Longitudinal Patterns and Predictors of Cancer Fears in Survivors of Childhood Cancer

WORKING GROUPS:
Psychology (Primary); Cancer Control (Secondary); Chronic Disease (Secondary)

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1.0 BACKGROUND

Fear of cancer recurrence (FCR) is defined as, “the fear, worry, or concern about cancer returning or progressing”[1] and is among the most prevalent and distressing concerns reported by survivors of adult-onset cancer.[2,3] In a pioneering paper, Lee-Jones and colleagues described FCR as a multifaceted experience with cognitive (e.g., perceptions of risk, beliefs about cancer), emotional (e.g., worry, hypervigilance), and behavioural (e.g., body checking, limited future planning, reassurance seeking) components.[4] Since then, numerous theoretical models of FCR have been proposed[5–8] and a robust body of literature has examined the prevalence, course, and determinants of FCR in survivors of adult-onset cancer.[9–11] While some degree of FCR is adaptive and to be expected, an estimated 60% of survivors of adult cancer experience FCR at moderate-to-high levels.[11,12] Moderate-to-high FCR has been associated with clinically significant distress and impairment, including psychological morbidity,[13] use of psychoactive medication,[14] and poor quality of life.[15] Higher levels of FCR have also been associated with greater self-reported physical (e.g., pain) and psychological (e.g., anxiety, depression) symptoms.[11,12,16] For some survivors, elevated FCR results in excessive heath care seeking behaviours, such as increased emergency room and outpatient medical visits adding to strain on the medical system.[14,17] For others, FCR has been associated with avoidance of cancer-related triggers, including lack of engagement with recommended surveillance programs (e.g., mammography) which may lead to delayed or missed diagnosis of late effects.[18] Currently, it is unclear which survivors with FCR become over users versus avoiders of the healthcare system. Longitudinal research in survivors of adult-onset cancer has found that trajectories of FCR are generally stable over time.[11,12] Thus, if left unaddressed, FCR can be a costly and debilitating issue that impacts survivors for the rest of their lives.

Numerous risk factors for elevated FCR have been identified, including younger survivor age, female gender, and lower educational attainment.[11,12] Across adult-onset cancer studies, younger survivor age is the most common and consistent predictor.[11,12] In a review of FCR in adult-onset cancers using individual patient data from 46 studies, patients under the age of 45 years reported the highest levels of FCR.[12] Despite the salience of FCR for younger survivors, FCR research to date has focused almost entirely on survivors of adult cancers. This is despite the fact that children are more likely to survive cancer compared to adults,[19] and with therapeutic advancements, more children than ever before are living well into adulthood following a cancer diagnosis.[20] Unfortunately, childhood cancer survivors become regular and lifelong users of the medical system

to mitigate the late effects of toxic treatments and monitor for signs of recurrence or a secondary cancer.[21] Childhood cancer survivors also have to plan for and navigate major life milestones (e.g., completing education, obtaining employment, family planning). In 2020, Tutelman & Heathcote proposed a conceptual model of FCR in survivors of childhood cancer over the developmental trajectory.[8] The model outlines cognitive and social factors specific to the experience of cancer during *childhood* that may differentially influence the experience of FCR over time as survivors grow and mature into adulthood.[8] Unlike survivors of adult cancers, it is possible that trajectories of FCR may fluctuate for survivors of childhood cancer as late effects begin to emerge, as survivors become older and more aware of their risks, or as life milestones are encountered. Emerging cross-sectional data suggests that FCR is a concern for adult survivors of childhood cancer,[22–24] and is associated with increased healthcare utilization and negative health behaviours.[23] However, there are no empirical data documenting how FCR may change over time or which survivors of childhood cancer are most at risk for persistent elevations, versus those who experience FCR at moderate, low, or fluctuating levels. Based on data in survivors of adult cancers which has identified a link between FCR and healthcare seeking behaviours,[14,17] it is possible that distinct trajectories of FCR in survivors of childhood cancer would be associated with varying patterns of healthcare utilization. Indeed, rates of adherence to recommended childhood cancer surveillance and follow up are low [25,26] and high levels of FCR could play a role. Characterizing associations between FCR and healthcare overutilization or avoidance is crucial for ensuring that survivors of childhood cancer receive recommended follow-up at the recommended intervals. FCR is a modifiable variable that is responsive to intervention.[27] Thus, an understanding of the longitudinal prevalence, risk factors, and consequences of FCR in survivors of childhood cancer is urgently needed to guide screening and intervention.

When conceptualizing FCR in survivors of childhood cancer, it is crucial to consider the clinical reality that childhood cancer treatment confers risk not only for recurrence, but also severe and potentially life-threatening late effects.[28,29] In fact, most survivors of childhood cancer are at higher risk for late effects compared to a recurrence of their primary cancer, particularly the longer they have been off treatment.[28,29] Therefore, it is possible that fears surrounding future health problems may be equally or more concerning than fears of cancer recurrence, especially for longer-term survivors of childhood cancer who may have been too young at diagnosis to recall their initial cancer experience. Examination of cancer-related fears in survivors of childhood cancer would be incomplete without simultaneous consideration of fear of future health problems.

2.0 SPECIFIC AIMS

1. To characterize trajectories of cancer fears in survivors from Baseline to FU5.

Hypothesis 1: Distinct trajectories of fear of cancer recurrence and fear of future health problems will be identified. Trajectories will be characterized by patterns of increasing FCR and fear of future health problems, decreasing FCR and future health problems, and stable FCR and fear of future health problems.

2. To examine demographic and clinical predictors of trajectory membership.

Hypothesis 2: Female sex, older age at diagnosis, young adults (< 45 years) at assessment, higher self-reported pain and psychological distress, and presence of more severe chronic health conditions will be associated with trajectories characterized by increasing or persistently elevated FCR and fear of future health problems.

3. To compare rates of healthcare utilization between trajectory groups over time.

Hypothesis 3: Survivors in trajectories characterized by elevated FCR and fear of future health problems will be associated with either high or lower healthcare utilization.

3.0 METHODS

3.1 Study population

Adult survivors who provided self-report data in the Baseline survey (original and expansion) and at least one applicable Follow-up survey (Follow-up 4 for original and/or Follow-up 5 for original and expansion).

3.2 Data Sources

3.2.1 Trajectory outcomes

a. Survivors' self-reported cancer-related fears measured as ordinal variables from "not at all concerned" to "very concerned"
    i. Please rate how concerned you are about your future health
    ii. Please rate how concerned you are about developing a cancer

3.2.2 Proposed predictors of trajectories (measured at Baseline unless otherwise specified)

a. Sex
b. Age at diagnosis, years
c. Current age, years
d. Time since diagnosis, years
e. Race/ethnicity
f. Cancer diagnosis
g. Relapse/SMN (yes/no, at each timepoint)
h. Treatment exposures (yes/no)
    i. Surgery (splenectomy, nephrectomy, amputation, other major surgery), Chemotherapy, Radiation (CNS directed), Radiation (non-CNS directed), Stem cell transplant (yes/no)
i. New onset of grade 3-4 chronic conditions (yes/no; at each timepoint)
j. Pain (yes/no; at each timepoint)
    i. No pain
    ii. Small amount of pain/medium amount of pain
    iii. A lot of pain/very bad, excruciating pain
    Or:
    iv. Current use of analgesics
k. Psychological distress (at each timepoint)
    i. Depression
        i. $T \geq 63$ on BSI Depression Scale
    ii. Anxiety
        i. $T \geq 63$ on BSI Anxiety Scale
    iii. Somatization
        i. $T \geq 63$ on BSI Somatization Scale
l. Current psychoactive medication use (at each timepoint)
    i. Antidepressants
    ii. Anxiolytics
m. Self-reported health status ("poor" to "excellent"; at each timepoint)
n. Health insurance status
o. Highest educational attainment (for survivors >=25 years old)
p. Employed during last 12 months (yes/no)
q. Household income
r. Marital status (for survivors >=30 years old)
s. Live alone (yes/no; at each timepoint)

3.2.3 Proposed healthcare utilization variables

a. During the last 2 years, how many times did you see a physician? (at each timepoint)
b. When was your most recent physical examination by a physician? (at each timepoint)
c. When was the last time you had a visit to a special clinic for cancer survivors? (FU 5)
d. Number of emergency room visits in the last year (FU 5)
e. Screening (at each timepoint)
    i. Last mammogram, pap smear (females)

3.3 Analytic Approach

Aim 1: Latent class growth analysis will be used to identify classes of survivors based on patterns of self-reported cancer fears from Baseline to Follow-up 5. Separate analyses will be conducted to establish distinct trajectories of: (1) fears about future health problems; and (2) fears about developing a cancer. Final models will be determined by a combination of factors such as the Bayesian information criteria value, the Lo-Mendell-Rubin

test, the bootstrap likelihood ratio test, size of classes (>5% sample in each), entropy values, and interpretability.[30] Average posterior probabilities of trajectory membership will be calculated, and values ≥ 0.8 will be considered good fits.[31] Missing data will be handled using maximum likelihood estimation.

Aim 2: Multinomial logistic regressions will be used to identify demographic and clinical predictors that distinguish membership in the trajectories, following the three-step approach.[32] Separate models will be run for the trajectories of fears about future health problems and fears about developing a cancer. Some predictors will be used from Baseline only (i.e., time invariant predictors), while others will be included at each timepoint to capture the relationship between new onset conditions and cancer fears (i.e., time-varying predictors). Initial univariate multinomial logistic analyses will be performed for each predictor individually to examine their unique effects. Subsequently, multivariate analyses will be conducted to examine the relative contribution of each predictor. Odds ratios with 95% confidence intervals will be estimated. Multiple imputation will be used to replace missing values on predictor variables as needed.

Aim 3: A series of chi square tests will be used to examine the relationship between various aspects of healthcare utilization (e.g., frequency of doctors' visits, most recent exam, screening behaviors, medication use) over time and trajectory membership.

5.0 PROPOSED STUDY TABLES

Table 1. *Participant Characteristics*

Characteristic	Survivors	
	n (%)	*M*(*SD*)
Sex		
Female		
Male		
Race/Ethnicity		
Non-Hispanic White		
Non-Hispanic Black		
Hispanic		
Other		
Age at diagnosis		
Age at baseline		
Time since diagnosis		
Cancer diagnosis		
Leukemia		
CNS Tumor		
Hodgkin's Lymphoma		
Non-Hodgkin's Lymphoma		
Wilms Tumor		
Neuroblastoma		
Soft Tissue Sarcoma		
Osteosarcoma		
Other		
Radiation therapy		
Yes		
No		
Chemotherapy		
Yes		
No		
Stem cell transplant		
Yes		
No		
Surgery		

	Splenectomy
	Nephrectomy
	Amputation
	Other major surgery
Education	
	<High school
	Completed high school
	High school & some college
	College/postgraduate
Employed	
	Full-time
	Part-time
	Student
	Retired
	No
Annual household income	
	≤$19,999
	$20,000-$59,999
	≥$60,000
Health insurance status	
	Yes or Canadian
	No
Marital Status	
	Single, never married
	Married/living as married
	Divorced/separated/Widowed

Table 2. *Model Fit Indices for Cancer Fear Variables*

Variable	AIC	BIC	LMR test	BLRT	Entropy	Class %
Future health problems						
1 class						
2 class						
3 class						
Developing a cancer						
1 class						
2 class						
3 class						

Table 3a. *Multivariable regression model predicting patterns of fears of future health problems*

Predictor	Class 1		Class 2		Class 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (Male vs Female)						
Age at baseline						
Age at diagnosis						
Race/Ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Diagnosis						
Leukemia						
Lymphoma						
CNS Tumor						
Solid Tumor						
Relapse/SMN (Y/N)*						
Radiation therapy (Y/N)						
Chemotherapy (Y/N)						
Stem cell transplant (Y/N)						
New Onset Grade 3-4 Chronic Condition (Y/N)*						
Pain (Y/N)*						
No pain						
Small/medium amount of pain						
A lot of/very bad, excruciating pain						
Current use of analgesics						
Self-reported health status*						
Poor						
Fair						
Good						
Very Good						
Excellent						
Psychological distress (Y/N)*						
Depression						
Anxiety						
Somatization						
Psychoactive medication use (Y/N)*						
Antidepressants						
Anxiolytics						
Education						
<High school						
Completed high school						
High school & some college						
College/postgraduate						
Employed (Y/N)						
Ever married (Y/N)						
Health Insurance (Y/N)						
Live alone (Y/N)*						
Annual household income						
≤$19,999						
≥$20,000						

*denotes time-varying predictor

Table 3b. *Multivariable regression model predicting patterns of fears of developing a cancer*

Predictor	Class 1		Class 2		Class 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (Male vs Female)						
Age at baseline						
Age at diagnosis						
Race/Ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Diagnosis						
Leukemia						
Lymphoma						
CNS Tumor						
Solid Tumor						
Relapse/SMN (Y/N)*						
Radiation therapy (Y/N)						
Chemotherapy (Y/N)						
Stem cell transplant (Y/N)						
New Onset Grade 3-4 Chronic Condition (Y/N)*						
Pain (Y/N)*						
No pain						
Small/medium amount of pain						
A lot of/very bad, excruciating pain						
Current use of analgesics						
Self-reported health status*						
Poor						
Fair						
Good						
Very Good						
Excellent						
Psychological distress (Y/N)*						
Depression						
Anxiety						
Somatization						
Psychoactive medication use (Y/N)*						
Antidepressants						
Anxiolytics						
Education						
<High school						
Completed high school						
High school & some college						
College/postgraduate						
Employed (Y/N)						
Ever married (Y/N)						
Health Insurance (Y/N)						
Live alone (Y/N)*						
Annual household income						
≤$19,999						
≥$20,000						

*denotes time-varying predictor

Table 4. *Healthcare Utilization By Class*

	Class 1	Class 2	Class 3
	n (%)	*n* (%)	*n* (%)
Frequency of physician visits, last 2 years			
None			
1-2 times			
3-4 times			
5-6 times			
7-10 times			
11-20 times			
>20 times			
Most recent physical exam	-	-	
<1 year ago			
1-2 years ago			
Between 2-5 years ago			
5 or more years ago			
Number of emergency room visits, last year (M ± SD)	-	-	
Last visit to a specialty survivorship clinic			
< 1 year ago			
1-2 years ago			
Between 2-5 years ago			
Never			
Last mammogram*			
Never			
<1 year ago			
1-2 years ago			
Between 2-5 years ago			
5 or more years ago			
Don't know			
Last pap smear*			
Never			
<1 year ago			
1-2 years ago			
Between 2-5 years ago			
5 or more years ago			
Don't know			

*females only

6.0 PROPOSED STUDY FIGURES

Figure 1. *Sample figure depicting frequency of cancer fears over time*

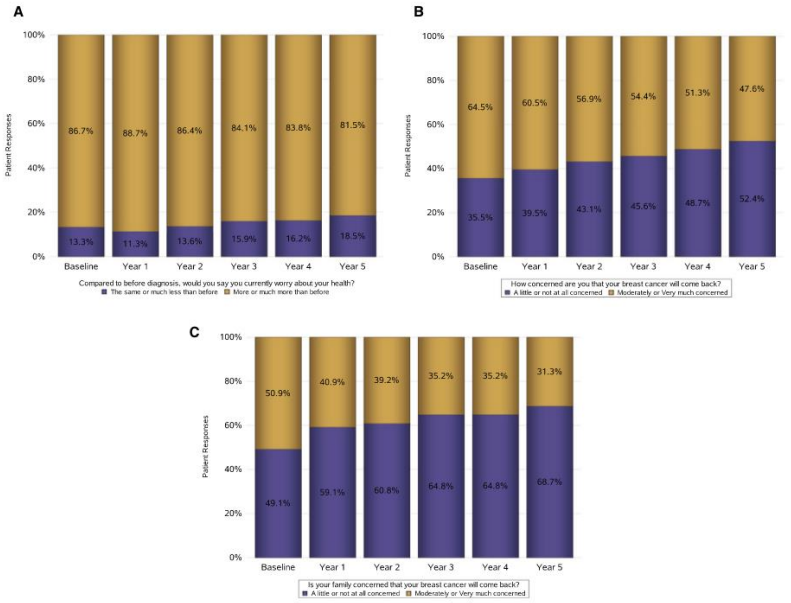

Figure 1. Prevalence of concerns about recurrence over time. (A) Prevalence of current concern about health: baseline through 5 years. (B) Prevalence of current concern about cancer returning: baseline through 5 years. (C) Prevalence of perceived family concern about cancer returning: baseline through 5 years.

Source: *Schapira L, Zheng Y, Gelber SI, Poorvu P, Ruddy KJ, Tamimi RM, et al. Trajectories of fear of cancer recurrence in young breast cancer survivors. Cancer. 2022;128(2):335–43.*

Figure 2. *Sample figure of trajectories*

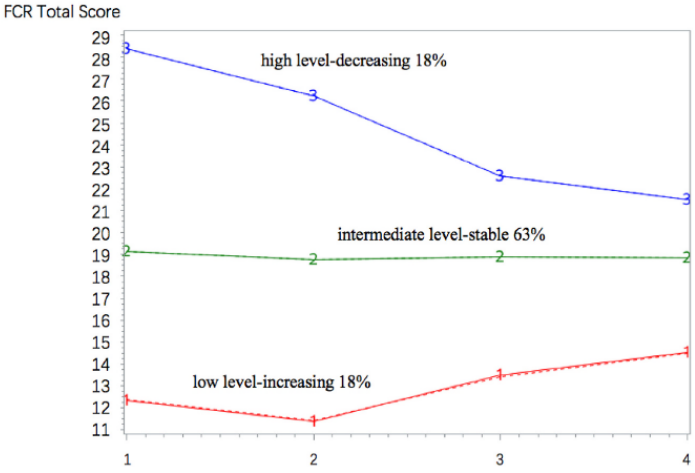

Fig. 2. Group-based trajectories for the FCR changes over 4 times of measurement.

Source: *Yang Y, Qi H, Li W, Liu T, Xu W, Zhao S, et al. Predictors and trajectories of fear of cancer recurrence in Chinese breast cancer patients. Journal of Psychosomatic Research. 2023;166:111177.*

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