Running title: Cognitive Aging

Childhood Cancer Survivor Study

Analysis Concept Proposal

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Project Title: Cognitive aging in adult survivors of childhood cancer

Working groups: Psychology (primary); Cancer Control, Chronic Disease, Epidemiology/Biostatistics

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Background:

The success of childhood cancer therapies has led to improved survival rates and a growing population of aging adult survivors of childhood cancer. It is currently estimated that one in every 640 young adults between 20 and 39 years of age is a survivor of childhood cancer.[1] However, this success has come at a cost, with many survivors at increased risk for late effects. For example, adult survivors of childhood leukemia often demonstrate memory impairment that are not enough to significantly impact daily functioning and structural brain changes that are consistent with mild cognitive impairment that often precedes dementia.[2] Studies have also shown that survivors with memory and other neurocognitive impairments are more likely to have reductions in hippocampus and parahippocampus volumes (anatomic regions essential for memory formation), as well as reduced white matter and cortical volumes similar to changes seen in elderly non-cancer populations.[3, 4]

Several factors have been identified that increase the risk for neurocognitive impairment in survivors of childhood cancer, such as younger age at diagnosis and central nervous system directed therapy.[5-8] Survivors are also at risk for the development of chronic health conditions, [9] which are associated with neurocognitive impairment.[10] For example, for every 5-year increase from onset of a chronic condition, there is a 3% to 8% higher risk of neurocognitive impairment,[10] demonstrating that chronic conditions may be associated with progressive decline in neurocognitive function.

In the general population, subtle declines in memory and neurocognitive function is seen with brain aging, however mild cognitive impairment can be an early indicator of dementia.[11] The incidence of cognitive decline and dementia in non-cancer population's increases with age by 5.0% for those age 71-79 to 37.4% for those aged 90 or older.[12] However, in those with moderate cognitive impairment (MCI), the rate of progression to dementia is 7.1% per year in contrast to 0.2% per year for persons with normal cognition.[13] Risk factors associated with the development of cognitive decline and dementia in

the general population include female sex, current smoking, lower education levels, heart failure, and head trauma.[14-16]

The direct effects of cancer therapy and indirect effect of chronic comorbidities may lead to early or accelerated cognitive aging. In particular, cancer related therapies can cause a spectrum of biological changes that can lead to cerebrovascular damage, stem cell depletion/mutation, and oxidative stress and inflammation. Ionizing radiation causes cellular senescence, epigenetic alterations and DNA disrepair.[17] Anthracyclines cause free radical generation, DNA damage, telomere shortening, cellular senescence, and stem cell exhaustion.[18-20] Cisplatin causes DNA damage and cellular senescence. Methotrexate causes epigenetic alteration and inhibits free radical reduction.[21] Finally, carmustine (BCNU), cytarabine (Ara-c) and cisplatin have been shown to increase cell death and reduce cell division of progenitor cells and oligodendrocytes in the hippocampus and corpus callosum.[22, 23] It is through these mechanisms that adult survivors of childhood cancer could be at increased risk for progressive cognitive decline and early onset dementia.

This study aims to determine if childhood cancer survivors are at increased risk for neurocognitive declines that outpace those associated with normal aging and if so, identify factors associated with faster decline over time. To this end, we propose the following specific aims.

Specific Aims:

Aim 1: Among the original cohort, to identify patterns of change in reported neurocognitive function from Follow-up 2 to Follow-up 5.

Hypothesis 1.1: Survivors in the original cohort will demonstrate one of four patterns of change in reported neurocognitive function from Follow-up 2 to Follow-up 5 : consistently non-impaired performance; consistently impaired performance; significant decline in performance; significant

improvement in performance. Of the four possible patterns, survivors will more frequently demonstrate consistently impaired or a significant decline in performance compared to siblings.

Aim 2: Among survivors, to examine demographic, treatment-related, chronic health, and behavioral health predictors of patterns of change in neurocognitive function over time.

Hypothesis 2.1: Survivors of female sex, younger age at diagnosis and those exposed to cranial irradiation will demonstrate greater risk for consistently impaired performance and a significant decline in performance compared to those of male sex, older age at diagnosis and not exposed to cranial irradiation.

Hypothesis 2.2: Survivors with Grade 3/4 chronic health conditions will demonstrate greater risk for consistently impaired performance and a significant decline in performance compared to survivors with less than Grade 3/4 chronic health conditions.

Hypothesis 2.3: Survivors with risky health behaviors (e.g. overweight/obese BMI, low physical activity, smoking) will demonstrate greater risk for consistently impaired performance and a significant decline in performance compared to survivors without behavioral risk factors (e.g. normal BMI, higher physical activity, non-smoker).

Aim 3: To evaluate associations between patterns of change in cognitive decline over time with quality of life.

Hypothesis 3.1: Survivors with a significant decline in performance will demonstrate greater risk for impaired health-related quality of life at Follow-up 5 compared to survivors with consistently good performance.

Hypothesis 3.2: Survivors with a significant decline in performance will demonstrate greater risk for unemployment, lower income and dependent living at Follow-up 5 compared to survivors with consistently good performance.

The results of this study will characterize those cancer survivors most at risk for a decline in neurocognitive function with age. However, if a sufficient number of survivors demonstrate significant improvement in performance, we will compare this group to those with consistently impaired performance to identify factors that may promote late neurocognitive recovery.

Analysis Framework:

Participants: CCSS survivors (N~XXXX) and siblings (N=232) who participated in Follow-up 2 and Follow-up 5, and who were ≥ 18 years attained age at completion of the Follow up 2 survey and completed the relevant survey questions for the outcomes of interest. We will compare survivors and siblings who completed both Follow-up 2 and Follow-up 5 to those who completed only Follow-up 2 to evaluate sample representativeness. Exclusion criteria includes a diagnosis of genetic disorder that would predispose the survivor to cognitive decline not related to cancer diagnosis or treatment, including Trisomy 21, Neurofibromatosis type 1, or Turner syndrome.

Outcome variables:

- Neurocognitive outcomes: We will assess neurocognitive outcomes using the CCSS neurocognitive questionnaire (NCQ) (follow-up 2 questions J1-25; follow-up 5 questions Q1-33. (25) The CCSS-NCQ was developed to screen for impairment in long term childhood cancer survivors. The questionnaire has been validated in childhood cancer survivors and assesses four domains: task efficiency, emotional regulation, organization and memory.[24] Impairment will be defined as a score that is ≥ 90^{th} percentile of the sibling cohort distribution. Survivors will be classified into non-impaired and impaired categories at follow up 2 and follow up 5 to identify

the four mutually exclusive categories: significant improvement performance (impaired at follow-up 2, not impaired at follow-up 5), significant decline (not-impaired at follow-up 2, impaired at follow-up 5), consistently non-impaired performance (not impaired at both follow-up 2 and follow-up 5), consistently impaired performance (impaired at both follow-up 2 and follow-up 5). This method is robust but may not be able to capture mild-to-moderate cognitive decline which is a predictor of later progression to dementia. As such, we will also explore the use of a reliable change index (RCI) to measure significant changes in the survivors. The formula $(X_{fup5} – X_{fup2})/SD$ will be calculated, where SD is the standard deviation of the difference in measures for siblings, X_{fup5} is the observed score in survivors at follow up 5 and X_{fup2} is the observed score at follow up 2. The outcome scores are considered a significant change if the difference observed in survivors exceeds the SD of the difference seen in siblings, in other words, the above quantity exceeds 1 or if less than -1.[25]

- Health-related quality of life outcomes: We will use the SF-36 Health-related Quality of life questionnaire (follow-up 5 questions O1-8, P1-3) to assess eight domains of general health and quality of life. The domains include: general health, physical function, physical role function, physical role limitation, pain, emotional role limitation, vitality, and social functioning. Scores for each domain will be treated as a binary variable (impaired vs not). Impairment will be classified as a T-score that falls below 40 (1 standard deviation below the mean).
- Social Attainment: Employment status will be assessed using follow-up 5 question A5 (full-time employment vs. other). Independent living (yes vs. no, follow-up 5 question M1). If a participant responded, “live with parent”, “Live with brothers and/or sisters”, “live with other relatives”, or specified they had nursing or caregiver support under “other” living arrangements will be considered as not living independently. Personal income (follow-up 5 question A9). The distribution of personal income will be reviewed and if frequencies are sufficient for analyses

this variable will be collapsed to compare those <$20,000 to ≥$20,000. For these social attainment outcomes, we will focus on associations between decline in neurocognitive performance and social attainment at Follow-up 5. We will also explore associations of decline in neurocognitive performance with change in social attainment from follow-up 2 to follow-up 5, should a large enough sample of survivors demonstrate such change.

Explanatory Variables:

- Radiation: body region dosimetry Y/N and maximum target dose (maxTD) for brain (total and per segmented region), neck, chest, abdomen, pelvis (in 10 Gy intervals) Age at cranial radiation treatment
- IT Methotrexate (mg/m^2)
- IV Methotrexate (g/m^2)
- Carboplatin(mg/m^2)
- Cisplatin (mg/m^2)
- Cytarabine (Ara-c; mg/m^2)
- Carmustine (yes/no; BCNU)
- Corticosteroids (yes/no)
- Bleomycin (U/m^2)
- Anthracycline (mg/m^2)
- Vincristine (mg/m^2)
- CNS surgery (yes/no)
- Shunt (yes/no)
- Endocrine abnormalities (CTCAE Grade 3-4)
- Cardiac CTCAE (FU2 vs FU5 and new at FU5, Grade 3-4)

- Pulmonary CTCAE (Grade 3-4)
- Neurologic CTCAE (Grade 3-4)
- Relapse (none, prior to FUP2, prior to FUP5 and after FU2, during FUP5)
- Second Cancers
- Age at diagnosis
- Sex
- Exercise (vigorous physical activity, moderate physical activity, no or low physical activity categories based on questionnaire definition. In addition, a metabolic equivalent (MET) value will be calculated as the MET value of activity level multiplied by the frequency of the reported activity.)
- Depression/Anxiety (BSI-18)
- Smoking (Never a smoker, >100 cig/lifetime but not currently smoking, >100 cig/lifetime and current smoker)
- Educational attainment at follow up 2 (College vs no college; as a predictor of neurocognitive decline from follow up 2 to follow up 5).

Analyses for Specific Aim 1: We will describe the demographics for the cohort as well as primary cancer diagnosis, treatment characteristics, employment, physical activity, smoking and alcohol use (Table 1). As described in the analysis framework, individual level changes in the domains of task efficiency, emotional tolerance, organization and memory scores at FU2 to FU5 will be calculated for each participant using two different methods. In the first method, the mean of each domain and standard deviation of sibling cohort will be measured at follow up 2 and follow up 5. Impairment will be classified as a score that is $\geq 90^{th}$ percentile of the sibling cohort distribution. Survivors will be classified into non-impaired and impaired categories at time point one, based on follow up 2 outcomes, and time point

two, based on follow up 5 outcomes. Each participant will be assessed to determine if they show a pattern of consistently good performance (scores < 90^{th} percentile); consistently impaired (scores ≥ 90^{th} percentile) performance; significant decline in performance; significant improvement in performance (Table 2). An effect size of ≥0.5 correlates with clinically important change and will be considered significant for this analysis.[24] Prevalence of each pattern type will be summarized and compared between survivors and siblings using chi-square test and multinomial logistic regression, adjusted for current age and sex. We will also compare continuous differences in scores from follow up 2 and follow up 5 between survivors and controls using a reliable change index, to determine if survivors demonstrate greater declines than controls. A significant change will be defined as a reliable change index that exceeds 1.0, that is, a change that is larger than 1 SD of the change seen in the sibling group. Group mean changes from follow up two to follow up 5 will also be examined using paired sample t-test. Bonferroni's correction, or comparable test, will employed for multiple comparison correction to reduce Type I errors.

Analysis of Specific Aim 2: We will develop multivariable models to determine associations between demographic and treatment factors and neurocognitive performance at follow up 5 among survivors with unimpaired neurocognitive performance at follow up 2 (Table 3a). If decline is a common event (>10%), we will directly estimate the relative risks of decline, among survivors who were unimpaired at follow up 2, using generalized linear models with log-link, Poisson error structure and robust variance estimates. Separate models will be calculated for Task efficiency, Emotional regulation, Organization and Memory. A second set of parallel models will be generated replacing treatment factors with chronic health conditions (Table 3b), and a third set of models will be generated adding health behaviors to the chronic condition models (Table 3c). If organ-specific categories of chronic health conditions are significantly associated with neurocognitive decline, we will explore contributions from specific

conditions within organ systems that demonstrate associations with neurocognitive decline. In each case, survivors with a significant decline in performance will be compared to those with consistently good performance. If treatment and chronic health/health behavior models are both associated with decline, we will examine mediation analysis to determine the contribution of the mediator (chronic health conditions) to the outcome. In this population, path analysis will also be considered to examine direct and indirect associations between multiple predictor variables (Treatment, Risky Health behaviors), mediator (Chronic Health Conditions) and neurocognitive decline. (Figure2). Also using generalized linear models, we will examine associations between depression and anxiety at follow up 2 and follow up 5 and neurocognitive decline among survivors demonstrating significant decline. However, given the long assessment intervals and acute nature of our emotional distress measures we will not be able to determine whether emotional distress contributes to neurocognitive or is a consequence of such decline.

Analysis of Specific Aim 3: We will develop multivariable logistic regression model to investigate associations between declines in NCQ measures from follow up 2 to follow up 5 with dichotomous quality of life (SF-36) outcomes (impaired vs. unimpaired general mental health, role limitation due to emotional problems, vitality and social function), as well as with personal income, employment, and living status at follow up 5 (Table 4a). These models will a priori be adjusted for sex, age at diagnosis and age at follow up 5.

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Table 1a: Characteristics of Study Population at Follow-up 2

	Survivors			Siblings			
	N (%)	Mean (SD)	Median (IQR)	N (%)	Mean (SD)	Median (IQR)	p
Sex							
Male							
Female							
Age at Diagnosis (Years)							
Age at Survey							
Education							
≤HS graduate							
≥College							
Employment							
unemployed							
Part-time employed							
Full-time employed							
Physical Activity [a]							
No or Low							
Moderate							
Vigorous							
Smoking Status							
Never							
Past							
Current							
Treatment							
Cranial Radiation							
Chest Radiation							
Neck Radiation							
Abdominal Radiation							

Pelvic Radiation							
IV Methotrexate							
IT Methotrexate							
Carboplatin							
Cisplatin							
Cytarabine							
Carmustine							
Dexamethasone							
Bleomycin							
Anthracyclines							
Vincristine							
CNS surgery (yes/no)							
Shunt (yes/no)							
Chronic Condition							
Endocrine abnormalities (CTCAE Grade 2-4)							
Cardiac CTCAE (Grade 2-4)							
Pulmonary CTCAE (Grade 2-4)							
Neurologic CTCAE (Grade 2-4)							
Relapse (yes/no)							

Note: [a] Categories based on questionnaire definition. In addition, a metabolic equivalent (MET) value will be calculated as the MET value multiplied by the frequency of the reported activity. [b]

Table 2. Stratification and comparison of four patterns of change in neurocognitive function from follow up 2 to follow up 5 in survivors and controls.

	CCSS-NCQ											
	Task Efficiency			**Emotional Regulation**			**Organization**			**Memory**		
	Sibling N (%)	Survivor N (%)	P	Sibling N (%)	Survivor N (%)	P	Sibling N (%)	Survivor N (%)	P	Sibling N (%)	Survivor N (%)	P
Consistently good												
Consistently impaired												
Significant decline												
Significant improvement												

Definitions: Consistently average performance; consistently impaired (score falling ≤ 10^{th} percentile) performance; significant decline in performance (Effect size of >0.5 decrease based on sibling variation or magnitude decrease greater than predicted by reliable change indices); significant improvement in performance (Effect size of >0.5 SD increase based on sibling variation or magnitude increase greater than predicted by reliable change indices).
Adjusted for demographic categories that differ in table 1.

Table 3a: (example) Multivariable logistic regression analysis of demographic and treatment factors associated with patterns of neurocognitive measures in the CCSS-NCQ from follow up 2 to follow up 5 among survivors with unimpaired neurocognitive function at FU2.

Significant decline*								
	Task Efficiency		**Emotional Regulation**		**Organization**		**Memory**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sex								
Male	1.0(ref)		1.0(ref)		1.0 (ref)		1.0 (ref)	
Female								
Age at diagnosis (years)								
Age at Survey (years)								
Physical activity (per energy expenditure)[a]								
Smoking Status								
Current (>100 cigs and current smoker)								
Past (>100 cigs and not currently smoking)								
Never	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
IV methotrexate (g/m^2)								
IT methotrexate								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Carboplatin (mg/m^2)								
Cisplatin (mg/m^2)								
Cytarabine (Ara-c; mg/m^2)								
Carmustine (BNCU)								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Dexamethasone								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	

Bleomycin (U/m^2)								
Anthracyclines (per 100mg/m^2)								
Vincristine								
Cranial radiation$^{\#}$ (per 10 Gy)								
Segment 1 (per 10Gy)								
Segment 2 (per 10Gy)								
Segment 3 (per 10Gy)								
Segment 4 (per 10Gy)								
Chest radiation(per 10Gy)								
Neck radiation (per 10Gy)								
Abd/Pelvic rad (per 10Gy)								
Age at CRT (years)								
CNS surgery								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Shunt								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	

*significant decline is in comparison to consistently good.

$^{\#}$All radiation doses are maximum target dose (maxTD), taken as the sum of the prescribed dose from all overlapping regions to the respective body regions.

Table 3b. (example) Multivariable logistic regression analysis of demographic and adverse events associated with significant declines in neurocognitive concerns measured by the CCSS-NCQ among survivors unimpaired at FU2.

Chronic health condition	Neurocogntive domain							
	Significantly decline**							
	Task Efficiency		Emotional Regulation		Organization		Memory	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cardiovascular								
Grade 0-2	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Grade 3-4								
Endocrine								
Grade 0-2	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Grade 3-4								
Pulmonary								
Grade 0-2	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Grade 3-4								
Neurology								
Grade 0-2	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Grade 3-4								

**significant decline will be compared to consistently good.

Note: We will examine the frequency of each grade and if possible, we will further categorize as Grade 0-1, 2, 3-4. Models adjusted for age, sex and age at diagnosis.

Table 3c. (example) Multivariate logistic regression analysis of demographic and health behaviors associated with significant declines in neurocognitive concerns measured by the CCSS-NCQ.

	Significant decline*							
	Task Efficiency		**Emotional Regulation**		**Organization**		**Memory**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Physical activity (per energy expenditure) [a]								
Smoking Status								
Current (>100 cigs and current smoker)								
Past (>100 cigs and not currently smoking)								
Never	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Alcohol consumption [b]								
Moderate								
Heavy								
None	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Illicit drug use								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Educational Attainment								
≥College graduate								
≤HS graduate	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Depression								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	
Anxiety								
Yes								
No	1.0(ref)		1.0(ref)		1.0(ref)		1.0(ref)	

[a] Energy expenditure will be calculated as the MET value multiplied by the frequency of the reported activity. [b] Male: 'moderate' classified as more than 4 drinks per day or 14 drinks per week, and 'heavy' classified as 6 or more drinks per day at least once per month. Female: 'moderate' classified as more than 3 drinks per day or 7 drinks per week, and 'heavy' classified as 5 or more drinks per day at least once per month. Models adjusted for age, sex and age at diagnosis.

Table 4a. (Aim 3) RR/OR of impaired quality of life at FU 5 by significant decline in NCQ (yes vs. no).

	General health	Physical function	Physical role limitation	Pain	Mental health	Emotional role limitation	Vitality	Social functioning
NCQ significant decline								
Task efficiency Yes vs no								
Emotional regulation Yes vs No								
Organization Yes vs No								
Memory Yes vs No								

Note: Models adjusted for sex, age at follow up, age at diagnosis and quality of life at FU2.

Table 4b. (Aim 3) RR/OR of unemployment, independent living and personal income in survivors by significant decline in NCQ (yes vs. no)

	Unemployment	**Low Personal Income**	**Dependent living**
NCQ significant decline			
Task efficiency Yes vs No			
Emotional regulation Yes vs No			
Organization Yes vs No			
Memory Yes vs No			

Note: Models adjusted for social attainment at FU2.

Figure 1: Consort Diagram for Study

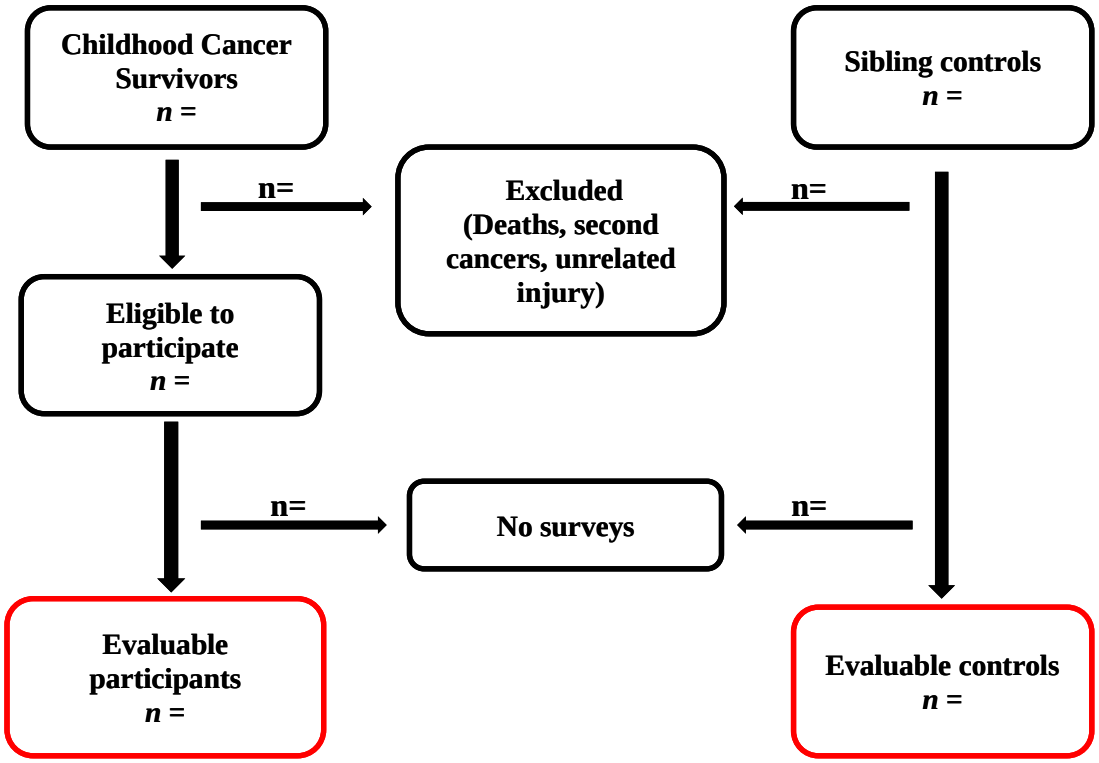

Figure 2. Diagram describing the proposed path model. Interaction effects with age at diagnosis, time since diagnosis and sex will be included in this model.