Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

Study Title
Perceptions of Risk for Sexual Dysfunction among Adult Male Survivors of Childhood Cancer

Primary Working Group: Psychology
Secondary Working Group: Chronic Disease

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Background and rationale:

Childhood cancer survivors are at increased risk of sexual dysfunction (SD) as a result of their cancer or treatment history. SD encompasses lack of desire for sex, arousal difficulties (erection, lubrication), inability to achieve climax/ejaculation, anxiety about sexual performance, climaxing/ejaculating too rapidly, physical pain during intercourse, and lack of pleasure.[1] SD is estimated to occur in 30-50% of childhood cancer survivors, and is widely under-recognized.[2-10] SD may occur as a result of physiologic changes, such as hormone changes or as a result of surgery or radiation, or psychosexual reasons, such as poor body image, concerns about fertility, and disruption of normal psychosexual development.[2,3,11] *Thus far, much of the research on male survivors has focused on erectile dysfunction, and male CCS who have other potentially less physiologic SD may have been overlooked.* Although the Children's Oncology Group Long-Term Follow-Up (COG LTFU) Guidelines recognize pelvic or spinal surgery to be risk factors for SD in male survivors, studies also suggest that having received chemotherapy (compared to no chemotherapy) and cranial or testicular irradiation may be treatment-related risk factors as well.[6-8,12-14] However, these treatment risk factors do not sufficiently explain the variation of SD incidence in survivors. Demographic factors such as age at diagnosis or at evaluation, lower income and mental or general health concerns also appear to be significant.[3-6,12,13,15] For these reasons, defining levels of risk for SD is difficult and consideration of education and screening is warranted for all childhood cancer survivors.

Despite risk for SD, childhood cancer survivors are not routinely assessed for this problem. While 21% of male and 24% of female adult cancer survivors report wanting help for sexual problems, they also report that this need was largely unmet.[16] In a study evaluating communication regarding sexual health in the adolescent/young adult (AYA) population, all study participants reported inadequate clinical support.[17] One study reported that 82% of oncologists reported discussing sexual function in fewer than half of their patients.[18] Similarly, 62% of general internists at a major academic medical center reported that they never or rarely addressed SD among their cancer survivor patients.[19] AYA patients note that they want to discuss sexual and reproductive health with their oncologists, but are hesitant to initiate conversations and prefer their provider take the lead.[17,20] While qualitative studies have described patients' desire to discuss sexual health/function concerns with their oncologists, no studies have quantified current perceptions of risk for SD. Providers report a lack of their own knowledge/awareness of the issue, and patient perceptions of their SD risk has not been described. Pediatric oncologists and internists cite many challenges in meeting sexual health needs, including lack of knowledge/experience/training, lack of resources/referrals, parent/family presence, concerns of patient or own discomfort, lack of rapport, low priority and limited time.[19,21]

To address inadequate screening and under-recognition of SD, education is necessary both for providers and patients. When providers don't routinely screen for SD in survivors, the healthcare system relies on the patient to raise his/her concerns. However, because patients are unlikely to recognize that their history of cancer/cancer therapy may put them at risk for SD, instead this issue is likely to go unnoticed.

Therefore, research is needed to 1) develop a feasible and effective approach to educating providers about the need to screen patients and 2) to develop a deliverable patient-centered approach to education and screening for SD. As previously mentioned, these endeavors must account for the complex pathophysiology of SD, variation in types of SD, and patients' current perceptions and information-seeking about SD. As such, this investigation seeks to take a comprehensive approach to understanding men's perceived risk for SD by exploring factors, including and beyond treatment exposures, which may influence their experiences and education with regard to SD. This is particularly true of AYA childhood cancer survivors, who may be especially vulnerable to discomfort related to discussions of sexuality and sexual function [20,22]. Completion of the proposed project will inform further research addressing screening and education, with the long term goal of promoting early identification of clinical dysfunction and intervention for this late effect of childhood cancer.

To improve existing clinical systems for assessing post-treatment SD in survivors, it is necessary to establish an understanding of the current state of patient perceptions of SD risk after cancer. As previously mentioned, while research demonstrates that patients feel that their sexual health needs are not being met in a survivorship setting, and, anecdotally, patient perceptions of their own risk for SD have not been quantified. *This study aims to use existing Childhood Cancer Survivor Study data to describe male perceptions of risk for SD (Aim 1), patient/treatment factors associated with perception of increased risk compared to those without perceived increased risk (Aim 2), and patient-identified attributions for increased risk for SD and sources of information (Aim 3). Understanding current patient perceptions and SD education is critical to implementing screening and developing interventions for SD.* This study will focus specifically on male survivors to utilize existing data available via the 2008-2009 Male Health Questionnaire (MHQ). The MHQ included questions addressing perception of SD risk; while the Women's Emotional Well-Being and Intimacy Survey assessed sexual function in survivors, this study did not evaluate perception of risk. An understanding of male survivors' perceptions of SD risk will set the groundwork for future studies implementing patient education and provider-initiated screening tools, ultimately aimed at improved recognition and treatment of SD in childhood cancer survivors.

Specific aims/objectives/research hypotheses:

Aim 1: *PERCEPTIONS OF SEXUAL DYSFUNCTION RISK*
To describe prevalence of perceived risk for sexual dysfunction among adult male survivors of childhood cancer.

Aim 2: *FACTORS ASSOCIATED WITH PERCEIVED RISK OF SEXUAL DYSFUNCTION*
To evaluate which patient, treatment, and therapy-related factors are associated with patient-perception of increased risk for sexual dysfunction.

> *Hypothesis:* Perceived increased risk for SD will be more common among male survivors of who were older at diagnosis, older at the time of study participation, have higher education levels, underwent pelvic or spinal surgery, received pelvic radiation, have a history of hypotestosteronism, or report lower quality of life.

Aim 3: *PERCEIVED RISK OF SEXUAL DYSFUNCTION: EDUCATION*
To describe attributions, sources, and settings of education about risk of sexual dysfunction among male survivors of childhood cancers who perceive that they are at increased risk for SD relative to their peers.

> *Hypothesis 3:* Male survivors of childhood cancers who identify themselves as being at risk for sexual dysfunction due to the cancer or therapy will report a wide variety of sources of information.

Analysis framework:

Aim 1: *PERCEPTIONS OF SEXUAL DYSFUNCTION RISK*
To describe prevalence of perceived of risk for sexual dysfunction among adult male survivors of childhood cancer.

Population

- Inclusion Criteria
    - All male survivors who responded to the MHQ and answered question F1c

Primary Outcome Variable

- Perception of risk for SD (MHQ F1c)
    - Group 1 – Perceived increase in SD risk: includes answers “slightly more”, “much more”
    - Group 2 – No perceived increase in SD risk: includes answers “much less”, “slightly less”, “about the same”

Statistical Analysis

Descriptive statistics of the primary outcome variable will be summarized as percent of the study population, for each of the two groups outlined above, and by specific response. Prior data in a similar cohort identified 340 men belonging to Group 1 and 873 men belonging to Group 2. For Group 1, descriptive statistics of the secondary outcome variable, patient-identified reason for risk, will be summarized as proportion of individuals reporting specific responses.

Aim 2: *FACTORS ASSOCIATED WITH PERCEIVED RISK OF SEXUAL DYSFUNCTION*

To evaluate for patient, treatment and therapy-related factors associated with patient-perception of increased risk for sexual dysfunction.

Population

- Inclusion Criteria
    - All male survivors who responded to the MHQ and answered question F1c
- Exclusion Criteria
    - None

Primary Outcome Variable

- Perception of risk for SD (MHQ F1c)
    - Group 1 – Perceived increase in SD risk: includes answers “slightly more”, “much more”
    - Group 2 – No perceived increase in SD risk: includes answers “much less”, “slightly less”, “about the same”

Covariates of Interest

- Patient characteristics
    - Age at assessment (date of MHQ-DOB)
    - Marital status (M2 – LTFU 2007)
    - Education level (A3 – LTFU 2007)
    - Prior participation in LTFU clinics (B6- 2007)
    - Sexual/reproductive health
        - Sexual activity in last year (MHQ G1)
        - History of delayed puberty (MHQ C1)
        - Current treatment with testosterone (MHQ B6)
        - History of treatment with erectile dysfunction therapy (MHQ B11)
        - History of fathering a child (Baseline through FU 2007)
        - Self-reported history of infertility (y/n):
            - YES will be operationalized as:
                - “Have you and a partner ever tried to become pregnant?” (MHQ C6) = yes

                  AND

                  “Has a female partner ever had difficulty (it took more than a year) becoming pregnant by you” (MHQ C7) = yes
            - NO will be operationalized as:
                - “Have you and a partner ever tried to become pregnant?” (MHQ C6) = yes

                  AND

                  “Has a female partner ever had difficulty (it took more than a year) becoming pregnant by you” (MHQ C7) = no

OR
"Have you and a partner ever tried to become pregnant?" (MHQ C6) = no

- Health status
  - SF-12 Health and Quality of life (MHQ D1-12)
    - HRQOL overall score
    - Physical Health composite score (<40 v. ≥40)
    - Mental Health composite score (<40 v. ≥40)
  - Depression (MHQ B1a)
  - Other major psychiatric illness (MHQ B1c)
- Disease characteristics
  - Diagnosis
  - Disease
    - Age at diagnosis (Date of Diagnosis -DOB)
    - History of GU cancer (Testicular/ pelvic)
  - History of recurrence (MRAF)
  - Secondary malignant neoplasm (SMN) (MFAF)
- Treatment characteristics (MRAF, Baseline Data)
  - History of gonadotoxic chemotherapy (alkylators or heavy metal)
  - History of GU/pelvic surgery (+ MHQ B3)
  - History of GU/pelvic radiation
  - History of spinal surgery (MRAF)
  - History of head/brain irradiation (MRAF)

Statistical Analysis
Descriptive statistics of the primary outcome variable will be summarized using standard measures for the entire sample and by two groups outlined above for each covariate. Univariate associations between covariates and perception group will be evaluated using logistic regression models with group membership as the binary outcome. Multivariate logistic regression analyses will be performed to identify factors independently associated with increased perception of risk. Factors chosen for models will be guided by inclusion of *a priori* selected factors (such as gonadotoxic treatment, history of infertility, history of erectile dysfunction therapy, physical health composite <40, mental health composite <40, history of recurrence or SMN), forward/backward selection model analyses, identified collinearities between risk factors and on minimizing Bayesian Information Criteria. We will examine cancer diagnosis group in separate models from treatment variables due to the high degree of collinearity between them. **Of note, because the pathophysiology of SD is complex/multifocal and the weight of discrete factors/risks are not yet known, it is not possible at this time to assign patients to a discrete "risk" for SD to compare perceptions to actuality.**

Aim 3: *PERCEIVED RISK OF SEXUAL DYSFUNCTION: EDUCATION*
To describe attributions, sources, and settings of education about risk of sexual dysfunction among male survivors of childhood cancers who perceive that they are at increased risk for SD relative to their peers.
Population

- Inclusion Criteria
  - All male survivors belonging to Group 1 above (responded to the MHQ and perceive that they are at risk for SD (MHQ F1c "slightly more" or "much more"))

Primary Outcome Variables

- Patient-identified reason for risk (MHQ F2c)
- Source(s) of information about risk of SD (MHQ F3c)
- Of those answering "your oncologist" or "your general practitioner/internist" to MHQ F3c: Timing/setting(s) of information about risk of SD (MHQ F4c)

Statistical Analysis
Descriptive statistics of the primary outcome variable, sources of information, will be summarized using standard measures for patients belonging to Group 1 (of Aims 1-2).

Tables

Aim 1

Table 1. Cohort demographics and patient-perceived risk of sexual dysfunction

Characteristic	**Full Cohort N (%) or Mean (SD)**	**Group 1: Perceived risk of SD N (%) or Mean (SD)**	**Group 2 No perceived risk of SD N (%) or Mean (SD)**
Age at assessment (Date of MHQ-DOB)			
Race (baseline) American Indian/Alaskan Native Asian Black Pacific Islander White Other			
Ethnicity (baseline) Hispanic Non-Hispanic			
Diagnosis type Bone cancer CNS tumor Hodgkin lymphoma Leukemia Neuroblastoma Non-Hodgkin lymphoma Soft tissue sarcoma Wilms tumor			
Perceived increased risk - Group 1 Slightly more Much more			
No Perceived increased risk - Group 2 Much less Slightly less About the same			
Education level 1-8 years (grade school) 9-12 years (high school) but did not graduate Completed high school/GED Training after high school, other than college Some college College graduate Post graduate level Other			
Participation in survivor care No Yes <1 year ago 1-2 years ago 2-5 years ago >5 years ago			
Marital Status			

Single Married Divorced Other			
Sexual activity in last year No Yes			
Overall Health Excellent Very good Good Fair Poor			
SF12 Physical Health Composite Score <40 ≥40			
SF12 Mental Health Composite score <40 ≥40			
History of depression No Yes			
Other major psychiatric illness No Yes			
History of delayed puberty No Yes			
Current testosterone therapy No Yes			
History of erectile dysfunction therapy No Yes			
History of infertility* No Yes			
History of fathering a child No Yes			
Age at diagnosis			
History of GU cancer No Yes			
History of gonadotoxic chemotherapy No Yes			
History of GU/pelvic surgery No Yes			
History of spinal surgery			

No Yes			
Meets COG LTFU Guidelines (pelvic *or* spinal surgery) No Yes			
History of GU/pelvic radiation No Yes			
History of HD hypothalamic radiation No Yes			

Aim 2

Table 2. Univariate comparison of perceptions of SD risk by patient demographic factors

	Group 1: Perceived risk of SD	Group 2 No perceived risk of SD	OR (95% CI)	*p-value*
Total	N (%)	N (%)	N/A	N/A
Age at assessment	M (SD)	M (SD)		
Education level Did not complete high school/GED Completed high school/GED Training after high school or some college College graduate Post graduate level Other	N (%)	N (%)		
Participation in survivor care No Yes <1 year ago 1-2 years ago 2-5 years ago >5 years ago	N (%)	N (%)		
Marital Status Single Married Divorced Other	N (%)	N (%)		
Sexual activity in last year No Yes	N (%)	N (%)		

Table 3. Univariate comparison of perceptions of SD risk by patient health history.

	Group 1: Perceived risk of SD	Group 2 No perceived risk of SD	OR (95% CI)	*p-value*
Overall Health Excellent Very good	N (%)	N (%)		

Good Fair Poor				
SF12 Physical Health Composite Score <40 ≥40	N (%)	N (%)		
SF12 Mental Health Composite score <40 ≥40	N (%)	N (%)		
History of depression or No Yes	N (%)	N (%)		
Other major psychiatric illness No Yes	N (%)	N (%)		

Table 4. Univariate comparison of perceptions of SD by known sexual health history.

	Group 1: Perceived risk of SD	Group 2 No perceived risk of SD	OR (95% CI)	*p-value*
History of delayed puberty No Yes	N (%)	N (%)		
Current testosterone therapy No Yes	N (%)	N (%)		
History of erectile dysfunction therapy No Yes	N (%)	N (%)		
History of infertility* No Yes	N (%)	N (%)		
History of fathering a child No Yes	N (%)	N (%)		

*History of infertility may also be examined in a subanalysis restricted to men who answer Yes to “Have you and a partner ever tried to become pregnant?”.

Table 5. Univariate comparison of perceptions of SD risk by cancer and treatment history.

	Whole Cohort	Group 1: Perceived risk of SD	Group 2 No perceived risk of SD	OR (95% CI)	*p-value*
Age at diagnosis	M (SD)	M (SD)	M (SD)		
Diagnosis	N (%)	N (%)	N (%)		
History of recurrence No Yes	N (%)	N (%)	N (%)		
History of SMN No Yes	N (%)	N (%)	N (%)		
History of GU cancer	N (%)	N (%)	N (%)		

No Yes					
History of gonadotoxic chemotherapy* No Yes	N (%)	N (%)	N (%)		
History of GU/pelvic surgery* No Yes	N (%)	N (%)	N (%)		
History of spinal surgery* No Yes	N (%)	N (%)	N (%)		
Meets COG LTFU Guidelines (pelvic *or* spinal surgery) No Yes	N (%)	N (%)	N (%)		
History of GU/pelvic radiation* No Yes	N (%)	N (%)	N (%)		
History of head/brain radiation* No Yes	N (%)	N (%)	N (%)		

*Because treatment data beyond 5 years post-diagnosis is not available, complete treatment data may not be available patients after recurrence or secondary malignant neoplasm. This will be accounted for in analysis but adjusting for patients experiencing these events.

Table 6+. Full Multivariable model results will be displayed in similar tables, with variables from the above tables combined into models based on selection procedures described above.

Aim 3

Table 7. Attributions, sources, timing, and setting of education regarding risk for SD.

Attribution of Risk	Group 1 (Any perceived risk) N (%)	Slightly more perceived risk N (%)	Much more perceive risk N (%)
Cancer Type			
Chemotherapy			
Radiation			
Surgery			
Source of Information	Group 1 (Any perceived risk) N (%)	Slightly more perceived risk N (%)	Much more perceive risk N (%)
Oncologist			
General Practitioner			
Family			
Printed Information			
Internet			
Other			
Timing/Setting	Group 1 (Any perceived risk) N (%)	Slightly more perceived risk N (%)	Much more perceive risk N (%)

At time of diagnosis			
During treatment			
After treatment			
By primary oncologist			
In LTFU Program			
Other			

References

1. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999;281(6):537-544.
2. van Dijk EM, van Dulmen-den Broeder E, Kaspers GJ, van Dam EW, Braam KI, Huisman J. Psychosexual functioning of childhood cancer survivors. *Psychooncology.* 2008;17(5):506-511.
3. Wettergren L, Kent EE, Mitchell SA, et al. Cancer negatively impacts on sexual function in adolescents and young adults: The AYA HOPE study. *Psychooncology.* 2017;26(10):1632-1639.
4. Zebrack BJ, Foley S, Wittmann D, Leonard M. Sexual functioning in young adult survivors of childhood cancer. *Psychooncology.* 2010;19(8):814-822.
5. Bober SL, Zhou ES, Chen B, Manley PE, Kenney LB, Recklitis CJ. Sexual function in childhood cancer survivors: a report from Project REACH. *J Sex Med.* 2013;10(8):2084-2093.
6. Haavisto A, Henriksson M, Heikkinen R, Puukko-Viertomies LR, Jahnukainen K. Sexual function in male long-term survivors of childhood acute lymphoblastic leukemia. *Cancer.* 2016;122(14):2268-2276.
7. Ritenour CW, Seidel KD, Leisenring W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer-A Report From the Childhood Cancer Survivor Study. *J Sex Med.* 2016;13(6):945-954.
8. Ford JS, Kawashima T, Whitton J, et al. Psychosexual functioning among adult female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol.* 2014;32(28):3126-3136.
9. van Iersel L, Li Z, Chemaitilly W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer. *JAMA Oncol.* 2018;4(11):1613-1616.
10. Weinfurt KP, Lin L, Bruner DW, et al. Development and Initial Validation of the PROMIS((R)) Sexual Function and Satisfaction Measures Version 2.0. *J Sex Med.* 2015;12(9):1961-1974.
11. Sundberg KK, Lampic C, Arvidson J, Helstrom L, Wettergren L. Sexual function and experience among long-term survivors of childhood cancer. *Eur J Cancer.* 2011;47(3):397-403.
12. Acquati C, Zebrack BJ, Faul AC, et al. Sexual functioning among young adult cancer patients: A 2-year longitudinal study. *Cancer.* 2018;124(2):398-405.
13. Carpentier MY, Fortenberry JD. Romantic and sexual relationships, body image, and fertility in adolescent and young adult testicular cancer survivors: a review of the literature. *J Adolesc Health.* 2010;47(2):115-125.
14. Children's Oncology Group. Long-Term Follow Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer, Version 5.0. October 2018; www.survivorshipguidelines.org, 2018.
15. Kiserud CE, Schover LR, Dahl AA, et al. Do male lymphoma survivors have impaired sexual function? *J Clin Oncol.* 2009;27(35):6019-6026.
16. Schover LR. Sexual quality of life in men and women after cancer. *Climacteric.* 2018:1-5.
17. Frederick NN, Recklitis CJ, Blackmon JE, Bober S. Sexual Dysfunction in Young Adult Survivors of Childhood Cancer. *Pediatr Blood Cancer.* 2016;63(9):1622-1628.
18. Krouwel EM, Albers LF, Nicolai MPJ, et al. Discussing Sexual Health in the Medical Oncologist's Practice: Exploring Current Practice and Challenges. *J Cancer Educ.* 2019.
19. Park ER, Bober SL, Campbell EG, Recklitis CJ, Kutner JS, Diller L. General internist communication about sexual function with cancer survivors. *J Gen Intern Med.* 2009;24 Suppl 2:S407-411.
20. Frederick NN, Revette A, Michaud A, Bober SL. A qualitative study of sexual and reproductive health communication with adolescent and young adult oncology patients. *Pediatr Blood Cancer.* 2019:e27673.
21. Frederick NN, Campbell K, Kenney LB, Moss K, Speckhart A, Bober SL. Barriers and facilitators to sexual and reproductive health communication between pediatric oncology clinicians and adolescent and young adult patients: The clinician perspective. *Pediatr Blood Cancer.* 2018;65(8):e27087.

22. Keegan TH, Lichtensztajn DY, Kato I, et al. Unmet adolescent and young adult cancer survivors information and service needs: a population-based cancer registry study. *J Cancer Surviv.* 2012;6(3):239-250.