Childhood Cancer Survivor Study
Concept Proposal

Project title: Chronic Health Conditions and Employment Status Transitions for Childhood Cancer Survivors

1. **Working Group:** The application will be submitted to the **Cancer Control** and **Chronic Disease** Working Groups. The proposed investigators are:

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2. **Background and Rationale:**

In the United States, there are over 328,000 survivors of childhood cancer. Childhood cancer survivors are a young, primarily working-age population; over 95% of survivors are under the age of 60, meaning that the vast majority have years of potential participation in the labor force.[1] Although advances in the treatment of childhood cancer have substantially improved survival for over the past several decades, the chemotherapy, radiation and surgery received by these patients predisposes many to a variety of health conditions that can affect them socially and economically throughout their lifetimes.

Employment status has increasingly been acknowledged as an important outcome for cancer survivors,[2,3] and is of particular interest for childhood cancer survivors who can face educational difficulties due to missed school days or from treatment complications. Although employment is an important determinant in the access to income and health insurance coverage for adult childhood cancer survivors,[4] employment is also a marker of social development for this population. Unlike adult survivors who have typically completed their education and had years of labor force experience preceding their illness, many childhood cancer survivors begin the transition into adult roles while managing treatment, follow-up care and health conditions from their cancer, all of which may complicate their ability to finish school or move into the labor force.

Several studies, including a meta-analysis of adult survivors of childhood cancer, have indicated higher levels of unemployment for survivors compared to unaffected comparison samples.[5-7] Unemployed survivors are also likely to report that health problems prohibit their ability to work.[6,7] Certain groups of survivors, such as those who were diagnosed at a younger age,[8] had central nervous system tumors or brain tumors, are at an increased risk of poor employment outcomes.[5,6] However, no studies have examined employment status for childhood cancer survivors to determine what happens to unemployed survivors over time – do they later transition into employment, or do they face ongoing health limitations that prohibit employment. Additionally, it is unclear whether employed survivors face poor long-term employment outcomes at a higher level than unaffected comparisons, such as job loss or transition into part-time employment, which can affect survivors' insurance access, income potential, ability to save for retirement, and career achievement.

Childhood cancer survivors often report ongoing chronic conditions from their treatment that range from mild to life-threatening. In the Childhood Cancer Survivor Study (CCSS), 62.3% of survivors over the age of 18 compared to 36.8% of siblings had at least one chronic condition. Two or more chronic conditions were

reported by 38% of survivors compared to only 13% of siblings.[9] These findings are not unique to the CCSS; other non-US childhood cancer survivor samples also report high levels of chronic conditions.[10] The types of health conditions reported by survivors include cardiovascular, endocrine, and neurological disorders, as well as other conditions such as secondary cancers. The cumulative incidence of many of these chronic conditions in survivors increases over time; that is, as survivors age, they face onset of new morbidity due to their treatment histories at higher levels than non-affected samples.[10] Conceivably, the ongoing development of these conditions over time could affect many aspects of work ability, from time out for doctors' appointments and treatments, to limitations in survivors' physical capacity, stamina, and ability to manage a busy work schedule.

Several studies have examined the link between general measures of health status and employment outcomes for survivors. Poor physical health, in particular, has been consistently associated with unemployment or limitations in the ability to work reported by adult survivors of childhood cancer, although other factors such as mental and neurocognitive limitations also play an important role in employment outcomes.[11-15] However, these studies have typically used generic assessments of health status, such as the Medical Outcomes Study Short Form (SF-36), to determine health limitations. Although such measures are useful to capture a general assessment of impairment within childhood cancer survivors and their association with unemployment, they are uninformative about both the types of health problems and the severity of these problems, which can differentially affect a survivor's ability to work.

We conceived the current study to investigate employment outcomes in the CCSS sample at two time-points and to assess the relationship between chronic disease status and unemployment. These aims will provide unique information about the types of employment transitions faced by survivors, and whether unemployment becomes more prevalent over time for this population than for non-affected siblings. We will also capture an assessment of the conditions faced by survivors who are unemployed, which can be used to develop interventions to target survivors with specific chronic conditions who may be more likely to need employment assistance. We will examine unemployment transitions among age and sex cohorts because of the differential labor force outcomes typical by age and sex.

We have four research aims of interest. First, we will investigate whether survivors have a higher increase between 2003 and 2007 in unemployment – particularly unemployment due to health and disability – as compared to siblings. Second, predictors of unemployment increases will be investigated within the survivor sample. Our third aim will investigate how chronic disease status predicts changes in unemployment between 2003 and 2007 for survivors and siblings. Because survivors are 6 times more likely to not work due to health problems compared to their siblings,[6] we will examine the severity and types of conditions reported by survivors who are unemployed due to illness or disability. In the final aim, we will investigate the relationship of chronic condition severity, type, and onset on the transition to unemployment for survivors.

Because we are investigating several aims, we anticipate publishing the results in two manuscripts, most likely Aims A and B as one manuscript, and Aims C and D as another.

3. **Specific Aims and Hypotheses**

Our analyses will be based on two samples. We will first conduct analyses using a sample of all respondents ages ≥25 at either FU2003 and FU2007 (called "Full Sample").

Aim - Full sample:

> **Aim A:** To assess whether survivors have a higher increase in the proportion unemployed from 2003 to 2007 compared to siblings.

We will examine the proportions of survivors and siblings reporting unemployment in 2003 and 2007. The main unemployment outcome of interest is unemployed due to illness or disability (aka "health-related unemployment"), but we will also examine unemployed but seeking work, as well as the proportion reporting not being in the labor force (caring for home or family; student; retired) and working full- vs. part-time. Because of differences in employment status by age and sex, we will examine the changes in these proportions within specific age cohorts at time of survey completion (e.g., ages 25-34; 35-44; ≥45) and separately for males and females.

> *Hypotheses: Survivors will be more likely to be unemployed at both 2003 and 2007, and in particular, the increase in health-related unemployment will be greater for survivors when compared to siblings. (See example Figure 1.)*

Aim B: To determine what factors are associated with an increase in unemployment from 2003 to 2007 for survivors.

We will examine predictors of increased unemployment based on the findings from the earlier Medical Care paper.[6] Predictors of interest will include factors that were important in this earlier analysis, such as higher dose cranial radiation and a cancer diagnosis of central nervous system tumor. Additionally, we will explore other factors such as chemotherapy and dose, other radiation sites, and surgery.

> *Hypotheses: Survivors who had higher doses of cranial radiation and had certain cancer diagnoses (central nervous system) will have a greater increase in health-related unemployment than those without. (See example Table 2.)*

Aims – Chronic Conditions Sample:

Our other analyses will examine the association between chronic disease and unemployment. Because the chronic disease questionnaire was asked in 2007 for the first time since the baseline questionnaire, we will limit subsequent analyses to participants who responded to both FU2003 and FU2007 (called "Chronic Conditions Sample"). Age of condition onset was ascertained in 2007, so we can examine chronic disease status at 2003 among the 2007 respondents.

Aim C: To examine unemployment changes of survivors and siblings from 2003 and 2007, and the relationship of chronic disease with these transitions.

We will investigate whether survivors who report health-related unemployment in 2003 continued to be unemployed in 2007, or if they are more likely to transition into other outcomes such as death than siblings. We will also describe the chronic disease status of these different employment transition groups, and how chronic disease status in 2003 predicts future employment.

> *Hypotheses: Survivors unemployed in 2003 will be less likely to transition back into work in 2007 than similarly unemployed siblings (See example Table 3). Survivors, in particular those with higher levels of chronic conditions, will be more likely to transition into unemployment or from full to part-time employment than siblings. (See example Table 4).*

Aim D: To evaluate the association of chronic conditions in 2003 with unemployment for survivors in 2003 and 2007. We will investigate what factors, including chronic disease status, predict a transition from being employed in 2003 to being unemployed in 2007. Additionally, we will examine whether chronic disease development during 2003-2007 is associated becoming unemployed during the same years, to address whether onset of a new chronic disease affects employment from 2003-2007.

We will examine the association of chronic disease status at 2003 with unemployment at 2003 and 2007. Types of conditions (e.g., cardiovascular or secondary malignancies) will also be investigated. We will examine these factors in age-stratified analyses and in separate models for males and females.

Hypothesis 1: Survivors with severe chronic conditions in 2003 will be unemployed at both 2003 and 2007 more often than survivors with no conditions or mild to moderate conditions. We hypothesize a significant interaction, such that there is higher increase in unemployment from 2003 to 2007 for survivors with severe conditions in 2003 compared to those with no conditions or mild to moderate conditions. (i.e. interaction between time and severe chronic conditions, see example Figure 2)

Hypothesis 2: Certain factors, such as more severe chronic disease, will predict a transition into unemployment in 2007 for survivors employed in 2003. (See example Table 5).

Hypothesis 3: Survivors who develop chronic conditions from 2003 to 2007 will be more likely to transition to being unemployed in 2007 than survivors who do not develop these conditions. (See example Table 5).

4. **Analysis framework:**

a) Target population:

The planned research population is all survivors who were ages ≥25 at FU2003 and FU2007. We will use two samples for these analyses. For Aims A and B ("Full Sample"), we will use all available respondents at 2003 and 2007, regardless of whether they responded to both surveys, to calculate the marginal proportions reporting our outcomes of interest by specific subgroups at the two time-points.

For Aims C and D, we will use respondents who completed both FU2003 and FU2007, in order to describe employment transitions and chronic disease status. Because of differences in the larger economic environment (i.e., the 2007 recession) that affect employment status, we will investigate the employment outcomes at 2003 and 2007 within specific age and sex cohorts, rather than aggregating the data to look at differences for specific age groups.

b) Outcomes of interest and predictors of interest:

The outcomes of interest come from the employment status question asked at both FU2003 and FU2007. The question asks:

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

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

Main outcome: Health-related unemployment (individuals who responded as "unable to work due to illness or disability" in FU2003 and/or FU2007)

Because participants were asked to choose all employment categories that applied, we will use the method described in the 2010 Medical Care manuscript to create mutually exclusive employment

categories.[6] We will assume that health status was the primary cause of unemployment for those who selected being unable to work because of illness or disability, unless they also reported being unemployed but seeking work. If this choice was selected, seeking work will be considered the primary unemployment outcome. We will consider participants not to be in the labor force if they reported being a student, retired, caring for home or family, or otherwise unemployed but not seeking paid work (commensurate with US Department of Labor Statistics definition of the labor force).[16]

Secondary outcomes: Additionally, we will investigate other potential differences in employment status, such as full vs. part-time work, being unemployed but seeking work, and decisions not to participate in the labor force at the two time-points. Vital status in FU2007 will also be examined.

Predictors of interest: Aims B and D:

Because employment status typically differs by age and sex, we will consider both of these variables in our analyses. Our examination of employment status at the two time-points will be done within age cohort groups (ages 25-34; 35-44; 44+) due to potential differences in employment outcomes by age and because employment status in 2003 and 2007 may be differentially affected within age groups by broader economic factors (such as the 2007 recession). Because labor force characteristics differ between males and females as characterized in our earlier manuscripts,[11,17] we will run sex-stratified analyses. Due to the small number of non-White survivors and siblings, we may be limited in our ability to examine race and ethnicity differences.

Other variables that will be examined as predictors of interest:

Variable	Categories
Age at diagnosis	
Specific diagnosis	Leukemia, Hodgkin disease, non-Hodgkin disease, Central nervous system tumor, Wilms tumor, Neuroblastoma, Soft tissue sarcoma, Bone
Other demographics	Education, personal/household income, health insurance coverage, marital status [because these variables are highly related to employment status, we will explore the impact of these variables on our models]
Any cancer recurrence	Yes, if recurred before FU2007, and include date of recurrence; no
Secondary cancers	Yes, if occurred before FU2007, including type (not including basal cell carcinoma) and date of onset; No; [also included with chronic dx measure]
Years since diagnosis	List the number of years
Treatment era	1970-73; 1974-77; 1978-81; 1982-86
Chemotherapy	Any; alkylating agent – score; anthracylcine – score; platinum; bleomycin; other; Maximum dose
Radiation	Any; brain; chest; abdominal; pelvic; limb (arm, leg, foot, or hand); total body; missing or unknown; Maximum dose
Surgery	Amputation; leg lengthening; leg shortening; CNS tumor resection; other
Specific combinations	Brain irradiation + platinum; chest irradiation + beomycin; chest irradiation + anthracycline; Maximum dose
Body mass index (BMI)	At FU2003 and FU2007
Smoking status	At FU2003 and FU2007

Predictor of interest (Aims C and D):

Chronic conditions (CTCAEv3) asked at FU2007. Respondents were asked to indicate the age of onset, so we can calculate whether they had the condition in 2003 or 2007. We will examine the type of condition, severity of condition, multiple conditions, and as relevant, the time of onset (by FU2003 or by FU2007).

- ▪ Severity grades: None; Mild/Moderate (grade 1-2); Severe/Life-threatening (grade 3-4)
- ▪ Severity grades within organ systems: for example, endocrine, cardiovascular, and secondary malignancies.

c) Analytic approach:

All statistical analyses will be done using Stata version 12.

Full Sample:

<u>Aim A</u>: To assess whether survivors have a higher increase in the proportion unemployed from 2003 to 2007 compared to siblings.
> *Hypotheses: Survivors will be more likely to be unemployed at both 2003 and 2007, and in particular, the increase in health-related unemployment will be greater for survivors when compared to siblings. (See example Figure 1.)*

Generalized linear models with generalized estimating equations (GEE) will be used to estimate the difference between survivors and siblings in the prevalence reporting health-related unemployment at 2003 and 2007. We will use a binomial distribution with a log-link to generate both relative risks and prevalence .[18] Family ID will be included as a cluster variable in the models to account for any within-family correlation. Robust standard errors will be used to correct for any incorrect assumptions about the response correlation. These models will be first fit by each age and sex cohort (e.g., females ages 25-34 in 2003), as well as in overall models. We will test for an interaction between time and sibling/survivor effects to see if survivors are more likely to have an increase in the proportion unemployed in 2007.

<u>Aim B</u>: To determine what factors are associated with an increase in unemployment from 2003 to 2007 for survivors.
> *Hypotheses: Survivors who had higher doses of cranial radiation and had certain cancer diagnoses (central nervous system) will have a greater increase in health-related unemployment than those without. (See example Table 2.)*

GEE regression methods will again be used to generate models to examine predictors of an increase in unemployment for survivors. We will use a binomial distribution with a log-link to generate proportions reporting the outcome of interest.[18] We will test for interactions between the predictors of interest and year, to evaluate whether certain factors increase the risk of unemployment over time.

Chronic Conditions Sample:

<u>Aim C</u>: To examine unemployment changes of survivors and siblings from 2003 and 2007, and the relationship of chronic disease with these transitions.
> *Hypotheses: Survivors unemployed in 2003 will be less likely to transition back into work in 2007 than similarly unemployed siblings (See example Table 3). Survivors, in particular those with higher levels of chronic conditions, will be more likely to transition into unemployment in 2007 or from full to part-time employment in 2007 than siblings. (See example Table 4).*

Adjusted proportions will be calculated to examine the proportion of survivors and siblings falling into different employment status categories at 2003 and 2007. We will adjust or possibly stratify by age, race and sex because of potential labor force differences for these demographic groups (Table 3). GEE models with a log-link will be used to generate the relative risk of transitioning to

unemployment or part-time work for survivors by chronic disease status compared to siblings.[18] Family ID will be included as a cluster variable in the models to account for any within-family correlation (Table 4).

Aim D: To evaluate the association of chronic conditions in 2003 with unemployment for survivors in 2003 and 2007. We will investigate what factors, including chronic disease status, predict a transition from being employed in 2003 to being unemployed in 2007. Additionally, we will examine whether chronic disease development during 2003-2007 is associated becoming unemployed during the same years, to address whether onset of a new chronic disease affects employment from 2003-2007.

> *Hypothesis 1: Survivors with severe chronic conditions in 2003 will be unemployed at both 2003 and 2007 more often than survivors with no conditions or mild to moderate conditions. We hypothesize a significant interaction, such that there is higher unemployment from 2003 to 2007 for survivors with severe conditions in 2003 compared to those with no conditions or mild to moderate conditions. (i.e. interaction between time and severe chronic conditions, see example Figure 2)*

> *Hypothesis 2: Certain factors, such as more severe chronic disease, will predict a transition into unemployment in 2007 for survivors employed in 2003. (See example Table 5).*

GEE regression methods will be used to investigate how chronic disease status in 2003 is associated with unemployment at both 2003 and 2007 for survivors. We will use a binomial distribution with a log-link to generate both relative risks and prevalence.[18] Family ID will be included as a cluster variable in the models to account for any within-family correlation. Additionally, robust standard errors will be used to correct for any incorrect assumptions about the response correlation. These models will be fit by each age and sex cohort (e.g., females ages 25-34 in 2003) (Figure 2). Generalized linear models will be used to calculate the relative risk of transitioning into unemployment by chronic disease status, cancer and demographic variables for survivors (Table 5).[18]

> *Hypothesis 3: Survivors who develop chronic conditions from 2003 to 2007 will be more likely to transition to being unemployed in 2007 than survivors who do not develop these conditions. (See example Table 5).*

For the third hypothesis, we will examine whether survivors who develop chronic conditions between 2003 to 2007 are more likely to transition into unemployment than survivors who do not report new conditions using generalized linear model regression methods.[18] We will examine whether the severity of disease development is also influential in affecting unemployment status. Because chronic disease onset and employment differ by sex, we will examine this in stratified models (Table 5).

5. Limitations

We will consider two limitations in our analyses due to potential response bias. First, there may be limitations in examining employment at two time-points due to differential drop-out by employment status. Also, chronic disease was only assessed at FU2007, which may bias the results due to non-response. We discuss these limitations below.

Available sample for FU2003 and FU2007:

Limited to those ages ≥25 at either year	Survivors	Siblings
2003 Questionnaire	9308	2951
2007 Questionnaire	8013	2377

Both 2003 and 2007	**7305 (78% of 2003)**	**2155 (73% of 2003)**

Participant drop-out from FU2003 to FU2007: We will evaluate whether there is differential drop-out at FU2007 among subjects who were unemployed at 2003 compared to those employed at this time. If subjects who are not employed are less likely to respond (or be available for follow-up), then it may appear that the unemployment prevalence is lower than it actual is at FU2007. Other epidemiologic studies using mailed health surveys have determined that non-responders typically have lower levels of education,[19] suggesting that if we observe any differential response, our results may be somewhat biased towards the null hypothesis. We will examine demographic characteristics germane to employment, such as gender and education, to determine whether there are any response differences.

Chronic conditions: Due to the chronic conditions questions being asked only in 2007, our exploration of chronic disease and unemployment will be limited to those who responded in 2007, which may potentially decrease the generalizability of our findings. We anticipate that those who do not respond in 2007 may have a higher level of chronic conditions, potentially attenuating any observed differences in the relationship of chronic disease and unemployment in our analyses.

Example Tables and Figures

Table 1: Characteristics of Survivors and Siblings in 2003 and 2007
A similar table will be created for both manuscripts although with the different samples (Full and Chronic Disease); chronic disease information will be included for Aims C and D

	Survivors			Siblings		
	2003 N (%)	2007 N (%)	p-value	2003 N (%)	2007 N (%)	p-value
Employment Status						
Employed full-time						
Employed part-time						
Seeking work						
Health-related unemployment						
Not in labor force						
Current age						
25–34						
35–44						
≥45						
Sex						
Male						
Female						
Race/ethnicity						
White, non-Hispanic						
Black, non-Hispanic						
Hispanic/Latino						
Other						
Education						
High school education or less						
Some college or more						
Marital status						
Married						
Not married						
Household Income						
<$20,000						
$20,000-39,999						
$40,000-59,999						
$60,000-79,999						
≥$80,000						
BMI – may include						
Smoking – may include						
Chronic disease – <u>Aims C and D</u>						
Chronic disease conditions						
Pulmonary						
Secondary malignancy						
Endocrine						
… etc…						
Number of chronic diseases						
0						
1						
≥2						

***Subsample of potential variables of interest and their categorization shown in table.**

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Aim A:

Figure 1: Survivor and sibling report of health-related unemployment at 2003 and 2007 by age cohort
Hypothesized relationship; sex-stratified figures may also be shown
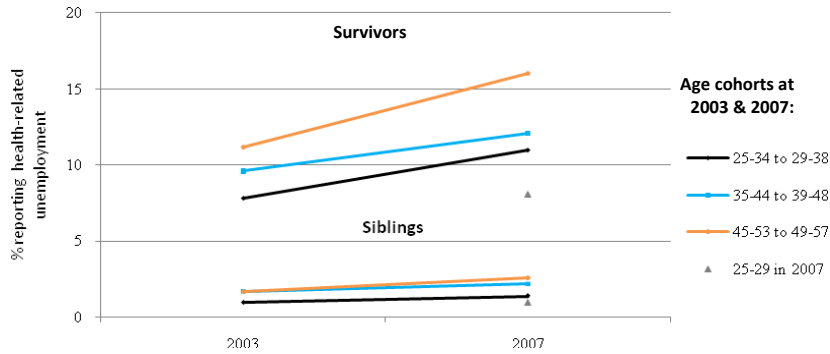
Aim B:

Table 2: Predictors of changes in health-related unemployment for male and female survivors

	Male			Female		
	% reporting health-related unemployment		Change %	% reporting health-related unemployment		Change %
	2003	2007		2003	2007	
Current age						
25–34						
35–44						
≥45						
Race/ethnicity						
White, non-Hispanic						
Black, non-Hispanic						
Hispanic/Latino						
Other						
Cranial Radiation						
None						
Scatter						
Scatter						
<18						
18–24						
≥25						
Recurrence						
No						
Yes						
Secondary cancers						
No						
Yes						
CNS tumor resection						
No						
Yes						

***Subsample of potential variables of interest shown in table. Different categorizations for variables, such as cranial radiation dose, will be explored.**

Table 3: Adjusted proportions of survivor and sibling employment from 2003 to 2007[1]
Hypothesized relationship shown for Full-Time employment (>30 hours/week) and Health-Related Unemployment

Employment Status in 2003		N	Employment Status in 2007[2]					Deceased
			Full-time	Part-time	Health-related unemployment	Seeking	Not in labor force	
Full-time	Survivor 67%	4762	**4100 (86%)**	250 (5.2%)	150 (3%)	75 (1.6%)	150 (3.1%)	47 (0.7%)
	Sibling 74%	1692	**1573 (93%)**	44 (3%)	17 (1%)	20 (2%)	35 (2%)	5 (0.5%)
Part-time	Survivor 8%	556						
	Sibling 8%	186						
Health-related unemployment	Survivor 9.3%	660	9 (1%)	12 (1.8%)	**610 (92%)**	0 (0%)	4 (0.5%)	24 (3.8%)
	Sibling 1.5%	35	4 (11%)	2 (6%)	**22 (63%)**	2 (6%)	4 (11%)	1 (3%)
Seeking	Survivor 5%	361						
	Sibling 2.7%	54						
Not in labor force	Survivor 11%	805						
	Sibling 14%	313						

HRU=health-related unemployment
[1]Adjusted for age at 2003, race and sex
[2]Proportions calculated as a percent of the row total for 2003

Table 4: Change in employment status from 2003 to 2007 for Survivors compared to Siblings by Chronic Disease Status in 2003

	Transition from Full- to Part-time Employment[1]		Transition from Employed to Unemployed[2]	
	RR	95% CI	RR	95% CI
Siblings (ref)	1		1	
All Survivors				
Survivors by chronic disease conditions				
Pulmonary				
Secondary malignancy				
Endocrine				
… etc…				
Survivors by number of chronic disease conditions				
0				
1				
≥2				

[1]Report of being employed full-time in 2003; report of being employed part-time in 2003
[2]Report of being employed either full or part-time in 2003; report of being unemployed in 2007 – either due to health reasons or due to seeking work

Figure 2: Chronic disease severity in 2003 and health-related unemployment in 2003 and 2007 by age cohorts for survivors

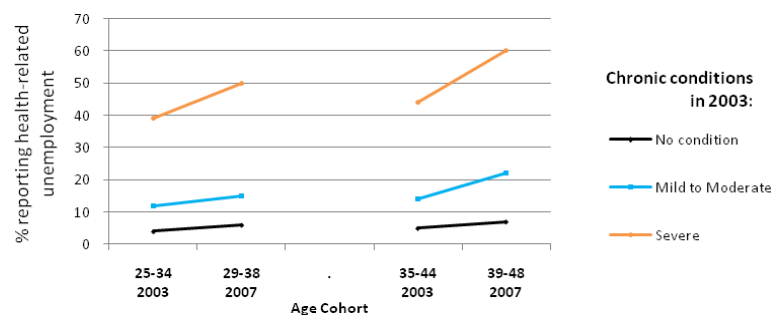*Hypothesized relationship; sex-stratified figures may also be shown*

Table 5: Predictors of transition to unemployment for survivors

	Male		p-value	Female		p-value
	Relative risk of becoming unemployed from 2003 to 2007			Relative risk of becoming unemployed from 2003 to 2007		
	RR	95% CI		RR	95% CI	
Current age						
25–34	1			1		
35–44						
≥45						
Race/ethnicity						
White, non-Hispanic	1			1		
Black, non-Hispanic						
Hispanic/Latino						
Other						
Cranial Radiation						
None	1			1		
Scatter						
Scatter						
<18						
18–24						
≥25						
Recurrence	1			1		
No						
Yes						
Secondary cancers						
No	1			1		
Yes						
CNS tumor resection						
No	1			1		
Yes						
Chronic disease in 2003						
0	1			1		
1						
≥2						
Change in chronic disease from 2003-2007						
No change						
Onset of 1 new chronic disease						
Onset of ≥2 new chronic disease						

**Subsample of potential variables of interest shown in table. Different categorizations for variables, such as cranial radiation dose, will be explored.

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