**CCSS Analysis Concept Proposal**

**Study title:** The impact of chronic conditions on the psychosexual function of adult female survivors of childhood cancer

**Investigators:**

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|---|---|
| Kari Bjornard | kari.bjornard@stjude.org |
| Wendy Leisenring | wleisenr@fredhutch.org |
| Geehong Hyun (analyst) | geehong.hyun@stjude.org |
| Jennifer Ford | fordj@mskcc.org |
| Charles Sklar | sklarc@mskcc.org |
| Todd Gibson | todd.gibson@stjude.org |
| Kevin Krull | kevin.krull@stjude.org |
| Kevin Oeffinger | kevin.oeffinger@duke.edu |
| Rebecca Howell | rhowell@mdanderson.org |
| Melissa Hudson | melissa.hudson@stjude.org |
| Les Robison | les.robison@stjude.org |
| Greg Armstrong | greg.armstrong@stjude.org |
| Dan Green | daniel.green@stjude.org |
| Kirsten Ness | kiri.ness@stjude.org |


**Working Groups:** Primary: Chronic conditions
Secondary: Psychology

**1. Background and rationale:**

As survival rates have improved for childhood cancer, the population of survivors living into adulthood has also increased. These survivors are at risk for early onset of chronic disease and disability, and also for adverse psychosocial outcomes, including changes in sexual function. Problems with sexual function have been noted to be a prevalent long-term complication of cancer therapy in adults[1, 2], and due to a variety of factors, including specific disease and treatment factors (e.g. tumor location and size, pelvic surgery, radiation therapy, mastectomy), psychological factors (e. g. depression, anxiety, body dysmorphia), declines in health-related quality of life (e.g. decreased physical functioning, fatigue, pain), or other changes post treatment, including chronic health conditions. However, data suggests that a fraction of women receive medical guidance regarding their sexual issues despite their interest in receiving care[3], highlighting an unmet need in cancer survivorship care.

Among childhood cancer survivors, male and female young adults, report inadequate clinical support regarding their sexual health, and desire for more information[4]. A study exploring psychosexual problems in male and female patients found that 20% of survivors indicated limitations in their sexual life due to their illness, with treatment for cancer during adolescence associated with delayed psychosexual development[5]. In female participants in the Childhood Cancer Survivor Study (CCSS), survivors of childhood cancer, compared to their siblings, experienced lower levels of sexual interest, desire, arousal and satisfaction[6]. Risk factors for poorer psychosexual functioning in this cohort of female survivors included older age at assessment, ovarian failure at a younger age, treatment with cranial radiation, and a cancer diagnosis during adolescence. Collectively, these findings suggest that female survivors of childhood cancer have compromised sexual functioning, as well as a strong desire for more information about their sexual health. Thus, a detailed examination into the role that disease,

treatment, psychological, hormonal, quality of life and chronic health factors play in sexual function is warranted.

Sexual dysfunctions are defined by the *Diagnostic and Statistical Reference Manual, 5th edition* as a heterogeneous group of disorders characterized by a clinically significant disturbance in an individual's ability to respond sexually or to experience sexual pleasure[7]. Among females, this includes sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, and female orgasmic disorder. An individual may experience multiple dysfunctions concurrently. As previous studies had identified childhood cancer survivors as more likely than peers to report lower sexual function[4-6, 8-9], in currently unpublished work from St. Jude Children's Research Hospital, we sought to: (i) confirm prevalence estimates of low sexual function; (ii) evaluate associations between socio-demographic, medical and treatment, and hormonal factors and low sexual function; and (iii) compare mental health and health related quality of life outcomes in those with and without low sexual function among adult women surviving childhood cancer using the St. Jude Lifetime Study (SJLIFE) cohort.

Participants were females enrolled in the St. Jude Lifetime Cohort Study (SJLIFE), a single-center cohort study of patients treated for a malignancy at St. Jude Children's Research Hospital, as well as a comparison group of healthy controls. Characteristics of study design, recruitment and characteristics of SJLIFE have been previously published[10]. Survivors and controls eligible for this analysis were female, had an IQ ≥ 70, completed an on campus visit, completed surveys, including the Women's Health Questionnaire (WHQ), and had sexual activity alone or with a partner in the month prior to completing the WHQ. The final sample included 712 female survivors and 122 female controls. To characterize sexual function, survivors and controls completed the Sexual Functioning Questionnaire (SFQ). This instrument is a validated, reliable measure of sexual functioning[11]. The SFQ is comprised of a multi-item scale that measures overall sexual functioning, as well as subscales: interest, desire, arousal, orgasm, satisfaction, activity, relationship and problems. Survivors who scored in the lowest 10th percentile of the control population were classified as having low sexual function.

19.9% of survivors had low psychosexual function compared to 10.7% of controls (Table 1). The most common impairments were problems (27.4%), orgasm (24.2%), satisfaction (17.6%), interest (17.2%), desire (15.4%), and arousal (12.5%) (Table 1). Survivors with low function reported poorer quality of life in both physical (21.1% vs. 12.7%, p=0.01) and mental health (36.5% vs. 18.2%, p<0.01) composite domains compared to those without low function. Hypogonadism was associated with low function (untreated: OR 3.20, 95% CI 1.69-6.42) for the problems subscale. Compared to controls, survivors with germ cell tumors (OR 8.82, 95% CI 3.17-24.50), renal tumors (OR 4.49, 95% CI 1.89-10.67) and leukemia (OR 3.09, 95% CI 1.50-6.38) were at greatest risk for low function. Though 40.7% of survivors perceived a higher risk for low psychosexual function compared to other women their age, only 2.9% reported receiving an intervention.

While childhood cancer survivors have an increased prevalence of low sexual function when compared to controls, studies, to date, have not identified specific treatment factors that consistently predict low function. We found that survivors with laboratory confirmed central or primary hypogonadism were more likely than those without to report sexual problems. This is interesting, as radiation exposure is associated with hypogonadism. Hypogonadism is also consistent with the accelerated aging phenotype that has been noted in childhood cancer survivors, which in turn is associated with chronic disease[12]. Because we found that low function is associated with psychosocial outcomes (body image, relationship satisfaction, depression, anxiety, and somatization) and with health related quality of life, identifying those at the greatest risk for low function is important.

**Table 1. Proportion of low sexual functioning among survivors and controls based on scores from SFQ**

| | Survivors | | Controls | | |
|---|---|---|---|---|---|
| SFQ Scores | % | 95% CI | % | 95% CI | p |
| Overall | 19.9 | (17.1-23.1) | 10.7 | (5.80-17.5) | **0.015** |
| Activity | 10.2 | (8.10-12.7) | 7.69 | (3.58-14.10) | 0.39 |
| Arousal | 12.5 | (10.1-15.1) | 5.79 | (2.36-11.56) | **0.03** |
| Desire | 15.4 | (12.8-18.3) | 6.56 | (2.87-12.5) | **<0.01** |
| Interest | 17.2 | (14.5-20.2) | 9.09 | (4.63-15.68) | **0.02** |
| Orgasm | 24.2 | (21.1-27.5) | 10.74 | (5.85-17.67) | **<0.01** |
| Problems | 27.4 | (24.2-30.9) | 11.48 | (6.42-18.50) | **<0.01** |
| Relationship | 7.2 | (5.30-9.52) | 8.85 | (4.33-15.67) | 0.54 |
| Satisfaction | 17.6 | (14.8-20.6) | 6.56 | (2.87-15.51) | **<0.01** |

Data indicating an association between hypogonadism and low sexual function suggests that chronic disease, more proximal to current function, may be a predictor, or a mediator, of the association between treatment exposures and low function. In the CCSS cohort, survivors of childhood cancer have a cumulative incidence of at least one severe, disabling, life-threatening or fatal health conditions of 53.6% by age 50 compared to a rate of 19.8% among siblings[13]. When multiple chronic conditions are considered, this figure is more striking. In the SJLIFE cohort, by age 50, survivors experienced, on average, 17.1 conditions of any grade, compared to an average of 9.2 conditions in community controls[14]. Among Hodgkin Lymphoma survivors from the SJLIFE cohort, the cumulative burden of experiencing at least one grade 3-5 cardiovascular condition among survivors by age 50 was 45.5% compared to 15.7% among community controls[15]. This burden of chronic conditions among survivors could be contributing to the excess of low sexual function. This hypothesis is supported by literature from other populations that report an increased prevalence of sexual disorders among persons with other chronic conditions. For women with type II diabetes mellitus, sexual dysfunction is found in 68%, compared to 17% of controls[16]. Occurrence of sexual dysfunction correlated with age of onset, and duration of diabetes, and was associated with depression. In a study of women with hypertension, females with an increased number of physical comorbidities reported a higher odds of sexual dysfunction[17]. In women with non-alcoholic fatty liver disease (NAFLD), those with NAFLD have lower sexual function scores overall, as well as for desire, arousal, orgasm, and satisfaction compared to controls[18]. Sexual dysfunction is also reported among women with chronic kidney disease, even in the pre-dialysis phase[19,20]. Thus, an investigation to evaluate associations between chronic health conditions and sexual dysfunction among female childhood cancer survivors in the Childhood Cancer Survivor Study is warranted.

## 2. Specific aims

2.1. Evaluate associations between chronic health conditions and sexual dysfunction among women childhood cancer survivors.

2.2. Describe the longitudinal effects of sexual dysfunction on psychological and quality of life outcomes among women childhood cancer survivors.

## 3. Hypotheses

3.1. The number, type and duration of chronic health conditions will be associated with sexual dysfunction in female childhood cancer survivors. We hypothesize that chronic conditions in cardiac, pulmonary, reproductive/gonadal and endocrine organs systems will be associated with poorer sexual function.

3.2. Sexual dysfunction at initial measurement will be associated with long-term psychological and quality of life outcomes.

## 4. Methods

4.1. Study Population:

Participants include individuals diagnosed with cancer when younger than 21 years of age who survived at least five years after diagnosis and were treated for their cancer between January 1, 1970 and December 31, 1986. Participants fill out extensive questionnaires covering demographic information, health behaviors, mental health, quality of life, and other factors. Also, detailed treatment information is abstracted from medical records. For these analyses, we will include adult female survivors and siblings who completed the Women's Health Questionnaire (2001-2003), and had sexual activity within the month prior to filling out the questionnaire. Survivors who answered yes to question J3 on the Baseline survey (Mental Retardation) are not eligible.

4.2 Outcome variables

4.2.1 The Women's Health Questionnaire includes the Sexual Functioning Questionnaire (SFQ) a gender specific, multi-item questionnaire that has been validated in cancer survivor cohorts and used previously in childhood cancer survivors[6, 11]. The SFQ has an overall score, and multiple subscales, that address activity, arousal, desire, interest, orgasm, masturbation, problems (will include both the physical problems such as pain/dryness, as well as psychological, such as anxiety), relationship and satisfaction. For this study, low function for survivors was defined as a score falling <10$^{th}$ percentile for the overall and each sub-score, based on data from non-cancer siblings, and was completed by 2586 adult female cohort members (2178 survivors and 408 siblings). Only scores from survivors and siblings who have had sexual activity with or without a partner are eligible (D2 in WHQ).

4.2.2 Emotional distress will be assessed with the BSI scales of somatization, depression and anxiety using the BSI-18 from the FU5 (2014) adjusted for scores coinciding with time they took the WHQ (FU1 or 2).

4.2.3 Health-related quality of life will be measured with the SF-36 from the FU5 (2014), with adjusted normative scores less than or equal to 40 representing poor HRQOL in that domain and adjusted for scores coinciding with time they took the WHQ (FU1 or 2).

4.3 Independent variables:

4.3.1 Age at diagnosis
4.3.2 Age at follow-up (SFQ questionnaire)
4.3.3 Time since diagnosis (between date of diagnosis and completion of SFQ)
4.3.4 Age at time of follow-up (FU5)
4.3.5 Cancer diagnosis (leukemia, CNS tumor, Hodgkin, Non-Hodgkin lymphoma, Wilms tumor, Neuroblastoma, soft tissue sarcoma, Ewing sarcoma, and osteosarcoma)
4.3.6 Chemotherapy (Data categorized as categorical variables identifying cumulative amounts: Anthracyclines, Alkylating Agents)
4.3.7 Radiation (Cranial, Chest, Abdominopelvic- dichotomous)

4.3.8 Surgery (surgery of pelvis- dichotomous)

4.3.9 Chronic Illness grading using NCI Common Terminology Criteria for Adverse Events for Cardiovascular, Pulmonary, and Endocrine conditions, specifically using the presence of any grade 3-4 chronic condition and within each organ category for the participant (cardiovascular, pulmonary, GI/hepatic, renal, reproductive/gonadal, endocrine, musculoskeletal, neurologic/sensory). (CCSS Late Effects Database variables, any grade 3-4). Chronic conditions must be documented as starting prior to, or concurrently with, filling out the SFQ questionnaire as part of the WHQ.

4.3.10 Duration of onset of grade 3-4 chronic conditions as measured between time of onset and completing SFQ, and separate models for each organ system

4.3.11 Duration of onset of chronic conditions as measured between time of onset and completing FU5

4.4 Statistical Analysis Framework:

4.4.1 This study aims to evaluate associations between chronic conditions and low sexual function among women childhood cancer survivors. The primary outcomes of interest are low sexual function (scoring in the lowest $10^{th}$ percentile of the sibling comparison group) and continuous scores on the individual components of the SFQ. The primary risk factors for these outcomes will be chronic conditions evaluated overall (any, grade 1-4, any grade 3-4) and as specific organ conditions (cardiovascular, pulmonary, GI/hepatic, renal, reproductive/gonadal, endocrine, musculoskeletal, neurologic/sensory), evaluated in separate models. Conditions documented as starting before or concomitant to the questionnaire data will be included. Multivariable regression models will be used to evaluate these associations, using either logistic regression or log-binomial models when the outcome is dichotomous or linear models when the outcomes are continuous. Models will include variables indicating the duration of the chronic condition(s) from onset, age at the questionnaire time point, and time since cancer diagnosis.

4.4.2 The second aim is to describe the effects of low sexual function on future psychological and quality of life measures among women childhood cancer survivors, while accounting for scores on QOL and psychological measures at the time of the WHQ. The outcomes of interest will be scores on the Brief Symptom Inventory and the SF-36, administered at the follow-up five survey. Low sexual function will be the primary indicator variable. Multivariable linear regression will be used to evaluate this association, adjusting for age, time since diagnosis, chronic health conditions and scores on the BSI and SF-36 administered in conjunction with the WHQ.

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Table 1. Demographic Characteristics of Female Survivors and Siblings

| Characteristic | Survivors No. | Survivors % | Siblings No. | Siblings % | p |
|---|---|---|---|---|---|
| Age at follow-up (time of SFQ) | | | | | |
| <25 yrs | | | | | |
| 25-34 yrs | | | | | |
| 35-44 yrs | | | | | |
| 45-54 yrs | | | | | |
| ≥55 yrs | | | | | |
| Marital Status (at time of SFQ) | | | | | |
| Never married | | | | | |
| Ever married | | | | | |
| Unknown | | | | | |
| Household Income ($) | | | | | |
| <20,000 | | | | | |
| ≥20,000 | | | | | |
| Educational attainment | | | | | |
| < HS graduate or GED | | | | | |
| High school graduate | | | | | |
| > HS education | | | | | |
| Race | | | | | |
| Non-Hispanic White | | | | | |
| Non-Hispanic Black | | | | | |
| Hispanic | | | | | |
| Other | | | | | |
| Health Insurance Status | | | | | |
| Yes | | | | | |
| No | | | | | |
| Lives independently | | | | | |
| Yes | | | | | |
| No | | | | | |
| Employment | | | | | |
| Unable to work | | | | | |
| Unemployed | | | | | |
| Employed/Student | | | | | |
| Chronic Conditions, n (%) | | | | | |
| None | | | | | |
| Any, grade 1-4 | | | | | |
| Any, grade 3-4 | | | | | |
| Cardiac | | | | | |
| Pulmonary | | | | | |
| Neurologic | | | | | |
| Gonadal/reproductive | | | | | |
| Endocrine/Metabolic | | | | | |
| GI/Hepatic | | | | | |
| Renal | | | | | |
| Musculoskeletal | | | | | |

Table 2. Diagnosis and treatment characteristics of female survivors with and without low sexual functioning

| Characteristic | | Survivors with low sexual function No. | % | Survivors without low sexual function No. | % | p |
|---|---|---|---|---|---|---|
| Age at diagnosis, n (%) | | | | | | |
| | 0-4 | | | | | |
| | 5-9 | | | | | |
| | 10-14 | | | | | |
| | 15-20 | | | | | |
| Year of diagnosis | | | | | | |
| | 1970-79 | | | | | |
| | 1980-89 | | | | | |
| | 1990-99 | | | | | |
| Time from diagnosis, y | | | | | | |
| | mean (±SD) | | | | | |
| | range | | | | | |
| Diagnosis, n (%) | | | | | | |
| | Leukemia | | | | | |
| | CNS tumor | | | | | |
| | Hodgkin lymphoma | | | | | |
| | Non-Hodgkin lymphoma | | | | | |
| | Kidney tumors | | | | | |
| | Neuroblastoma | | | | | |
| | Soft tissue sarcoma | | | | | |
| | Bone Cancer | | | | | |
| CNS Radiation therapy received | | | | | | |
| | No | | | | | |
| | Yes | | | | | |
| | Unknown | | | | | |
| Chest Radiation therapy received | | | | | | |
| | No | | | | | |
| | Yes | | | | | |
| | Unknown | | | | | |
| Abdominopelvic Radiation therapy received | | | | | | |
| | No | | | | | |
| | Yes | | | | | |
| | Unknown | | | | | |
| Anthracycline dose, mg/m2 | | | | | | |
| | None | | | | | |
| | 1-249 | | | | | |
| | ≥250 | | | | | |
| Alkylating Agents | | | | | | |
| | None | | | | | |
| | 0-8000 CED | | | | | |
| | 8001-12000 CED | | | | | |
| | ≥12000 CED | | | | | |
| Chronic Conditions | | | | | | |
| | None | | | | | |
| | Any condition, grades 3-4 | | | | | |
| | Cardiac | | | | | |
| | Pulmonary | | | | | |
| | Neurologic | | | | | |
| | Gonadal/reproductive | | | | | |
| | Endocrine/Metabolic | | | | | |
| | GI/Hepatic | | | | | |
| | Renal | | | | | |
| | Musculoskeletal | | | | | |

Table 3. Number and proportion of female cancer survivors with low sexual function by grade 3-4 chronic conditions

| | Overall | | Interest | | Desire | | Arousal | | Satisfaction | | Masturbation | | Relationship | | Activity | | Problems | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chronic Conditions | no. | % | no. | % | no. | % | no. | % | no. | % | no. | % | no. | % | no. | % | no. | % |
| None | | | | | | | | | | | | | | | | | | |
| Any, grade 3-4 | | | | | | | | | | | | | | | | | | |
| Cardiac | | | | | | | | | | | | | | | | | | |
| Pulmonary | | | | | | | | | | | | | | | | | | |
| Neurologic | | | | | | | | | | | | | | | | | | |
| Gonadal/reproductive | | | | | | | | | | | | | | | | | | |
| Endocrine/Metabolic | | | | | | | | | | | | | | | | | | |
| GI/Hepatic | | | | | | | | | | | | | | | | | | |
| Renal | | | | | | | | | | | | | | | | | | |
| Musculoskeletal | | | | | | | | | | | | | | | | | | |

Table 4. Psychosexual function among female survivors by chronic condition

| | Overall | | | Interest | | | Desire | | | Arousal | | | Satisfaction | | | Masturbation | | | Relationship | | | Activity | | | Problems | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p |
| Age at questionnaire (SFQ) v. 18-30 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 31-53 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Time since diagnosis v. <10 yrs | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 11-15 yrs | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >15 yrs | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Marital Status v. ever married | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Never married | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chronic Conditions v. none | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Any, grade 1-4 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Any, grade 3-4 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiac | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pulmonary | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Neurologic | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Gonadal/reproductive | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine/Metabolic | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| GI/Hepatic | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Duration of conditions v. never | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1-5 yrs | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ≥5 yrs | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table 5. Adjusted mean scores of health-related quality of life variables at FU5 of survivors with and without low sexual functioning*

| | Low Sexual Function | | Without low sexual function | |
|---|---|---|---|---|
| Domain | Mean | SD | Mean | SD |
| Physical functioning | | | | |
| Role physical | | | | |
| Bodily pain | | | | |
| General health | | | | |
| Vitality | | | | |
| Social functioning | | | | |
| Role emotional | | | | |
| Mental health | | | | |
| Mental composite score | | | | |
| Physical composite score | | | | |

*adjusted for age at questionnaire, age at diagnosis, chronic health conditions and SF-36 scores administered in conjunction with the WHQ. Each line is a separate model

Table 6. Adjusted mean BSI scores variables at FU5 of survivors with and without prior report of low sexual functioning*

| | Low Sexual Function | | Without low sexual function | |
|---|---|---|---|---|
| Variable | Mean | SD | Mean | SD |
| Depression | | | | |
| Anxiety | | | | |
| Somaticizing | | | | |

*adjusted for age at questionnaire age at diagnosis, chronic health conditions and BSI-18 scores administered in conjunction with the WHQ. Each line is a separate model.