to create more individualized trajectories over time if needed.

- Figure 2 a-c: Cumulative incidence of CVRF (individual variables) for AYA cancer survivors within Models A, B, C. A separate figure for any CVRF, hypertension, diabetes, dyslipidemia, overweight, and obesity with time since diagnosis on the x-axis, and cumulative incidence on the y-axis, and each treatment group represented in a different color.

- Figure 3 a-c: Cumulative incidence of CVD events (individual variables) for AYA cancer survivors within Models A, B, C. A separate figure for any CVD, heart failure, valvular heart disease, ischemic heart disease/myocardial infarction, and stroke with time since diagnosis on the x-axis, and cumulative incidence on the y-axis, and each treatment group represented in a different color.

- Figure 4 a-c: Cumulative incidence of CVRF for adult survivors of AYA cancers comparing patients for exercise/treatment combination Models A, B, C of treatment groups. A separate figure for any CVRF, hypertension, diabetes, dyslipidemia, overweight, and obesity with time since diagnosis on the x-axis, and cumulative incidence on the y-axis, and each treatment group represented in a different color.

- Figure 5 a-c: Cumulative incidence of CVD for adult survivors of AYA cancers comparing patients for exercise/treatment combination Models A, B, C of treatment groups. A separate figure for any CVD, heart failure, valvular heart disease, ischemic heart disease/myocardial infarction, and stroke with time since diagnosis on the x-axis, and cumulative incidence on the y-axis, and each treatment group represented in a different color.

Appendix 1: Cardiotoxic Treatments	
Groups	**Medications**
Anthracyclines (doxorubicin equivalence dose)	Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, and Mitoxantrone
Alkylating agents (cyclophosphamide equivalence dose)	Busulfan, Carmustine (BCNU), Chlorambucil, Cyclophosphamide-All Routes, Cyclophosphamide-IV/IM, Cyclophosphamide-PO, Dacarbazine (DTIC), Ifosfamide, Lomustine (CCNU), Mechlorethamine (N. Mustard), Melphalan-All Routes, Melphalan-IV/IM, Melphalan-PO, Procarbazine, Thiotepa-All Routes, Thiotepa-IT, Thiotepa-IV/IM
Platinum-based	Carboplatin, Cisplatin
Antimetabolites	fluorouracil (5-FU)
Topoisomerase inhibitors	etoposide (VP-16)-all routes, etoposide (VP-16)-IV/IM, etoposide (VP-16)-PO

Appendix 2. Predictor Variables (Primary AIM). Proposed predictor variables and time points at which they are assessed for Baseline (1999, 2007 and 2008) and T2 from 2014 Follow-up surveys.		
	Baseline (original cohort (OC) (1999, 2007) and expanded cohort (EC) (2008)	**T2 2014 FU 5 OC & EC**
Demographics		
Age	x	-
Biological sex	x	-
Race	x	-
Ethnicity	x	-
Social Determinants of Health (as identified from Healthy People 2030)		
Education (highest level of educational attainment; HS graduate or less, some college/vocational school, college graduate, post college education)	x	x
Employment (current/at time of survey not currently working, full time, part time, caring for home/family, unemployed, unable to work due to illness/disability, retired, student)	x	x
Household Income (currently: $0-19,999, $20,000-39,999, $40,000-59,999, $60,000-79,999, $80,000-99,999, +$100,000)	x	x
Insurance (private insurance, federal insurance, or none)	x	x
Marital status (currently: living with a spouse/partner, living with parents, living with roommate, living with brother/sister, living with other relatives (other than minor children), living alone)	x	x
Zip code	x	x
Cancer Variables (Diagnosis, Treatment, and Time) (abstracted from medical records at baseline)		
Cancer diagnosis (see table 4)	-	-
Cancer treatment (see table 5)	-	-
Treatment decade (see table 6)	-	-
Time since diagnosis (see table 6)	-	-
Comorbid Conditions Affecting Physical Activity		
Comorbid Conditions (Not grade 3 or 4)		

Seizure	x	-
Epilepsy	x	x
Osteoporosis	x	x
Pain Diagnosis	x	x
Depression	x	x
Asthma	x	x
Tremors	x	x
Weakness Legs	x	x
Weakness Arms	x	x
Neuropathy	x	x
Comorbid Conditions (Grade 3 or 4)		
Cataracts (grade 3)	x	x
Blindness (3,4)	x	x
Thyroid Nodules (3)	x	x
Diabetes (3)	x	x
Emphysema (3)	x	x
Lung Fibrosis (3)	x	x
Heart Attack (3,4)	x	x
Congestive Heart Failure (3,4)	x	x
Arrhythmias (3)	x	x
Hypertension (3)	x	x
Valvular Disease (4)	x	x
Stroke (3,4)	x	x
Pericardial Diagnosis (3)	x	x
Blood Clot (3)	x	x
Blood Disease (3)	x	x
Surgery for Intestinal Obstruction (3)	x	x
Dialysis (3,4)	x	x
Urinary Incontinence (3)	x	x
Amputation (3)	x	x
Joint Replacement (3)	x	x
Balance (3,4)	x	x
Paralysis (4)	x	x
Loss of Hearing (3,4)	x	x
$\geq$ 2 grade 3 and/or 4 conditions	x	x
Health Behavior		
Smoking (current/past/never)	x	x
Alcohol Consumption (current/past/never)	x	x

X = present in survey

- = not present in survey

Appendix A and B identify specific survey questions for each variable for each survey year.

Will work with CCSS team to understand missing data and how to best impute missing data in proposed analyses based on percent missing and whether random or not if missing data is => 5%.

Appendix 3: Control Variables (AIM 2): Variables to be controlled for and time points at which they are assessed for Baseline (1999, 2007 and 2008) and T2 from 2014 Follow-up surveys.		
	Baseline (original cohort (OC) (1999, 2007) and expanded cohort (EC) (2008)	**T2 2014 FU 5 OC & EC**
Demographics		
Age	x	-
Biological sex	x	-
Race	x	-
Ethnicity	x	-
Social Determinants of Health (as identified from Healthy People 2030)		
Education (highest level of educational attainment; HD graduate or less, HS + some college/vocational school, college graduate, post college education)	x	x
Employment (current/at time of survey) not currently working, full time, part time, caring for home/family, unemployed, unable to work due to illness/disability, retired, student	x	x
Household Income (currently: $0-19,999, $20,000-39,999, $40,000-59,999, $60,000-79,999, $80,000-99,999, +$100,000)	x	x
Insurance (private insurance, federal insurance, or none)	x	x
Marital status (currently: living with a spouse/partner, living with parents, living with roommate, living with brother/sister, living with other relatives (other than minor children), living alone)	x	x
Zip code	x	x
Health Behaviors		
Smoking (current, past, never)	x	x
Alcohol (current, past, never)	x	x
Cancer Variables (Diagnosis, Treatment, and Time) Variables (abstracted from medical records at baseline)		
Cancer diagnosis (see table 4)	-	-
Cancer treatment (see table 5)	-	-
Treatment decade (see table 6)	-	-
Time since diagnosis (see table 6)	-	-

Comorbid Conditions		
Other Comorbid Conditions (Not grade 3,4)		
Seizure	x	x
Epilepsy	x	x
Osteoporosis	x	x
Pain Diagnosis	x	x
Depression	x	x
Asthma	x	x
Tremors	x	x
Weakness Legs	x	x
Weakness Arms	x	x
Neuropathy	x	x
Comorbid Conditions (Grade 3 or 4)		
Cataracts (3)	x	x
Blindness (3,4)	x	x
Thyroid Nodules (3)	x	x
Emphysema (3)	x	x
Lung Fibrosis (3)	x	x
Blood Disease (3)	x	x
Surgery for Intestinal Obstruction (3)	x	x
Dialysis (3,4)	x	x
Urinary Incontinence (3)	x	x
Amputation (3)	x	x
Joint Replacement (3)	x	x
Balance (3,4)	x	x
Paralysis (4)	x	x
Loss of Hearing (3,4)	x	x
≥ 2 grade 3 and/or 4 conditions	x	x
Physical Activity		
Vigorous Physical Activity (VPA)	x	x

X = present in survey

- = not present in survey

Appendix A and B identify specific survey questions for each variable.

Will work with CCSS team to understand missing data and how to best impute missing data in proposed analyses based on percent missing and whether random or not if missing data is => 5%.

Appendix 4: Outcome Variables (AIM 2): Outcome Variables and time points at which they are assessed for Baseline (1999, 2007 and 2008) and T2 from 2014 Follow-up surveys.		
	Baseline from original cohort (OC) (1999/2007), expanded cohort (EC) (2008)	**2014 FU 5 OC & EC**
Cardiovascular Outcomes (self reported)		
Cardiovascular Risk Factors		
BMI (height/weight)	x	x
Overweight (BMI 25-<30)	x	x
Obese (BMI ≥ 30)	x	x
Hypertension	x	x
Dyslipidemia	x	x
Diabetes	x	x
Multiple CVRF (≥ 2)	x	x
Cardiovascular Disease		
Congestive Heart Failure	x	x
Valvular Heart Disease	x	x
Myocardial Infarction	x	x
Coronary Heart Disease	x	x
Blood Clot	x	x
Stroke	x	x
Pericardial Disease	x	x
Valvular disease	x	x
Arrhythmias	x	x
Multiple CVD (≥ 2)	x	x

Will work with CCSS team to understand missing data and how to best impute missing data in proposed analyses based on percent missing and whether random or not if missing data is => 5%.

Appendix 5: Cancer Diagnosis	AYA Cancer Survivor (N=4244, %)
Leukemia	
Acute Lymphocytic Leukemia	
Acute Myeloid Leukemia	
Other Leukemias	
Central Nervous System (CNS) Tumors	
Astrocytoma	
Medulloblastoma/PNET	
Other CNS malignancy	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Kidney tumors (Wilms)	
Neuroblastoma	
Soft tissue sarcoma	
Bone malignancy	
Ewings sarcoma	
Osteosarcoma	
Other bone malignancy	

[Note: The public data tables do not give this level of detail for the AYA age group, will need CCSS to provide.]

Appendix 6: Cancer Treatment for Primary and Secondary AIM [20,30,32]	AYA Cancer Survivor (N=4244, %)
Group A: no treatment	
Group B: Chemo + RT + surgery	
Group C: Chemo + RT	
Group D: Chemo + surgery	
Group E: Chemo only	
Group F: Anthracycline exposure (doxorubicin dose 0 - < 250 mg/m2)	
Group G: Anthracycline exposure (doxorubicin dose >= 250 mg/m2)	
Group H: Alkylating agent (cyclophosphamide equivalent dose 0 - < 4000 mg/m2),	
Group I: Alkylating agent (cyclophosphamide equivalent dose >= 4000 - < 8000 mg/m2)	
Group J: Alkylating agent (cyclophosphamide equivalent dose >= 8000 mg/m2)	
Group K: Platinum based exposure	
Group L: Antimetabolites	
Group M: Topoisomerase inhibitors	
Group N: RT + Surgery	
Group O: RT only	
Group P: brain RT <20 Gy	
Group Q: brain RT 20- <30 Gy	
Group R: brain RT 30 - <40 Gy	
Group S: brain RT 40 - <50 Gy	
Group T: brain RT 50+Gy	
Group U: chest RT <20 Gy	
Group V: chest RT 20- <30 Gy	
Group W: chest RT 30 - <40 Gy	
Group X: chest RT 40 - <50 Gy	
Group Y: chest RT 50+Gy	
Group Z: neck RT	
Group AA: spine RT	
Group BB: abdomen RT	
Group CC: pelvis RT	
Group DD: limb (arm/leg)	
Group EE: total body RT	
Group FF: Surgery only	
Group GG: Medical data not available.	

RT= radiation treatment

[Note: The public data tables do not give this level of detail for the AYA age group, will need CCSS to provide.]

Appendix 7: Treatment Decade and Time Since Diagnosis	AYA Cancer Survivor (N=4244, %)
Treatment Decade	
1970-1979	
1980-1989	
1990-1999	
Time Since Diagnosis	
10-15 years	
15-20 years	
20-25 years	
25-30 years	
30-35 years	
35-40 years	
40-45 years	
45 + years	

[Note: The public data tables do not give this level of detail for the AYA age group, will need CCSS to provide.]

Appendix 8: PHYSICAL ACTIVITY QUESTIONS BY NUMBER AND TIME POINTS					
Questions on exercise/physical activity	**Original Cohort (OC) Baseline**	**FU 4 OC (2007)**	**Expanded Cohort (EC) Baseline**	**FU 5 OC/EC (2014)**	**FU 7 (OE/EC) (2020)**
On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breath hard (e.g., dancing, jogging, basketball, etc)?	N9	-	O15	-	Needs to be added when available
Now thinking about vigorous physical activity, 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 cases large increases in breathing or heart rate? Exercise	-	N16	-	N16	
How many days per week do you do these vigorous activities for at least 10 minutes at a time?	-	N17	-	N17	
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?	-	N18	-	N18	
Now thinking about moderate physical activity, 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? Note this is PA – when you determine your time points – that will dictate which measures you are looking at if you are assessing only Exercise in your analyses or if you are covering PA.	-	N19	-	N19	

How many days per week do you do these Moderate activities for at least 10 minutes at a time?	-	N20	-	N20	
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?	-	N21	-	N21	
Now thinking about light physical activity, you do in a usual week, do you do light activities for at least 10 minutes at a time, such as slow causal walk, or anything that does not cause an increase in breathing or heart rate?	-	-	-	N22	
How many days per week do you do these light activities for at least 10 minutes at a time?	-	-	-	N23	
On days when you do light activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?	-	-	-	N24	

Appendix 9: OUTCOMES OF INTEREST AND QUESTION LOCATION IN CCSS FOR AYA'S				
Variable	**Original Cohort (OC) (1999) Baseline**	**FU4 (2007) OC only**	**Expanded Cohort (EC) (2007) Baseline**	**FU5 OC/EC (2014)**
CARDIOVASCULAR RISK FACTORS (CVRF)				
Hypertension				
Medication	B.8.12	C.8.5	B.8.5	C.2.5
Diagnosis	F5	G5	F5	F5
Diabetes				
Medication	B.8.7, E6, E7	C.8.4, E6, F7	B.8.4, E6, E7	C.2.4, G6, G7
Diet treatment	E5	F5	E5	G5
Dyslipidemia				
Medication	B.8.16	C.8.6	B.8.16	C.2.6
Diagnosis	n/a	F12	F12	F12
Overweight/Obesity				
Height	A10	A1	A3	A1
Weight	A11	A2	A4	A2
CARDIOVASCULAR DISEASE (CVD)				
Heart Failure				
Diagnosis	F4, F6	G1, G4	F1, F4	F1, F4
Valvular Disease				
Diagnosis	F13	G9	F9	F9
Ischemic Heart Disease/ Myocardial Infarction				
Medication	F10	G6	F6	F6
Diagnosis	F3, F5	G3, G2	F3, F4	F3, F2
Stroke				
Diagnosis	F9	K14	F10	K14
TREATMENT				
Chemotherapy	A	n/a	A	n/a
Radiation	A	n/a	A	n/a

PHYSICAL ACTIVITY				
Vigorous Physical activity	N9	N16-18	O15	N16-18
Moderate physical activity	n/a	N19-21	n/a	N19-21
Light physical activity	n/a	n/a	n/a	N22-24

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