CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. TITLE: Patient-reported concerns in survivors of childhood cancer

2. WORKING GROUP AND INVESTIGATORS

Working group: This proposed study will be within the Cancer Control Working Group.
Collaborating investigators will include (to date):

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3. BACKGROUND AND RATIONALE

Survival after childhood cancer diagnosis has improved dramatically in recent decades, and there are estimated to be over 370,000 childhood cancer survivors living in the US [1]. Improvements in survival have prompted increased recognition of the importance of adverse “late effects” experienced by survivors, often attributable to cancer treatments. These late effects include an increased risk of abnormalities of growth and development, organ dysfunction, infertility, and development of subsequent neoplasms that may adversely impact survivors’ physical and emotional health, as well as psychosocial outcomes [2-5]. Elevated awareness of late effects in the medical community has resulted in expansive guidelines for care and screening of childhood cancer survivors [6], but the level of concern survivors themselves have about specific future issues remains unclear.

Numerous studies have examined psychosocial issues in survivors using comprehensive scales capturing constructs such as quality of life, health beliefs, and psychological distress. General measures of anxiety have been examined in studies of psychological distress utilizing the Brief Symptom Inventory 18 (BSI-18), which includes an anxiety subscale. Generally, childhood cancer survivors report significantly greater levels of anxiety according to this BSI subscale compared to siblings [3]. A study by Kazak et al. more specifically examined health beliefs in a small group of adolescent and young adult survivors using the Health Competence Beliefs Inventory, which was used to assess four factors: health perceptions, satisfaction with health care, cognitive competence, and autonomy [7]. Young survivors were found to have significantly different health beliefs compared to peers in a medical setting, despite no significant differences in scales measuring psychological distress or quality of life. In a CCSS ancillary study, 978 survivors completed the Health Care Needs Survey (HCNS), which included a series of questions regarding worries/fears about future health, beliefs about future health risks and attitudes about medical care. Cox et al. used latent class analysis to identify three separate survivor classes based on levels of affective response, cognitive appraisal, intrinsic motivation, and extrinsic motivation measured in the HCNS [8]. The three classes were labeled as “worried”, “self-controlling” and “collaborative”, and class membership was associated with participation in follow-up care [8, 9]. While these studies clearly suggest an important level of anxiety surrounding future health-related concerns, they provide limited insight into specific issues of concern among survivors.

A number of small studies have documented the existence of worries about issues such as recurrence, late effects, fertility, and general health [10-14]. In a larger study of 303 survivors under age 30, Zebrack and Chesler reported on cancer-specific worries (e.g. having a relapse, getting another cancer, ability to have children, getting medical/life insurance) and general health worries, finding associations with gender and age [15]. Langeveld et al. used the same questionnaire to compare worries between 400 childhood cancer survivors and 560 disease-free controls in the Netherlands [16]. For specific items, they found survivors had a significantly higher degree of worry about health relative to their peers, fertility, getting or changing jobs, and obtaining life or medical insurance. Based on a specific question in the CCSS questionnaire, Hudson et al. found that 13% of CCSS survivors reported having anxiety or fear as a direct result of cancer or its treatment [3]. The CCSS provides a unique resource containing data from over 14,000 childhood cancer survivors, including longitudinal data on a large subset of the study population. Additional questions in the baseline CCSS questionnaire asking about levels of concern with future health, developing cancer, ability to have children, and ability to get medical or life insurance have not yet been examined in the literature. Improved understanding of specific survivor concerns, as well as changes in these concerns over time, may inform targeting of education, screening, and intervention efforts in childhood cancer survivors.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES

Objective: To determine the level of concern reported by childhood cancer survivors for five specific issues (future health, ability to have children, developing a cancer, ability to get health insurance, ability to get life insurance), how these levels of concern are associated with more general anxiety, how they change over time, and how they compare to levels of concern reported by siblings of survivors.

Aim 1a. Examine the level of concern reported by survivors in the baseline questionnaire for each of the five issues. Determine the correlation between levels of concern across the five items, and enumerate the prevalence of multiple concerns.

Hypothesis: Levels of concern within individuals will be significantly correlated across the five concern items.

Aim 1b. Examine the levels of concern reported by siblings in the baseline questionnaire, and compare levels of concern between survivors and siblings - both overall and for each specific item.

Hypothesis: Survivors will report significantly higher levels of concern compared to siblings for all five items.

Aim 2. Identify baseline characteristics associated with elevated levels of concern among survivors, both overall and for each specific item. Identify factors associated with concern levels in participants with and without elevated global anxiety as measured by the BSI-18.

Hypothesis: Characteristics associated with a higher level of concern among survivors will be age at diagnosis, sex, education level, and treatment. Cancer diagnosis will not be associated with levels of concern after adjustment for age at diagnosis and treatment. Characteristics associated with elevated concern will differ between those with and without elevated global anxiety.

Aim 3. Examine how levels of concern for a specific issue compare to the presence or absence of treatment-related risk factors relevant to that concern (i.e. are participants at higher risk of the outcome more concerned about that outcome, and vice versa). Specifically, examine levels of concern for developing a cancer by receipt of genotoxic therapy (e.g. alkylating agents, radiation), and examine levels of concern for ability to have children by exposure to alkylating agents or platinum-based therapies. Explore potential associations between receipt of aggressive chemotherapy/radiation and levels of concern for future health.

Hypothesis: Levels of concern will be only weakly associated with actual risk as predicted based on treatments received.

Aim 4: Describe changes in levels of concern among survivors who completed both the baseline and Follow-up 2007 questionnaires. Identify characteristics associated with increased or decreased levels of concern over time. Compare with changes over time in siblings.

Hypothesis: Survivors will generally be more concerned about these five issues as they increase in age, and to a greater degree than siblings. Characteristics associated with changes in concern over time may include attained age, changes in income or marital status, and development of chronic health conditions.

Aim 5 (may or may not pursue in this analysis based on timing of data availability): If all necessary components of the Expansion data freeze are completed in a timely manner (including chronic conditions by CTCAE criteria), we will incorporate the Expanded Cohort into these analyses. In this case, we will also examine and compare baseline levels of concern across calendar decades of cancer diagnosis to examine potential trends over time. Inclusion of the Expanded Cohort will provide useful data on more recently diagnosed survivors, but we do not feel it is essential for completion of a high quality manuscript on this topic.

Hypothesis: Survivors diagnosed in more recent years will have significantly lower levels of concern for all five items compared to those diagnosed previously.

Analysis Framework

Population: The population for Aims 1a, 2 and 3 will include all CCSS participants (original cohort, diagnosed 1970-1986) who completed a baseline questionnaire, excluding proxy respondents for participants age 18 years or older. We will examine participants under age 18 at baseline (i.e. parent/guardian responses) separately. Similarly, Aims 1b and 4 will examine all CCSS survivors and siblings 18 years or older who self-completed a baseline questionnaire, with separate examination of parent responses for survivors and siblings less than 18 years of age (as possible based on numbers). The population for Aim 4 will be restricted to those participants who completed both the baseline and Follow-up 2007 (F07) questionnaires (with appropriate characterization of participants and nonparticipants).

Primary Outcomes: The primary outcomes will be assessed using responses to the following question (Section R on the original baseline questionnaire):

"Please rate how concerned you are about the following issues.

1. Your future health
2. Your ability to have children
3. Developing a cancer
4. Your ability to get health insurance
5. Your ability to get life insurance
6. Any other issues (please specify)"

Respondents were asked to choose one of the following for each question: (1) Very concerned (2) Somewhat concerned (3) Concerned (4) Not very concerned (5) Not at all concerned.

For each type of concern (excluding "any other issues"), we propose to create three primary outcome measures using these responses:

1) Each subject will be assigned an ordinal value corresponding to their response (1 = "Not at all concerned" through 5 = "Very concerned")

2) A binary outcome created by dichotomizing as "Very concerned" vs. less than "Very concerned".

3) A binary outcome depicting "At Least Concerned" created by dichotomizing as respondents answering any of Very concerned, Somewhat concerned, or Concerned vs. those with less concern. We will evaluate actual response frequencies to check the suitability of using these *a priori* definitions.

We will also create three summary outcomes for each participant to capture their overall concern status:

1) A binary outcome created by dichotomizing as "Very concerned about at least one of the five concern types" vs. no responses of "Very concerned".

2) Mean score across all five concern questions (excluding missing responses).

3) An ordinal outcome corresponding to the number of "Very concerned" responses across the five concerns types (i.e. prevalence of multiple strong concerns).

Covariates:

1. Sex
2. Race/Ethnicity
3. Age at diagnosis
4. Treatment (radiation only, chemotherapy only, radiation and chemotherapy, neither)
5. Radiation therapy (none, <20 Gy, ≥20 Gy)
6. Cranial radiation therapy (none, <20 Gy, ≥20 Gy)
7. Chemotherapy (none, alkylating agents [doses TBD], anthracyclines [doses TBD], other)
8. Grade 1-2 chronic conditions
9. Grade 3-4 chronic conditions
10. Attained age
11. Childhood cancer diagnosis
12. Education
13. Income (baseline and change over time)
14. Marital status (baseline and change over time)
15. Clinical level of psychological distress (T-score ≥ 63)
    -Three subscales – depression, anxiety and somatization
16. Self-reported health status

Analysis Plan:

Note: The initial analysis will examine survivors and siblings who reported their own levels of concern, and therefore will include only those participants who were at least age 18 when answering the baseline questionnaire (and will exclude proxies). We will perform a similar set of analyses in the separate group under age 18, where parents/guardians reported their levels of concern for the child.

Aims 1a and 1b:

1) Identify CCSS survivors and siblings who answered at least one item for the set of concern questions (Section R for survivors and siblings age ≥ 18). Compare baseline characteristics between participants

who did and did not complete at least one item in this section. Report and discuss implications of any significant differences. Among respondents, compare baseline characteristics between siblings and survivors (Table 1).

2) For each of the five items (future health, develop a cancer, ability to have children, ability to get health insurance, ability to get life insurance), determine the three primary outcome measures for all survivors and siblings who provided a response on that item and summarize them using means (standard deviation) for continuous measures and percents for binary measures (Table 2). We will statistically compare levels of concern between survivors and siblings using t-tests (numeric concern score) or chi-square/logistic regression (binary outcomes, including models with adjustment for sex and age at diagnosis). Figure 1 shows a graphical presentation of a hypothetical distribution of concern levels among survivors and siblings for each individual item. A figure of this type is unlikely to be presented in a manuscript, but will be useful in comprehensively visualizing the data.

3) To examine correlation between concerns, we will calculate the Goodman-Kruskal Gamma coefficient between participants' level of concern for "future health" and each of the other four concern types.

Aims 2 and 3:

Analyses for these aims will be performed in three stages. In the first stage, a series of univariate ordinal proportional odds regression models will be examined to determine associations between baseline characteristic variables and higher levels of concern, as outlined in Table 3. In the second stage, multivariable models with a uniform set of potential confounding variables (e.g. sex, race/ethnicity, age at diagnosis) will be examined for each additional covariate. If sample size allows for robust modeling, the third stage will include a full multivariable model examining associations adjusted for all other covariates of interest – including efforts to determine the most parsimonious multivariable model. Fertility concerns will be examined separately in men and women. If initial examination of the regression models indicates failure of the proportional odds assumption then further diagnostic analyses will be performed to determine suitability of this model type, with a generalized ordinal regression model that relaxes the proportionality assumption or unordered multinomial logistic regression as possible alternatives.

Additionally, logistic regression models will be used to examine associations between baseline characteristics and the binary outcomes of being "Very concerned" or "At least concerned", defined as previously described.

Global anxiety as measured by the BSI-18 is included as a covariate in the analyses described above, so we will examine whether anxiety is associated with levels of specific concerns. In addition, analyses will be stratified by the presence or absence of clinical anxiety to evaluate whether factors associated with elevated concern are similar in these two groups.

Aim 4.

We will first identify CCSS survivors who provided a response to each question in both the Baseline and Follow-up 2007 (F07) questionnaires, and compare baseline characteristics of participants who completed the F07 questionnaire with those who did not. Significant differences by participation in F07 will be reported, and we will explore possibilities such as the use of inverse probability weighting to account for potential participation bias. Analyses of concern levels over time will examine only the subset of participants that provided data at both time points for each particular question, but may need to be interpreted in the context of differential participation in the follow-up survey.

We will examine two potential methods for analysis:

1. Identify patterns of concern over time, similar to Brinkman et al. "Longitudinal patterns of psychological distress in adult survivors of childhood cancer" [17]. For a single concern item, this will result in a simple set of patterns: "consistently low levels of concern" (low at BL and F07, defined as a score of 1 or 2 at both time points), "consistently high levels of concern" (high at BL and F07, defined as a score of 3 or greater at both time points), "increased concern over time" (defined as a score of 1 or 2 at BL followed by a score of 3 or greater at F07), and "decreased concern over time" (defined as a score of 3 or greater at BL followed by a score of 1 or 2 at F07). An overall pattern will be defined in the same way based on the mean score across the five concerns at BL and F03. We will then examine multivariable logistic regression models predicting longitudinal class membership, with "consistently low levels of concern" as the reference pattern (Table 4).
2. Focus on characteristics associated with large increases or decreases in concern over time. This would involve two separate analyses. First, among all survivors reporting a score of 4 or 5 at baseline (e.g. very or somewhat concerned), use generalized linear models to identify factors associated with a decrease of two or more units from BL to F07 compared to those without such a decrease. Second, among all survivors reporting a score of 1 or 2 at baseline (e.g. not at all or not very concerned), identify factors associated with an increase of two or more units from BL to F07. This method focuses on extreme changes by excluding survivors reporting moderate concern (score=3) at BL. The goal would be to identify factors associated with dramatic shifts from one extreme to the other. Again, the same analysis can be performed for concern overall by comparing mean concern scores at BL and F03.

5. References

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Table 1. Baseline characteristics of CCSS participants and siblings who completed at least one concern question

	Survivors		Siblings		
	N	%	N	%	*P**
Total					
Age at baseline (years)					
<18					
18-20					
21-24					
25-29					
30-34					
35-39					
40-49					
50-59					
60+					
Race/Ethnicity					
White (non-Hispanic)					
Black (non-Hispanic)					
Hispanic					
Other					
Not Specified					
Household Income ($/year)					
< 20,000					
20,000-59,999					
60,000+					
Not specified					
Marital Status					
Single					
Married/living as					
Widowed					
Divorced/separated					
Not specified					
Educational status					
1-12 years (not HS grad)					
High school grad					
College grad, postgrad					
Not specified					
Cancer diagnosis					
Leukemia					
CNS					
Hodgkin's					
NHL					
Kidney (Wilms)					
Neuroblastoma					
Soft tissue sarcoma					
Bone cancer					
Age at cancer diagnosis (years)					
0-5					
5-10					
10-15					
16-20					
Cancer treatment					
Radiation					
Chemotherapy					
Radiation and Chemotherapy					
Neither radiation nor chemotherapy					
Clinical Distress					
Depression					
Anxiety					
Somatisation					
Self-reported health status					
Fair or poor					
Good, very good, or excellent					

* Test for heterogeneity comparing survivors and siblings

Table 2. Self-reported concerns on the baseline questionnaire for childhood cancer survivors and siblings

	Survivors				Siblings				
	N	Mean Score (SD)	% Very Concerned	% At Least Concerned	N	Mean Score (SD)	% Very Concerned	% At Least Concerned	*P**
Future Health									
Develop a Cancer									
Ability to Have Children									
Ability to Get Health Insurance									
Ability to Get Life Insurance									
Composite Concerns									

* *P* for difference in mean score between CCS and siblings (we will also test for differences in proportions "very concerned" or "at least concerned"

Figure 1. Distribution of responses for the concern questions on the baseline questionnaire for childhood cancer survivors (CCS) and siblings (Sib), age 18 or older at time of questionnaire

Sample data for illustration:

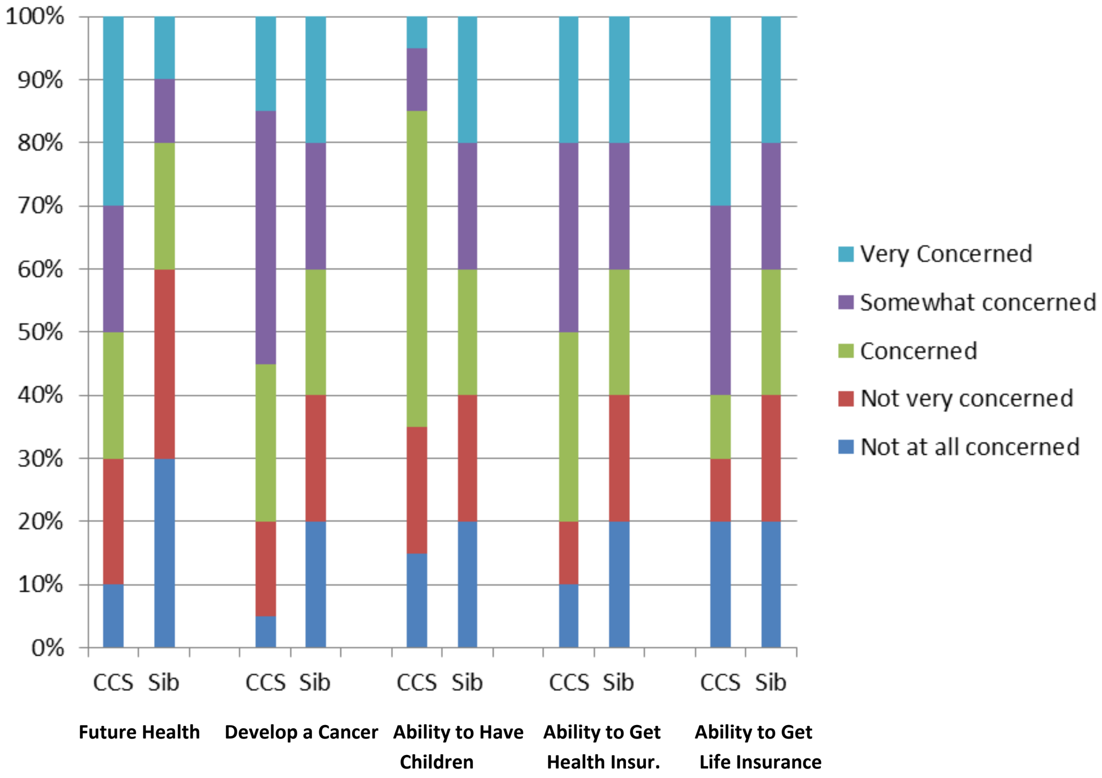

Table 3. Proportional odds models to determine odds ratios for having a higher degree of concern

	Future Health N = xx	Develop a Cancer N = xx	Ability to Have Children N = xx	Ability to Get Health Insurance N = xx	Ability to Get Life Insurance N = xx	Composite Concern Score N = xx
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female sex						
Non-white race/ethnicity						
Low household income at BL						
Age at questionnaire						
18-24	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25-29						
30-39						
40-49						
50-59						
60+						
Cancer diagnosis						
Leukemia	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
CNS						
Hodgkin’s						
NHL						
Kidney (Wilms)						
Neuroblastoma						
Soft tissue sarcoma						
Bone cancer						
Age at cancer diagnosis (years)						
0-5	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
5-10						
10-15						
16-20						
Cancer treatment						
No radiation or chemo	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Radiation only						
Chemotherapy only						
Radiation and Chemo						
Radiation therapy						
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<20 Gy						
≥20 Gy						
Cranial radiation therapy						
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<20 Gy						
≥20 Gy						
Chemotherapy						
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Alkylating agents						

Anthracyclines						
Other						
Chronic conditions at BL						
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Grade 1-2 Only						
Grade 3-4						
Psychological distress at BL (distressed vs not)						
Depression						
Anxiety						
Somatisation						
Self-reported health status						
Good, very good or excellent	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Poor or fair						

Note: Income categories to be determined

Table 4 Option A. Multivariable models predicting longitudinal class membership (adapted from Brinkman et al, BJC 2013)

Note: Pattern 1=consistent low levels of concern; 2=consistent high; 3=increased over time; 4=decreased over time

	Future Health	Develop a Cancer	Ability to Have Children	Ability to Get Health Insurance	Ability to Get Life Insurance	Composite Concerns
Pattern	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Radiation Treatment (vs none)						
Any radiation						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
< 20 Gy radiation						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
≥ 20 Gy radiation						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Cranial radiation (will examine stratified by dose)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						

3						
4						
Any chemotherapy (vs none)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Alkylating agents (vs none)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Anthracyclines (vs none)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Baseline chronic medical conditions (vs none)						
Mild/moderate						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Severe/disabling						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Developed one or more additional severe/disabling conditions (vs none or stayed the same)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Improved health status (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Worsened health status (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Female sex						
1	1.00	1.00	1.00	1.00	1.00	1.00

2						
3						
4						
Reduced employment (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Acquired employment (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Lost health insurance (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Gained health insurance (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Decreased income (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Increased income (vs. no change)						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Marital status change (vs. no change)						
Single to married						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						
Married to single						
1	1.00	1.00	1.00	1.00	1.00	1.00
2						
3						
4						

Table 4 Option B. Multivariable models predicting longitudinal class membership, each concern presented in a separate table

Note: Under this option there would potentially be six separate tables similar to the one below, each with results for a specific concern (or composite)

	Pattern 1 OR (95% CI)	Pattern 2 OR (95% CI)	Pattern 3 OR (95% CI)	Pattern 4 OR (95% CI)
Female sex	1.00			
Radiation therapy (vs none)	1.00			
< 20 Gy	1.00			
≥ 20 Gy	1.00			
Cranial radiation (vs none)	1.00			
< 20 Gy	1.00			
≥ 20 Gy	1.00			
Any chemotherapy (vs. none)	1.00			
Alkylating agents	1.00			
Anthracyclines	1.00			
Others?	1.00			
Chronic medical condition (vs. none)				
Mild/moderate	1.00			
Severe/disabling	1.00			
Changes in status (vs no change)				
Worsened health status	1.00			
Improved health status	1.00			
Reduced employment	1.00			
Acquired employment	1.00			
Decreased income	1.00			
Increased income	1.00			
Single to married	1.00			
Married to single	1.00			