Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

1. **Study Title**
   Intolerance of Uncertainty and Fear of Cancer Recurrence in Adult Survivors of Childhood Cancer

2. **Working Group:** Psychology

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4. Background and Rationale:

Survivors of childhood cancer are at risk for a range of physical and mental health late effects.[1] Morbidities frequently observed following surgery, chemotherapy, and radiotherapy for childhood cancer include severe and disabling chronic health conditions,[2] psychological distress,[3] fatigue and insomnia,[4,5] subsequent malignancies,[6] and reduced quality of life.[7] Childhood cancer survivorship, including managing these late effects and coping with their unpredictable course, is therefore marked by significant uncertainty.

Intolerance of Uncertainty

Although all cancer survivors face uncertainty, there is likely significant variability in how individuals cope with this uncertainty. Previous research has shown that the extent to which individuals are comfortable tolerating uncertainty, as well as the feelings of discomfort that it triggers, sits on a continuum.[8] Intolerance of uncertainty is defined as a "dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" (p.31).[9] Individuals who are high in intolerance of uncertainty tend to overestimate the likelihood that something negative will happen and tend to perceive themselves as unable to cope – which can result in maladaptive cognitive, behavioral, and emotional responses.[10,11] Maladaptive responses such as avoidance commonly play a role in the development and maintenance of mental health disorders. A substantial body of literature has also shown that elevated intolerance of uncertainty is implicated in the development of mood and anxiety disorders in the general population.[12,13] Within the cancer context, previous findings have shown intolerance of uncertainty to be associated with elevated stress levels as well as lower psychological well-being in adults currently receiving cancer treatment.[14] Furthermore, intolerance of uncertainty has been linked to greater likelihood of developing cancer-related distress in survivors of adult-onset cancer.[15]

It has also been proposed that intolerance of uncertainty, directly and indirectly, contributes to chronic pain.[16] Pain and chronic pain are inherently uncertain – particularly when experienced in the context of childhood cancer survivorship. Intolerance of uncertainty may serve as an important underlying factor in pain-related anxiety,[17] which in turn may contribute to the development and maintenance of chronic pain.[18] Experimental pain studies have provided evidence that intolerance of uncertainty may increase pain-related anxiety and perceived pain intensity.[19–21] Recent clinical research among youth with chronic pain has also demonstrated that youth and parent intolerance of uncertainty contribute to increases in youth pain interference over time through several pain-related factors, including increased pain catastrophizing.[22]

Finally, among adolescent and young adult cancer survivors (aged 11-25 years), intolerance of uncertainty was significantly correlated with average pain intensity and pain interference.[23]

Given the uncertain nature of survivorship, intolerance of uncertainty may be critical to the experience of childhood cancer survivors as they move through the survivorship trajectory – particularly in relation to survivors' experience of anxiety and depressive symptoms as well as chronic pain. Nonetheless, no studies have examined intolerance of uncertainty specifically among adult survivors of childhood cancer, including its potential association with psychological distress and chronic pain.

Fear of Cancer Recurrence

Fear of cancer recurrence is defined as "the fear, worry or concern relating to the possibility that cancer will come back or progress" [24] and is among the most common and distressing problems reported by survivors of adult-onset cancer.[25,26] Fear of cancer recurrence is generally considered to be a multidimensional construct that sits along a continuum ranging from a normal response to a clinically significant fear.[27] At low levels, fear of cancer recurrence is often a temporary emotional reaction that can lead to adaptive monitoring for signs of recurrence and engaging in recommended health behaviors (e.g., physical activity, regular cancer screenings). However, a substantial minority of survivors report experiencing elevated levels of fear of cancer recurrence that impact daily functioning and are associated with psychological distress (i.e., depression and anxiety), poor quality of life, and increased use of outpatient hospital services and psychotropic medications.[25,28]

Little is known about fear of cancer recurrence among survivors of *childhood cancer*. Recent calls for increased research in this area have highlighted the need for studies focused on developing an understanding of the prevalence, characteristics, as well as risk and protective factors of fear of cancer recurrence across the childhood cancer survivorship trajectory.[29] Thus far, examinations of the prevalence of fear of cancer recurrence among childhood cancer survivors have largely been limited to adolescent and young adult (AYA) survivors (i.e., 15-39 years at cancer diagnosis), with prevalence rates varying widely. For example, in a recent systematic review, 29% to 85% of AYA survivors reported some level of fear of cancer recurrence and 13% to 62% reported high levels.[30]

In our recent study of fear of cancer recurrence among adult survivors of childhood cancer in the St. Jude Lifetime Cohort Study (n=3211),[26] 64% of survivors reported worry about subsequent malignancy and 33% reported worry about relapse. Moreover, elevated anxiety, depression, and pain were associated with an increased risk of worry about relapse and worry about subsequent malignancy. Although this study improved our understanding of fear of cancer recurrence among adult survivors of childhood cancer, similar to previous studies of fear of cancer recurrence among AYA survivors[31], it was limited by measurement of fear of cancer recurrence that was based on single survey items and that lacked associated cut-off scores necessary to determine the proportion of survivors experiencing clinically significant levels of fear of cancer recurrence. Thus far, *no studies* have examined the prevalence, risk factors (e.g., treatment-related factors, disease characteristics), or associated psychological and somatic symptoms of fear of cancer recurrence in adult survivors of childhood cancer using a validated and comprehensive measure of fear of cancer recurrence. Additionally, past studies of fear of cancer recurrence among AYA and adult survivors have failed to consider the potential role of intolerance of uncertainty. As previously mentioned, a substantial body of literature has shown that elevated intolerance of uncertainty is associated with depression and anxiety in the general population. Emerging research has also shown associations between intolerance of uncertainty and pain within the general populations and AYA survivors. The current study will therefore aim to replicate our findings from the St. Jude Lifetime Cohort Study using new and more comprehensive data (i.e., full validated measure of fear of cancer recurrence), examine the association between fear of cancer recurrence and psychological (depression and anxiety) and somatic factors (pain), and assess the role of intolerance of uncertainty in these potential associations.

EASE Ancillary Study

The primary aims of the *Exploring Aspects of Survivors' Experience of Pain* (EASE) ancillary study were to examine the prevalence of chronic pain and describe the occurrence of pain interference among adult long-

term survivors of childhood cancer as well as evaluate demographic, diagnostic, treatment-related and psychosocial factors associated with chronic pain and pain interference. Using an ecological momentary assessment approach, the daily patterns of pain, pain interference, and related variables (e.g., depression, anxiety, sleep quality) among survivors with chronic pain across a 14-day period was also described. A random sample of survivors enrolled in CCSS (n=700) were recruited and invited to download Eureka – an mHealth app where all study activities were completed. After study eligibility was assessed and informed consent obtained, all participants completed baseline measures. Participants who reported baseline chronic pain completed a brief daily survey via the app for 14 days. A total of 38% of recruited survivors downloaded the mHealth app and 35% provided informed consent. The final study sample included 233 survivors. Results thus far from EASE indicate that 41.2% [95% CI:36.5%-49.8%] of survivors reported chronic pain, of whom 24% reported severe pain interference. Chronic pain was associated with intravenous methotrexate (OR [95% CI]; 2.67 [1.13-6.61]), respiratory (5.55 [1.99-18.12]), gastrointestinal (3.68 [1.46-10.00]), musculoskeletal (3.38 [1.25-9.81]) and neurological (2.69 [1.20-6.20]) conditions, as well as clinically significant depression with anxiety (18.28 [4.43-126.02]) or either depression or anxiety (2.89 [1.37-6.19]), and unemployment (2.01 [1.03-3.94]). Higher pain interference was associated with cardiovascular conditions (B [95% CI]; 9.72 [3.01-16.43]), neurological conditions (11.06 [3.36-18.76]), clinically significant levels of depression with anxiety (23.44 [14.75-32.31]), either depression or anxiety (9.70 [2.76-16.64]), and unemployment (12.04 [5.06-19.01]). The manuscript summarizing these findings is currently in preparation and two associated conference abstracts have been presented.

We are interested in examining both intolerance of uncertainty and fear of cancer recurrence among adult survivors of childhood cancer via the EASE study. The measures used to assess these and related outcomes are summarized below. It should be noted that the current aims were not included in the original approved EASE concept. Alex Pizzo, MSc (Master's student in Clinical Psychology in my lab at Concordia University) will be leading this project under my supervision. Aims related to examining fear of cancer recurrence will form the basis of Alex's Master's Thesis. Aims related to intolerance of uncertainty form the basis of an undergraduate Psychology Honours Thesis (E. Lamoureux) in my lab, which Alex is also assisting with.

In addition, except for demographic, diagnostic and treatment-related data, the proposed aims and associated analyses only use data that was already collected as a part of EASE.

5. Specific Aims:

Aim 1: To describe the occurrence of intolerance of uncertainty among adult survivors of childhood cancer

Aim 1b: To identify demographic, diagnostic, and treatment-related factors associated with intolerance of uncertainty in adult survivors of childhood cancer.

Aim 1c: To examine the association between intolerance of uncertainty and depression as well as anxiety in adult survivors of childhood cancer

Aim 1d: To examine the association between chronic pain and intolerance of uncertainty in adult survivors of childhood cancer

Aim 1e: To examine the association between intolerance of uncertainty and pain intensity, pain interference, and pain catastrophizing among adult survivors of childhood cancer with chronic pain

Aim 2: To estimate the prevalence of fear of cancer recurrence among long-term survivors of childhood cancer

Aim 2b: To identify demographic, diagnostic, and treatment-related factors associated with fear of cancer recurrence in long-term survivors of childhood cancer

Aim 2c: To evaluate associations between fear of cancer recurrence and depression, anxiety, and chronic pain

Aim 2d: To examine the role of intolerance of uncertainty in the observed associations between fear of cancer recurrence and depression, anxiety, and chronic pain – specifically, whether intolerance of uncertainty mediates the relationship between pain and fear of cancer recurrence depression, and anxiety in adult survivors of childhood cancer.

6. Analysis Framework:

Study population: Adult survivors who took part in the EASE ancillary study. The final EASE sample included 233 survivors, of which, 96 survivors reported chronic pain.

- **Inclusion criteria:**
  - Participant in the EASE study
  - CCSS survivors ≥ 18 years of age
  - Speak and read English
  - Own a smartphone
  - Access to data/Wi-Fi/Internet

Outcomes of interest:

All participants completed the measures below. The measures below with * were not administered to participants who did not endorse chronic pain on the initial chronic pain question.

- **Intolerance of uncertainty** will be assessed by the Intolerance of Uncertainty Scale – Short Form (IUS-12), a widely-used and validated measure of intolerance of uncertainty (ref). The IUS-12 includes 12 items that describe individuals' responses to uncertainty, ambiguous situations, and the future. Each item is rated on a 5-point Likert scale ranging from 1 (*not at all characteristic of me*) to 4 (*entirely characteristic of me*). Participants indicate the degree to which each item is representative of them. A total score is calculated by summing all items, with higher scores indicating greater intolerance of uncertainty. Please see **Appendix A** for a copy of the IUS-12.

- **Fear of cancer recurrence** will be assessed by the Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF), a well-validated measure of fear of cancer recurrence or progression among adult cancer survivors (ref). The FCRI-SF contains 9-items that assess the severity of fear of cancer recurrence. Each item is rated on a scale ranging from 0 (*not at all, not at all at risk, never, or I don't think about it*) to 4 (*a great deal, a great deal of risk, several times a day, several hours, or several years*). A summed score is created ranging from 0 to 36, with higher scores indicating greater fear of cancer recurrence. A score of ≥ 22 on the FCRI-SF has been used to identify survivors with clinical levels of fear of cancer recurrence.[32] Please see **Appendix B** for a copy of the FCRI-SF.

- **Chronic pain**:
  - Do you have any persistent or recurrent pain, more than aches and pains that are fleeting and minor?

        - This question is derived from the definition of chronic pain developed and recommended by the International Association for the Study of Pain (IASP).[2] This definition and the specific wording (i.e., "persistent," "recurrent") have been recommended for use in epidemiological studies of chronic pain.[39]
    - If so, how long have you been experiencing this pain (in months)?

- **Worst Pain Intensity*** will be assessed by an item adapted from the BPI and past research examining chronic pain, where participants will respond on an 11-point Likert scale ranging from 0 (*no pain*) to 10 (*pain as bad as I can imagine*):
    - Please rate your pain at its WORST during the **past week**.

- **Average Pain Intensity*** will be assessed by an item adapted from the Brief Pain Inventory (BPI) and past research examining chronic pain, where participants will respond on an 11-point Likert scale ranging from 0 (*no pain*) to 10 (*pain as bad as I can imagine*):
    - Please rate your pain on AVERAGE during the **past week**.

- **Pain interference*** will be assessed by the interference scale of the Brief Pain Inventory (BPI), a well-validated and widely used measure of pain interference. The 7-item pain interference subscale of the BPI asks individuals how much pain has interfered with their daily activities. Each item is rated on a scale ranging from 0 (*does not interfere*) to 10 (*completely interferes*). A total score is calculated using a mean of the seven items, with higher scores indicating greater pain interference.

- **Pain catastrophizing*** will be assessed by the Pain Catastrophizing Scale (PCS), a widely-used 13-item measure of the magnification of the threat of, rumination about, and perceived inability to cope with pain. Each item is rated on a 5-point Likert scale ranging from 0 (*not at all*) to 4 (*all the time*). Participants indicate the degree to which each item is characteristic of their thoughts and feelings when experiencing pain. A total score and three subscale scores (measuring rumination, magnification, and helplessness) are calculated by summing the items, with higher scores indicating greater pain catastrophizing.

- **Depression** will be assessed by the Patient Health Questionnaire – 8 item (PHQ-8), a well-validated and widely used measure of depression. The PHQ-8 includes 8 items that assess the severity of depressive symptoms. Each item is rated on a 4-point Likert scale ranging from (*not at all*) to 3 (*nearly every day*). Participants indicate how much each item has been a problem in the past two weeks. A total score is calculated by summing responses to all 8 items. Higher scores indicate greater symptom severity. A total score of ≥10 is indicative of a DSM-IV diagnosis of depression.

- **General anxiety** will be assessed by the Generalized Anxiety Disorder – 7 item (GAD-7), a well-validated and widely used measure of anxiety symptoms. The GAD-7 includes 7 items that assess anxiety symptom severity. Each item is rated on a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*). Participants indicate how much each item has been a problem in the past two weeks. A total score is obtained by summing responses to all 7 items. Higher scores indicate greater symptom severity. A total score of ≥10 is indicative of a DSM-IV diagnosis of an anxiety disorder.

Exploratory variables:

- **Cause of pain*** will be assessed by the following item:
    - What do you think this pain was due to?
        - Response options will include: 1) Your childhood cancer treatments; 2) Medical procedures and tests you had during your childhood cancer; 3) Your cancer as a child; 4) Medical condition(s) other than your cancer (e.g.,

arthritis); 5) Past injury (e.g., back injury, muscle strain) 6) Not sure 7) Other (please specify)
        - *Note*: Option 7 will include an open text field.

- **Interpretation of pain as cancer threat*** will be assessed by the following items, where participants will indicate their response on a 5-point Likert Scale ranging from 0 (agree very little) to 4 (agree very much)
    - When I feel pain, I worry that the pain is caused by **my cancer coming back**.
    - When I feel pain, I worry that the pain is caused by **me having a new type of cancer**.

- **Sleep** will be assessed by the PROMIS Sleep Disturbance 4 – item (PROMIS-SD), a well-validated measure of sleep quality in adults with chronic health conditions including chronic pain.

- **Pain location*** will be assessed by the following item:
    - Please indicate the **location** of your pain:
        - Response options will include: 1) Arm(s), 2) Leg(s), 3) Stomach, 4) Chest, 5) Lower Back, 6) Neck, 7) Head, 8) Pelvis 9) Feet, 10) Hands 11) Other (please specify)
        - *Note*: Participants will be able to select multiple locations. Option 11 will include an open field text.

Covariates:

- **Demographic (from FU5 or most recent survey):** age at evaluation, sex, race/ethnicity, household income, education, employment, marital status, assistance with routine needs

- **Clinical (from FU5 or most recent survey):** obesity (BMI), relapse/subsequent neoplasms, CTCAE musculoskeletal & connective tissue disorders, sexual reproductive, gastrointestinal, neurologic, pulmonary, endocrine, and cardiovascular. Only *active* conditions will be coded.
    - Grade/severity score (mild, moderate, severe, life-threatening or disabling) of each condition will be considered.
    - Number of Grade 3-4 chronic health conditions (multiple: ≥ 2, ≥ 3)
    - To estimate the impact of multiple chronic health conditions of varying severity, we will calculate a severity/burden score, according to previously published methods that take into account the frequency and grade of conditions.[33,34] Here disease burden will be calculated for each survivor, rather than at the aggregated level.

- **Treatment-related (from MRAF frozen data):** age at diagnosis, primary diagnosis, radiation (cranial and non-cranial), chemotherapy, major treatment-related surgery, and amputation.

7. Statistical Analyses:

We will explore sex differences on all outcome variables and stratify analyses if appropriate. It should be noted that for Aims 1a, 1b, 1c, and 1d all 233 survivors in the EASE sample are eligible. For Aim 1e, only survivors with chronic pain (*n*=96) will be included in the analysis. All 233 survivors are eligible for Aims 2a, 2b, 2c, and 2d.

Intolerance of Uncertainty

Aim 1: To describe the characteristics of intolerance of uncertainty among adult survivors of childhood cancer.

For aim 1, we will describe the mean, SD, and range obtained on the IUS-12 (total score; total score calculated by summing all items, with higher scores indicating greater intolerance of uncertainty). We will

then describe and discuss how this compares to current literature on intolerance of uncertainty in other populations (e.g., general population, other health populations).

Aim 1b: To identify demographic, diagnostic, and treatment-related factors associated with magnitude of intolerance of uncertainty in adult survivors of childhood cancer.

For aim 1b, we will examine the distribution of intolerance of uncertainty and use appropriate regression models, most likely linear regression, but considering transformations or non-parametric versions as needed, to examine each treatment, clinical, and demographic factors as predictors of IU (Table 2).

Aim 1c: To examine the association between intolerance of uncertainty and depression as well as anxiety in adult survivors of childhood cancer

For aim 1c, we will use Pearson correlations to examine the association between intolerance of uncertainty (total score on the IUS-12) and depression (total score on the PHQ-8) as well as the association between intolerance of uncertainty (total score on the IUS-12) and anxiety (total score on the GAD-7) (Table 2). Associations will also be examined using established clinical cut-offs for depression (≥10 on the PHQ-8) and anxiety (≥10 on the GAD-7). We will generate graphs to visually illustrate the two-way relationships and will explore linear regression models with adjustment factors to account for confounding.

Aim 1d: To examine the association between chronic pain and intolerance of uncertainty in adult survivors of childhood cancer

For aim 1d, we will use an independent-samples *t*-test to compare mean intolerance of uncertainty (total score on the IUS-12) among survivors with chronic pain compared to survivors without chronic pain. To account for potential confounding variables, we will carry out a comparable linear regression analysis, adjusted for age, sex and race/ethnicity.

Aim 1e: To examine the association between intolerance of uncertainty and pain intensity, pain interference, and pain catastrophizing among adult survivors of childhood cancer with chronic pain

For aim 1e, among the 96 survivors with chronic pain, we will use a hierarchical multiple linear regression analysis to examine associations among intolerance of uncertainty and: 1) pain intensity; 2) pain interference; and 3) pain catastrophizing among survivors with chronic pain. In Step 1 of the analysis, participant sex, age, and race/ethnicity will be entered as predictors in the model, given their known associations with intolerance of uncertainty and mental health outcomes more generally (McEvoy et al., 2019). In Step 2, pain catastrophizing (PCS total score), pain intensity (BPI Pain Intensity score), and pain interference (BPI Pain Interference score) will be entered as predictors in the model (see Table 4).

Fear of Cancer Recurrence

Aim 2: To estimate the prevalence of fear of cancer recurrence among long-term survivors of childhood cancer

For aim 2, we will describe the mean, SD, and range obtained on the FCIR-SF (total score; total score calculated by summing all items, with higher scores indicating greater fear of cancer recurrence). We will also calculate the percentage of survivors who have clinical levels of fear of cancer recurrence, using a cut-off score (≥ 22) that has been established in the adult-onset cancer survivor literature.

Aim 2b: To identify demographic, diagnostic, and treatment-related factors associated with fear of cancer recurrence (defined using the clinical cut-off score of ≥22) in long-term survivors of childhood cancer

For aim 2b, we will examine the fear of cancer recurrence and use appropriate linear regression models to examine each treatment, clinical, and demographic factors as predictors of clinical levels of fear of cancer recurrence.

Aim 2c: To evaluate associations between fear of cancer recurrence (defined using the clinical cut-off score of ≥22) and depression, anxiety, and chronic pain

For aim 2c, we will examine the fear of cancer recurrence and use appropriate linear regression models to examine depression (PHQ-8 total score), anxiety (GAD-7 total score), and chronic pain (endorsement of chronic pain survey item) as a predictor of clinical levels of fear of cancer recurrence.

Aim 2d: To examine the role of intolerance of uncertainty in the observed associations between fear of cancer recurrence and depression, anxiety, and chronic pain – specifically, determine whether intolerance of uncertainty mediates the relationship between pain and fear of cancer recurrence depression, and anxiety in adult survivors of childhood cancer. To accomplish this, we will follow the recommendations summarized in Hayes and Rockwood,[35] defining mediation as existing if a test of the indirect effect of the causal variable (pain) on the outcome (fear of cancer recurrence, depression, anxiety) via the mediator (intolerance of uncertainty) is significantly different from zero. That is, if the effect of the pain on fear of cancer recurrence, depression or anxiety (effect α) multiplied by the effect of intolerance of uncertainty on the fear of cancer recurrence, depression or anxiety (effect β) is significantly different from 0 (i.e., reject H0: $\alpha.\beta = 0$). In addition, to meaningfully interpret any mediation effects, we will estimate the overall indirect effect ($\alpha.\beta$) with bootstrapped 95% confidence intervals (CIs) along with α and β separately, taking particular note of the sign and magnitude of each effect. The PROCESS method[36] or Structural Equation Modelling (SEM)[37] approaches will be used to accommodate simultaneous evaluation of the multiple pathways together in models allowing serial or parallel considerations of multiple mediation and moderator relationships. We will estimate direct and indirect effects along with bootstrapped confidence intervals.

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Table 1. Demographic and clinical characteristics of the study population (N=233)

	M (SD)	N (%)
Age at evaluation, years		
Age at diagnosis, years		
Time since diagnosis, years		
Sex		
Male		
Female		
Race/Ethnicity		
White, non-Hispanic		
Black		
Other		
Diagnosis		
Leukemia		
CNS tumor		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Osteo/Ewing sarcoma		
Soft tissue sarcoma		
Other non-CNS solid tumor		
Other		
Radiation		
Cranial radiation		
≥20Gy		
<20Gy		
None		
Non-cranial radiation		
None		
Chemotherapy		
Antimetabolites		
Corticosteroids		
Anthracyclines		
Alkylating agents		
Other/none		
Surgery		
Amputation		
Limb sparing		
Other major therapeutic surgery		
None		
Prior Relapse/SMN		
Yes		
No		
Obesity (BMI)		
Underweight (<18.5)		
Normal (18.5 - 24.9)		
Overweight (25 – 29.9)		
Obesity (≥30)		

Pain Medication(s)
  Non-opioid analgesics
  Opioids
  None
Musculoskeletal & connective tissue disorders
  None
  Grade 1 or 2
  Grade 3 or 4
Sexual reproductive disorders
  None
  Grade 1 or 2
  Grade 3 or 4
Gastrointestinal disorders
  None
  Grade 1 or 2
  Grade 3 or 4
Neurologic disorders
  None
  Grade 1 or 2

Table 2: Risk Factors for Intolerance of Uncertainty in Adult Survivors (additional variables to be added to table based on modelling results).

Risk Factor	B	95% CI	P-Value
Model 1: demographics, treatment			
Age at diagnosis			
Years of follow-up			
Female			

Table 3: Summary of Means, Standard Deviations and Intercorrelations for Scores on the IUS-12, GAD-7, PHQ-8, and PCS

	Chronic Pain				
	Yes (N=96)		No (N=137)		
	N (%)	Mean (SD)	N (%)	Mean (SD)	P-Value
Intolerance of uncertainty					
Total score					
Anxiety					
Minimal; mild					
Moderate					
Severe					
Depression					
None; mild					
Moderate					
Moderately severe; severe					
Pain catastrophizing					
Total score					
Rumination subscale					
Helplessness subscale					
Magnification subscale					

Pearson Correlation Coefficients				
Measure	*1*	*2*	*3*	*4*
1. IUS-12	--			
2. GAD-7		--		
3. PHQ-8			--	
4. PCS				--

Note: IUS-12 = Intolerance of Uncertainty Scale – 12; GAD-7 = Generalized Anxiety Disorder Scale – 7 item; PHQ-8 = Patient Health Questionnaire – 8 item; PCS= Pain Catastrophizing Scale.

Table 4: Hierarchical Multiple Regression Analyses Predicting Intolerance of Uncertainty

	B	*SE B*	β
Predictor			
Step 1			
Control variables[a]			
Step 2			
Pain catastrophizing			
Pain intensity			
Pain interference			

Note: R2 = X for Step 1, ΔR^2 = X for Step 2. * $p < .001$. [a]Control variables include sex, age, and race/ethnicity.

Table 5: Summary of Means, Standard Deviations and Intercorrelations for Scores on the FCIR-SF, IUS-12, GAD-7, and PHQ-8

	N (%)	Mean (SD)
Fear of cancer recurrence		
Total score		
Problematic levels		
Clinical levels		
Intolerance of uncertainty		
Total score		
Anxiety		
Minimal; mild		
Moderate		
Severe		
Depression		
None; mild		
Moderate		
Moderately severe; severe		
Pain catastrophizing		
Total score		
Rumination subscale		
Helplessness subscale		
Magnification subscale		

	Pearson Correlation Coefficients			
Measure	*1*	*2*	*3*	*4*
1. FCIR-SF	--			
2. IUS-12		--		
3. GAD-7			--	
4. PHQ-8				--

Note: FCIR-SF = Fear of Cancer Recurrence Inventory – Short Form; IUS-12 = Intolerance of Uncertainty Scale – 12; GAD-7 = Generalized Anxiety Disorder Scale – 7 item; PHQ-8 = Patient Health Questionnaire – 8 item.

Table 6: Risk Factors for Fear of Cancer Recurrence in Adult Survivors

Risk Factor	B	95% CI	P-Value
Model 1: demographics, treatment			
Age at diagnosis			
Years of follow-up			
Female			
Model 2: psychological and somatic factors			
Depression			
Anxiety			
Chronic pain			

Appendix A: Intolerance of Uncertainty Scale – Short Form

Intolerance of Uncertainty Scale - Short Form

(Carleton, Norton, & Asmundson, 2007)

Please circle the number that best corresponds to how much you agree with each item.

	Not at all characteristic of me	A little characteristic of me	Somewhat characteristic of me	Very characteristic of me	Entirely characteristic of me
1. Unforeseen events upset me greatly.	1	2	3	4	5
2. It frustrates me not having all the information I need.	1	2	3	4	5
3. Uncertainty keeps me from living a full life.	1	2	3	4	5
4. One should always look ahead so as to avoid surprises.	1	2	3	4	5
5. A small unforeseen event can spoil everything, even with the best of planning.	1	2	3	4	5
6. When it's time to act, uncertainty paralyses me.	1	2	3	4	5
7. When I am uncertain I can't function very well.	1	2	3	4	5
8. I always want to know what the future has in store for me.	1	2	3	4	5
9. I can't stand being taken by surprise.	1	2	3	4	5
10. The smallest doubt can stop me from acting.	1	2	3	4	5
11. I should be able to organize everything in advance.	1	2	3	4	5
12. I must get away from all uncertain situations.	1	2	3	4	5

Score:_____

Appendix B: Fear of Cancer Recurrence Inventory – Short Form (FCRI-SF)

Fear of Cancer Recurrence Inventory- Short Form (FCRI-SF)
Screening

Most people who have been diagnosed with cancer are worried, to varying degrees, that there might be a recurrence of the cancer. **By recurrence, we mean the possibility that the cancer could return or progress in the same place or in another part of the body.** This questionnaire aims to better understand the experience of worries about cancer recurrence. Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

0 Not at all	1 A little	2 Somewhat	3 A lot	4 A great deal

1. I am worried or anxious about the possibility of cancer recurrence 0 1 2 3 4
2. I am afraid of cancer recurrence 0 1 2 3 4
3. I believe it is normal to be worried or anxious about the possibility of cancer recurrence 0 1 2 3 4
4. When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family) 0 1 2 3 4
5. I believe that I am cured and that the cancer will not come back 0 1 2 3 4
6. In your opinion, are you at risk of having a cancer recurrence?

0 Not at all at risk	1 A little at risk	2 Somewhat at risk	3 A lot at risk	4 A great deal at risk

7. How often do you think about the possibility of cancer recurrence?

0 Never	1 A few times a month	2 A few times a week	3 A few times a day	4 Several times a day

8. How much time per day do you spend thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few seconds	2 A few minutes	3 A few hours	4 Several hours

9. How long have you been thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few weeks	2 A few months	3 A few years	4 Several years