1. **STUDY TITLE:** Treatment related dermatologic conditions and health related quality of life in adult survivors of childhood cancer.

2. **WORKING GROUP AND INVESTIGATORS:**

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3. **BACKGROUND AND RATIONALE:**

   Advances in the field of pediatric oncology medicine have lead to remarkable increases in overall survival into adulthood [1]. However, it is widely accepted that the effects of chemotherapeutic agents and radiation on young, developing bodies continue to manifest years after therapy completion [2]. Resulting late effects include: obesity, thyroid dysfunction, premature menopause, hepatitis, cardiovascular abnormalities, and secondary neoplasms; including non-melanoma skin cancers [2, 3, 4]. Since many of these conditions are life threatening, dermatologic issues may be overlooked and understudied. In the literature there has been less focus on specific dermatologic late effects.

   The impact of dermatologic conditions in the adult childhood cancer survivor population was recently reported by Kinahan et al (2009) [5]. This team described dermatologic issues in a small sample of 78 childhood cancer survivors (ages <1-21 yrs old at time of diagnosis). The objective was to describe dermatologic issues that presented after initial cancer treatments and manifested years after cancer remission. In addition, they described the various conditions their cohort reported, effects on their quality of life (QOL), course of action (i.e. did the patient see a dermatologist), and financial deficits directly attributed to dermatologic concerns. One of the findings of their study was that dermatological issues were experienced by 59.0% of the survivors in their cohort and that 50% saw a dermatologist at least once for these concerns. Also alarming was that 33.3% reported scarring related to cancer therapy and that 96% of survivors with scars reported that their scars were permanent. Hair loss (alopecia), skin cancer (BCC and melanoma) and hyperpigmentation were other dermatological issues the cohort described. The effects of dermatologic issues on the survivor's quality of life were

measured using Finlay's Dermatology life quality index (DLQI) [6]. Dermatologic-related quality of life was generally high in this sample of survivors and only 15.4% of survivors reported that their dermatologic issues had any adverse impact on their quality of life. However, the DLQI was not an ideal tool to assess issues in the long term survivor population as it measures broad categories of dermatologic symptoms experienced within the "last week" [6]. A study by Kantoch et al. using a cohort of adult survivors with congenital heart disease looked at the significance of cardiac surgery scars (thoracotomy and sternotomy). Their results demonstrated that 18-20% of patients indicated a negative effect of surgical scars on self-esteem and self-confidence respectively [7].

To date, impact of cancer related dermatologic conditions on survivor's health related quality of life (HRQOL) has not been evaluated in the CCSS. A substantial proportion of survivors report significant symptoms of global distress and physical limitations, but not limitations due to emotional problems on the HRQOL. Fortunately, results of past CCSS studies show that other than brain tumor survivors, most childhood cancer survivors report both good present and expected future life satisfaction [8]. However, risk factors for psychological distress and poor HRQOL include female sex, lower educational attainment, unmarried status, annual household income less than $20,000, unemployment, lack of health insurance, presence of a major medical condition, *and treatment with cranial radiation and/or surgery* [8]. We propose to use the CCSS database to examine the association between HRQOL and dermatologic conditions. Should such an association be identified, opportunities may come available for practitioners to implement a discussion of coping strategies for groups at highest risk for adverse dermatologic effects after childhood cancer.

Preliminary examination of data from the CCSS baseline survey suggests scarring as a prevalent issue. Participants reported a prevalence of head or neck scarring of 25.95%, chest or abdomen scarring of 38.79 % and scarring of the arms or legs at 19.61%. Also related to HRQOL is the reported persistent hair loss by 15.23% and "other disfigurement or disability" reported by 8.76% of the baseline survey participants. (B.9)(C.14 second survey) Based on these findings and findings reported by Kinahan et al. we believe additional research in a larger, longitudinal childhood cancer survivor study is warranted. We would like to further examine the risk factors associated with the development of these dermatologic conditions. In addition, we would like to examine the impact that these dermatologic conditions have on health related quality of life.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Specific Aims:
   1. Describe the prevalence and types of dermatologic conditions experienced in long-term survivors of childhood cancer and their sibling controls as reported in the baseline survey (these will not include secondary skin cancers).

   2. Examine the association between disease and treatment related factors and the risk for dermatologic conditions in long-term survivors of childhood cancer.

3. Examine the association between dermatologic conditions reported at baseline and health related quality of life and emotional distress among long-term survivors of childhood cancer and sibling controls.

4.2. Objectives:
The results of this study will serve as pilot data to secure funding for a future CCSS ancillary study that would assess body image and its relation to HRQOL and psychosocial functioning. Should high rates of dermatologic issues be detected and should these issues impact quality of life and functional outcome, additional data collection via questionnaires through an ancillary study would be justified and proposed in a subsequent application.

4.3. Hypotheses:

1. Survivors will report increased prevalence of dermatologic related conditions compared to their sibling controls.

2. Survivors of childhood cancer treated with surgery and radiation will report higher prevalence of dermatological conditions compared to survivors not treated with surgery or radiation.

3. Survivor reporting dermatologic conditions at baseline will report reduced health related quality of life and more emotional distress on the 2003 Follow-up survey compared to survivors without dermatologic conditions.

5. ANALYSIS FRAMEWORK:

5.1. Subject population: CCSS Survivor and Sibling Cohort for Baseline survey and Follow-up 2003

5.1.1. Inclusion criteria
- Survivors and siblings who completed Baseline Survey.
- Cancer survivors who completed BSI and SF-36 questionnaires on Follow-up 2003 survey.

5.1.2. Exclusion criteria
- Survivors with secondary skin cancers

5.2. Primary Outcome Variables

5.2.1. Dermatologic Conditions (Yes/No) from Baseline Survey question B.9 (for Hypotheses 1 and 2).
- Head or neck scarring
- Arm or leg scarring
- Chest or abdomen scarring

- Persistent hair loss
- Loss of a limb or digit

5.2.2. Health related Quality of Life *(SF-36)* from Follow-up 2003 survey (for Hypothesis 3): Physical function, physical role, bodily pain, general health, vitality, social function, role emotional, mental health, physical component summery, mental component summary. Factor scores will be dichotomized, with impairment defined as being at least one standard deviation below the mean using standardized norms.

5.2.3. Brief Symptom Inventory *(BSI)* from Follow-up 2003 survey (for Hypothesis 3): Anxiety, Depression, Somatization, and Global Status Index. Factor scores will be dichotomized based on whether the performance is considered "impaired" or not (Yes/No), with impairment defined as a performance falling $\geq 90^{th}$ percentile based on standardized norms.

5.3. Independent Variables
- Cancer diagnosis
- Chemotherapy (Yes/No)
- Surgery (Yes/No)
- Radiation (Yes/No)
- If Yes to surgical procedures (Baseline I 1-31, FU2003) frequency count for each variable will be conducted initially to more clearly understand the frequency distribution. We anticipate that variables will be grouped into a two, three, or four level categorical variables depending upon the distribution. A two-level variable would be yes/no to surgery. Alternatively, a four-level variable might be no/ minor surgery (i.e. cataract)/ major surgery/ amputation.
- Health care in past 2 years (A1)

5.4. Covariates
- Age at diagnosis
- Age at interview (Baseline A.1, and or FU 2003)
- Gender (Baseline A.2)
- Race/ethnicity (Baseline -A4, 4a)
- Insurance status (FU 2003 section M)
- Household income (Baseline Q8)

5.5. Analysis
- Frequency distributions will be examined to categorize relevant outcome variables and covariates according to reasonable groupings and consistent with previous CCSS manuscripts. Descriptive statistics will be reported for all predictors, outcomes, and covariates.

Related to the specific hypotheses, the following analyses will be conducted:

5.5.1. Hypothesis 1: Survivors will report increased prevalence of dermatologic related conditions compared to their sibling controls.

- General linear model methods will be used to compare rates of dermatologic conditions between survivors and siblings making appropriate adjustments for intra-familial correlations.

5.5.2. Hypothesis 2: Survivors of childhood cancer treated with surgery and radiation will report higher prevalence of dermatological conditions compared to survivors not treated with surgery or radiation.
- Univariate logistic regression analyses will be conducted to identify individual variables significantly contributing to each dermatologic outcome.
- Variables that are significant in univariate analyses at $p < 0.10$ will be included in multiple variable logistic regression analyses for each outcome.
- Log linked regressions will be used to obtain relative risk estimates with 95% confidence intervals reported for predictors and covariates that significantly contribute to the multivariable models.

5.5.3. Hypothesis 3: Survivor reporting dermatologic conditions at baseline will report reduced health related quality of life and more emotional distress on the 2003 Follow-up survey compared to survivors without dermatologic conditions.
- Univariate logistic regression analyses will be conducted to identify dermatologic variables significantly contributing to each outcome from the SF-36 and BSI-18.
- Variables that are significant in univariate analyses at $p < 0.10$ will be included in multiple variable logistic regression analyses for each outcome.
- Covariates will include treatment factors from 5.3 and demographic factors from 5.4 above.
- Relative risk ratios with 95% confidence intervals will be reported for predictors and covariates that significantly contribute to the multivariable models.

6. Specific Tables/Figures

Table 1. Demographics

Characteristics	Survivors (N=) No. (%)	Siblings (N=) No. (%)	P-Value
Age at Interview			
18-24 years			
25-34 years			
35+ years			
Patient Gender			
Male			
Female			
Race/Ethnicity			
White, NH*			
Black, NH*			
Hispanic/Latino			
Asian/Pacific Islander			
Health Insurance			
Yes			
Household income			
Less than $9,999			
$10,000 - $19,999			
$20,000 - $39,999			
$40,000 - $59,999			
Over $60,000			

*NH= Non-Hispanic

Table 2. Clinical characteristics of survivors

Characteristics	Survivors (N=) No. (%)
Age at Diagnosis	
0-4	
5-9	
10-14	
15-19	
20-21	
Diagnosis	
ALL	
AML	
Other Leukemia, NOS	
Astrocytoma	
Medulloblastoma/PNET	
Other CNS Tumor	
Hodgkin's Disease	
Non-Hodgkin's Lymphoma	
Kidney Tumor	
Neuroblastoma	
Soft Tissue Sarcoma	
Ewing Sarcoma	
Osteosarcoma	
Other Bone Tumor	
Treatment	
Surgery only	
Radiation only	
Chemotherapy only	
Radiation and Chemotherapy	
Radiation and Surgery	
Surgery and Chemotherapy	
Surgery, Radiation and Chemotherapy	
Radiation Therapy	
Cranial	
Total Body	
Chest	
Facial	
Pelvis	
…etc	

Table 3. Frequency and t-test of Scarring in Childhood Cancer Survivors and Siblings

Scarring location	Survivors (N=) No. (%)	Siblings (N=) No. (%)	P-Value
Head/neck			
Arm/leg			
Chest/abdomen			
Persistent hair loss			
Loss of limb/digit			

Table 4.

Relative Risk rations for the prediction of scarring

	Head/neck scar			Arm/leg scar			Chest/abdomen scar			Persistent hair loss		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Cancer type *												
Surgery												
Radiation												
Chemotherapy												

*Due to collinearity, we will either include type of cancer OR treatment. This will be determined in univariate analyses.

Relative Risk ratios for the prediction of scarring (continued)

	Loss of limb or digit			Skin cancer			Graft versus Host Disease					
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Cancer type *												
Surgery												
Radiation												
Chemotherapy												

Table 5.
Relative Risk ratios for the prediction of BSI

	BSI: Depression			BSI: Anxiety			BSI: Somatization			BSI: Global Status Index		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Head/neck scar												
Arm/leg scar												
Chest/abdomen scar												
Persistent hair loss												
Loss of limb or digit												

Table 6.
Relative Risk ratios for the prediction of SF-36

	Physical function			Role physical			Bodily pain			General health		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Head/neck scar												
Arm/leg scar												
Chest/abdomen scar												
Persistent hair loss												
Loss of limb or digit												

Relative Risk ratios for the prediction of SF-36 (continued)

	Vitality			Social function			Role emotional			Mental health		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Head/neck scar												
Arm/leg scar												
Chest/abdomen scar												
Persistent hair loss												
Loss of limb or digit												

Relative Risk ratios for the prediction of SF-36 Component Scores (continued)

	PCS			MCS		
	RR	95% CI	p	RR	95% CI	p
Head/neck scar						
Arm/leg scar						
Chest/abdomen scar						
Persistent hair loss						
Loss of limb or digit						

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