Predicting risk for serious chronic health conditions among female survivors in the Childhood Cancer Survivor Study

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Working groups: Chronic Disease (Primary) and Biostatistics / Epidemiology (Secondary)

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Our current R01 funded program of research investigates the ability to improve the survivorship care as well as cancer screening guideline adherence among female survivors of childhood cancer who were treated with chest radiotherapy. One of the key elements of this program has been to provide primary care physicians (PCPs) with survivorship care plans. However, one challenge is that both PCPs and patients often lack guidance as to a patient's individual risks. Our work has demonstrated that childhood cancer survivors are in fact at high risk of adverse events, and that roughly a third of survivors of common childhood cancers will experience a serious or lethal late event by age 40. The risk of these events are almost twice as likely to occur in women, and can include several serious chronic health conditions such as cardiovascular disease (congestive heart disease, coronary artery disease), pulmonary conditions (chronic obstructive pulmonary disease [COPD]), renal dysfunction, and/or development of subsequent malignant neoplasms (SMNs). However, despite the known increased relative risks, particularly in females, we are currently unable to provide PCPs and patients with more specific guidance as to the risk of having a serious event within a specified period of time. There is therefore a critical need for practical risk prediction tools for these patients and their providers that can be used to help guide and encourage optimal survivorship care.

In this supplemental proposal, we propose to test the United Kingdom (UK) risk calculator for childhood cancer survivors to provide robust, readily available risk information to PCPs in the context of the current EMPOWER-II Study, being conducted through the Childhood Cancer Survivor Study (CCSS).

We will use all adult female survivors in the CCSS cohort to investigate the ability of an existing risk calculator to predict the incremental 5-year risk of serious events (Grade 3-5). The CCSS contains data for 10,947 women and provides up to 20 years follow-up for both the original and expansion cohorts. To predict risk, we will use the UK calculator, which provides simplified risk stratification for childhood cancer survivors as a function of their treatment. Patients will be assigned either a risk of low (surgery and/or low intensity chemotherapy), intermediate (anthracyclines or alkylating moderate intensity chemotherapy), and high (radiation therapy, intense chemotherapy/transplant) in accordance with the UK risk model. We will then test the model's ability to predict the rate of serious events that occur within specified 5-year intervals as a function of patient time from diagnosis and current age.

Aim 1: To predict 5-year interval mortality in females within the CCSS cohort using the UK risk categorization. Using the UK calculator we will place females in low, intermediate, or high risk categories and compare interval 5 year mortality by risk category. We will conduct our study with interval mortality being assessed starting at **A) 10 years** after initial diagnosis, **B) 15 years after diagnosis**, **C) 25 years of age**, and **D) 30 years of age** to assess to what extent these risks can be consistently assessed over time.

Aim 2: To predict 5-year incident serious chronic health conditions (grade 3-5) within the CCSS cohort using the UK risk categorization. We will examine the interval incidence of serious chronic health conditions including cardiovascular, pulmonary, renal conditions, and development of SMNs. We will assess the 5-year interval risk of a patient developing new serious conditions starting at **A) 10 years** after initial diagnosis, **B) 15 years after diagnosis**, **C) 25 years of age**, and **D) 30 years of age.** Women will be limited to those without any evidence of chronic health conditions at each time point, with the focus being to identify incident late events in previously healthy women.

Upon successful completion of these aims we will have evaluated the ability of the UK calculator to inform patient risks over a horizon with respect to both overall survival and the development of a serious late health condition. This will then provide us with a platform for future R01-supported studies to refine the risk calculator, if needed, and implement in clinical practice. This study is an important women's health initiative which will provide patients and providers with individualized, intermediate-term risk profiles to encourage appropriate and optimal survivorship care.

1. SIGNIFICANCE

1.1 There is a critical and pressing need to implement risk-stratified survivorship care in the US. The unique needs of cancer survivors came to the attention of the IOM in 2005, which prompted a report describing their long-term health risks and underscored the need for ongoing care.[1] Risk-stratified survivorship has been highlighted by the American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), and the National Cancer Institute (NCI) as a priority research topic. Researchers at the NCI recently (February 2019) published a systematic review highlighting the need for risk-stratified care research and concluded that there is

an urgent need to expand survivorship research specifically to 1) multiple cancer sites (not just breast cancer) and 2) longer-term (>5 years) survivors.[2] The proposed study addresses these shortcomings in survivorship research by examining multiple cancer sites and high quality data with extended (15+ years) follow-up.

1.2 Adult survivors of childhood cancers are a high risk group of cancer survivors.[4-6] By age 50, just over 50% of all adults within the Childhood Cancer Survivor Study (CCSS) developed a disabling, life-threatening, or fatal health condition. Even among survivors who reached age 35 years without severe effects, ~25% experienced new onset of a severe or fatal condition within 10 years.[7]

1.3. Female childhood cancer survivors are at particularly high risk of late events and secondary primary neoplasms (SPNs). In the initial publications of the CCSS, we showed that females were at 40-60% higher risk of having any conditions, severe conditions, or multiple conditions as compared to males.[8] In fact, one could consider the risks and long-term health care of females to be understudied and represent a critically important issue in women's health.

1.4 We previously observed that a key barrier to risk-based health care is an understanding of personalized risk and survivorship care plans. However, most (80%) oncologists do not currently provide formal plans to help transition survivors from oncology-centered to PCP or other provider care. Formal Survivorship Care Plans (SCPs) are recommended to be created within 6 months of treatment completion to convey signs and symptoms of recurrence, late, and long-term effects, and recommendations for healthy living.[18] However, only 1 in 5 oncologists report routinely creating an SCP.[19] Barriers to SCP creation include time, lack of reimbursement, concerns regarding standardization, and a lack of sustainability.[18] Studies of survivors in the UK and Netherlands have indicated that patients have different preferences for follow-up care of their cancer as a function of cancer type, supporting the need to create an acceptable SCP for every survivor.

1.5 Robust prediction of late effects is feasible for childhood cancer survivors. A study of 607 adult 5-year+ survivors of childhood cancers in the United Kingdom examined the feasibility of predicting[20] low, medium, and high risk groups of adverse health outcomes. Level 1 (low risk) patients were those that underwent surgery alone or received only low risk chemotherapy. Level 2 (medium risk) patients received moderate intensity chemotherapy or low dose cranial radiation (≤ 24 Gy). Level 3 (high risk) patients were those that received any other form of radiation (i.e. chest radiation) or intensive chemotherapy (i.e. bone marrow transplant). Using these risk groups, the study team was able to predict categories of low (12%), medium (36%), and high (65%) prevalence of late effects (**Figure A**). This "UK risk calculator"[20] demonstrated the ability to potentially distinguish childhood survival risk profiles and forms the basis of the risk calculator to be used in this proposed study.

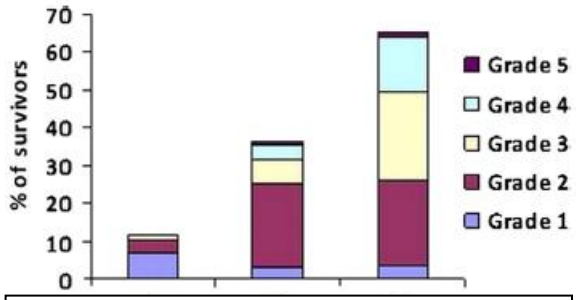


Fig A. Severity of late effects for low (left), medium (middle), and high (right) risk childhood cancer survivors per the UK risk calculator (Wallace et al.)

Summary: Childhood cancer survivors, particularly females, are at high risk of serious late effects from their cancer. However, few of these patients receive appropriate follow-up despite formal guidelines. In our parent R01, we are conducting an interventional trial (EMPOWER-II) to try to improve guideline-concordant cancer screening in female survivors of childhood cancer. We found that one of the key barriers to screening adherence is a lack of personalized risk information for patients and providers, particularly over discrete time horizons. In other words, we currently lack the ability to tell an otherwise healthy cancer survivor their risk of having a new onset of a severe or even fatal late event within a specified time frame (e.g. the next 5 years). In this study, we propose to use a validated UK risk calculator and apply it to adult female cancer survivors from the overall CCSS study population to identify low, medium, and high risk patient groups. Using these categories of patients, we will evaluate their discriminating abilities with regard to 5-year rates of new onset severe late effects and mortality.

This supplemental project will provide proof of concept and feasibility of use of personalized risk assessment for childhood cancer survivors. This will lay the groundwork to 1) develop more comprehensive risk models for childhood cancer survivors, 2) understand the ability of personalized risk estimates to improve screening behaviors, and 3) consider development of personalized, risk-based screening recommendations. This supplement proposal therefore is consistent with the goals of NOSI NOT-CA-20-038 to validate algorithms that categorize survivors into meaningful low, medium, and high risk-stratified groups using existing parent study data (CCSS), and thereby inform future development of risk-stratified care pathways in cancer survivors.

2. INNOVATION

This proposal is innovative via the following:

- **Evaluation of personalized risk stratification** to enable rapid risk assessment by physicians *AND patients* using a large sample (10,000+ survivors) and long-term (15+ year) follow-up data.
- We and others have previously studied risk factors for late effects in childhood survivors of cancer within the CCSS.[7,8,21,22] However, this will be the **first childhood cancer survivor-based risk**

calculator validated within a U.S. cohort to provide individual risk categories **over a broad set of outcomes** that could be readily and robustly applied to individual patients at the point of care.

- **Use of a 5 year horizon to provide discrete risk estimates** that can be easily discussed and understood by survivors and primary care physicians (PCPs).
- **Risk estimates based on both time from diagnosis & patient age**. We will conduct our study with survival being defined at 10 & 15 years after initial diagnosis, but also using patient age (20 or 30 years of age) to assess to what extent these risks can be consistently assessed over time.

3. APPROACH

3.1 Conceptual framework and hypotheses:

This administrative supplement will provide proof of concept and feasibility of personalized risk assessment for female childhood cancer survivors using an existing risk calculator within the CCSS data cohort. The goal of the study is not to solve the overarching challenge of risk-stratified care in childhood cancer survivors. Instead, the goal is to provide the initial proof of concept that can be used to justify future, larger investigations pursuing risk-stratified care approaches in childhood cancer survivors. This supplement will use an existing risk-stratification system developed previously within a UK cohort of childhood cancer survivors which categorizes survivors into low, medium, and high risk groups with respect to the incidence of severe or lethal late effects of their cancer treatment. Using the UK calculator, we will investigate the ability to predict the 5-year interval risk of mortality (**Aim 1**) and new onset severe morbidity (**Aim 2**). This will be investigated both as a function of patient age at diagnosis and time elapsed since diagnosis. We will focus on female childhood cancer survivors due to their i) high risk of late effects and ii) well documented deficiencies in survivorship care being studied in the parent R01.

This proposal will **investigate risk-stratification via UK risk categories** in previously healthy **adult female survivors of childhood cancer within the CCSS** cohort to **test the following hypotheses:**

- High risk survivors will exhibit significantly higher 5-year mortality vs. low risk survivors.
- High risk survivors will exhibit significantly higher 5-year rates of incident grade 3-5 chronic health conditions vs. survivors in low risk categories.
- Younger age at diagnosis and older age at time of evaluation will predict increased risks of late effects.
- Late effects from cancer treatment will occur more frequently as time from diagnosis increases

3.2 Data source:

Childhood Cancer Survivor Study (CCSS): The CCSS is the parent data set of the R01 accompanying this administrative supplement. The CCSS is the largest United States cohort of childhood (≤ 20 years old at diagnosis) cancer survivors.[6] The first cohort was collected for children diagnosed between 1970-1986, and then an expansion cohort was added from 1987-1999, thereby providing a dataset spanning three decades. The CCSS includes 5-year survivors of common childhood cancers (leukemia, tumors of the CNS, Hodgkin lymphoma, non- Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumors) who were diagnosed before the age of 21 years and from 1970 to 1999 in North America. However, it does not include patients diagnosed with histiocytosis or germ cell tumors, which were, for example, included in the UK study. The CCSS data contain limited information on disease stage but robust information on treatments received. There are a total of 23,601 survivors within the study for which initial treatment details (surgery, chemotherapy, radiation) overall survival, and severe chronic health conditions are available, with additional data for chronic health conditions for ~5,000 matched siblings.

3.3. Target population & study cohort:

i. Study population: The parent study cohort for the EMPOWER-II trial is limited to the subset of women treated with chest radiation, regardless of primary cancer type, over age 25, who were available to participate in an interventional study. Roughly two-thirds of this population had an initial diagnosis of Hodgkin lymphoma. The proposed administrative supplement study will be expanded to include all females within the CCSS cohort. There are a total of 11,096 females in the CCSS cohort, all diagnosed between 1970-1999 before age 21 per the overall CCSS inclusion criteria. By design, all patients within the CCSS cohort are alive at 5 years following their initial diagnosis. The median follow-up of the overall cohort is 21 years and it currently contains mortality data through 2018 and new onset chronic conditions through 2015, which will provide 15+ years of survival and chronic condition data for all patients within the study population.

ii. Control population: There is no explicit control population given that the goal of this study is to provide absolute estimates of adverse events during specific time-windows for multiple strata of the survivor population. Outcomes will be compared between the high, medium, and low risk groups at specified time points.

3.4 Primary study endpoints:

Aim 1: 5 year incremental survival/interval mortality: The primary endpoint of Aim 1 will be overall survival. Overall survival data is available through 2017 and therefore a minimum of 17 years of survival data is available for all patients. Survival will be evaluated over 5 year windows, conditional on survival to the beginning of that

interval. Survival 5-year windows will start at **A) 10 years after diagnosis**, **B) 15 years after diagnosis**, **C) 20 years of age**, and **D) 30 years of age** to assess to what extent these risks can be consistently estimated over time. The discriminating ability of the risk stratification will be further assessed with respect to age at diagnosis (A&B) and time from diagnosis (C&D).

Aim 2: 5 year incremental new onset serious chronic health conditions (grade 3-5): The primary endpoint of Aim 2 will be the development of a new grade 3-5 chronic health condition, conditional on a patient having no current serious health conditions. Chronic condition data is available through 2015 with potential for at least 15 years of chronic health condition data for all patients. Chronic health conditions have been previously reported within the CCSS [6] and include cardiovascular disease (congestive heart disease, coronary artery disease), pulmonary conditions (chronic obstructive pulmonary disease [COPD]), renal dysfunction, and/or development of subsequent malignant neoplasms (SMNs). Chronic health conditions will be examined over 5 year windows starting at **A) 10 years after diagnosis, B) 15 years after diagnosis**, **C) 20 years of age**, and **D) 30 years of age** to assess to what extent the stratification provides meaningful differences in risks over time.

Key independent variable: UK risk categorization: We propose to use the UK risk calculator as described by Wallace et al.[20] and described in the significance section of this proposal. However, we have made minor clarifications and adjustments to allow the UK risk categories to fit the CCSS cohort (**Table 1**), which differs slightly from the UK cohort. Adjustments were made to include specific threshold doses of anthracycline chemotherapy (doxorubicin-equivalent dose), alkylators (cyclophosphamide-equivalent dose), cisplatin, and bleomycin given the known toxicity of these agents and their propensity to cause long-term problems. Patients for whom exact chemotherapy doses are missing will be categorized as medium risk.

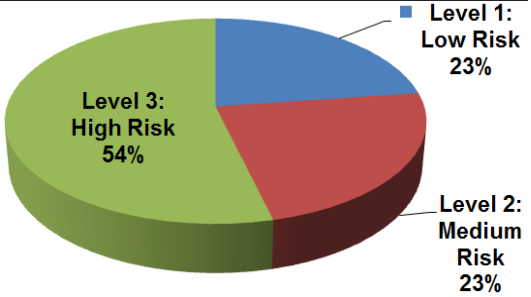
Table 1. Proposed risk categories based on Wallace et. el with modifications

Risk Category	Treatment	Example
1: Low	• Surgery only • ALL treated with chemotherapy only with DED <100 mg/m^2 • Wilms tumor without radiation or doxorubicin	• Early stage Wilms tumor s/p with surgery alone • ALL s/p low intensity chemo
2: Medium	• Patients not meeting criteria for level 1 or 3 • Patients missing chemotherapy dose	• ALL with mod dose chemo • AML
3: High	• Autologous or allogenic hematopoietic transplant • Cranial radiotherapy > 24 Gy • Neck, chest, abdomen, or pelvis radiation therapy ≥ 10 Gy • High dose chemotherapy: DED ≥ 250 or cisplatin ≥ 400 mg/m^2 or bleomycin ≥ 120 IU/m^2 or CED ≥ 10 grams/m^2	• HL s/p adjuvant radiation • Sarcoma s/p surgery, chemotherapy, and radiation

DED: doxorubicin-equivalent dose; CED: cyclophosphamide-equivalent dose; AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia, NHL: Non-Hodgkin- Lymphoma, HL: Hodgkin- lymphoma

3.5 Preliminary Data/Results & Power Calculations: This proposed administrative supplement will use the 11,096 female patients within the CCSS study cohort. The most common diagnosis was ALL (N=2,836, 26%) followed by Hodgkin lymphoma (N=1,369, 12%), astrocytoma (N=1,207, 11%), Wilms tumor (N=1,154, 10%), neuroblastoma (8%), soft tissue sarcoma (7%), Non-Hodgkin Lymphoma (6%), osteosarcoma (5%), and less common cancers including Ewing sarcoma, AML, medulloblastoma, and other CNS tumors (all <5%). Using the adapted UK risk categorization above, we have conducted a preliminary analysis to determine the number of low, medium, and high risk patients within the proposed study cohort. A total of 5,973 (54%) patients were high risk, 2,591 (23%) patients were medium risk, and 2,532 (23%) patients were low risk (Figure B). Within the low risk category, 40% were survivors of ALL, 22% of astrocytoma, 16% of Wilms tumor, and 11% of neuroblastoma. Of medium risk patients, ALL was most common (45%), followed by NHL (11%), and AML (7%). Among high risk patients, Hodgkin lymphoma was most common (20%) followed by Wilms tumor and AML (11% each), soft tissue sarcoma (9%), astrocytomas (8%), and neuroblastoma and osteosarcoma (each 7%).

Fig B – UK risk categories within the proposed study population. N = 11,096



Power calculation: Previous application of the UK risk categorization were associated with significantly different rates of cumulative serious chronic health events at the time of last follow-up. At a median of 11 years from initial diagnosis, prevalence of serious (grade 3-5) late events were 12% (low), 36% (medium), and 65% (high). Our primary study endpoints will be estimated within 5 year windows, conditional on not having an event prior to the start of that window. We assume that we will therefore observe roughly 6% (low), 18% (medium), and 32% (high) proportion of patients with new onset serious late events within any given 5 year period (roughly half that observed at 11 years within the UK study). Based on preliminary data from CCSS, at 10 years post-diagnosis,

there will be 2165, 2004 and 3918 survivors in the low, medium and high risk categories, respectively, who have not yet developed a grade 3-5 chronic health condition. Our primary comparison of interest is to compare differences in conditional cumulative incidence of serious late events over a 5 year interval. Using a two-sided alpha of 0.01 and 90% power, with at least 1000 survivors per group and assuming a 5-year incidence rate of 6% in the low risk group, we would be able to detect a difference of ≥5% between low risk and medium or high risk groups. Given our sample size, we will have ample survivors in each group to detect clinically meaningful differences. Moreover, we will also have sufficient leeway to be able to evaluate the impact of age at diagnosis

3.6 Study team:

Dr. Oeffinger (PI) is a leading figure in cancer survivorship and chair of the CCSS chronic disease working group with numerous high impact publications in the field of cancer survivorship[6,8,9,15,21,23-25] including seminal work in NEJM reporting initial estimates of chronic late effects of childhood cancer treatment from the CCSS cohort.[8] He is the founding Director of the Duke Center for Onco-Primary Care, Director of the Duke Cancer Supportive Care and Survivorship Center, and Professor of Medicine in Medical Oncology within the Department of Medicine.

Dr. Dinan (Co-Investigator) is Associate Professor in the Department of Population Health Sciences and an oncology health services researcher with expertise in large secondary database analysis and risk-stratified care in oncology. Dr. Dinan was a founding member of the Duke Cardio-Oncology Working group in 2014. In 2018, Dr. Dinan was invited along with Dr. Oeffinger to present to the American Cancer Society (ACS) in Washington D.C. to present on the landscape of available datasets and strategies for analyses related to risk-stratified cancer survivorship.[26] She serves on the Executive Committee for the Duke Cancer Institute's Cancer Control and Population Sciences Program where she co-leads the Patient Outcomes and Survivorship Focus Area.

Dr. Leisenring is a Professor in both the Clinical Research Division as well as the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center. She is a biostatistician who plays a key role in the design and analysis of a wide variety of clinical studies, largely focused on assessment of health conditions occurring after treatment for cancer. She has been the lead statistician for the CCSS for over a decade and has led analyses for more than 150 publications from the CCSS study data.

Ms. Stratton is a statistical research associate in the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center who works closely with Dr. Leisenring and has led many analyses using data from the Childhood Cancer Survivors Study.

In addition to this primary study team, we will also work closely with CCSS working group chairs as well as the following individuals: Eric Chow, MD, MPH; Yutaka Yasui, PhD; Emily Tonorezos, MD, MPH; Chaya Moskowitz, PhD; Jennifer Yeh, PhD; David Noyd, MD, MPH (Pediatric Hematology and Oncology Fellow at Duke) and Greg Armstrong, MD, MSCE.

3.7 Statistical analysis:

Statistical Framework: It is critical to note that the goal of the proposed work is **not** to produce a risk categorization method with maximal predictive accuracy, but rather to conduct a proof of concept initial investigation using the existing UK model. As such, our goal in this study is to introduce minimal alteration into our risk categorization model, but still provide enough prognostic information to conceivably support patient-provider decision making. **For the purposes of this study, model predicted probabilities are not the goal, rather it is to generally classify survivors into low, medium, or high risk categories with meaningful differences in clinical prognosis.**

The primary outcomes for these analyses will be defined as death (Aim 1) and development of a severe or life-threatening grade 3-5 chronic health condition (Aim 2). Both types of events will be analyzed as time-to-event outcomes, with age and cause of death available from a National Death Index search through December 31, 2017, which will be used as the censoring time, for all CCSS participants. Self- or proxy reported age at first occurrence of all grade 3-5 chronic health conditions have been graded from all relevant CCSS surveys, with censoring time at each participant's last submitted survey, and treating death due to a cause other than the grade 3-5 chronic condition of interest as a competing risk event. Kaplan-Meier (for mortality) and cumulative incidence (for severe heath conditions) will be used to evaluate conditional 5-year estimates of incidence. Comparisons of 5-year mortality, any severe late health condition, and potentially the most common severe late health conditions, between risk stratum will be carried out using log-rank tests, Gray's test, Cox proportional hazards models or the Fine-Gray competing risks model (see below). Multivariable Cox proportional hazards models will be used to examine the impact of age at diagnosis, age at the beginning of the 5-year window and decade of treatment on the utility of the risk stratum in discriminating patient outcomes, via testing interactions and potentially stratifying analyses further.

Modeling Approach: We considered several potential modeling approaches, and different methods will be relevant for mortality (where there are no competing risks) and for severe chronic health conditions. For mortality, standard methods (Kaplan-Meier, logrank and Cox proportional hazards will be used). For severe life-threatening chronic health conditions, the choice was between a competing risk framework (Find-Gray sub-distribution hazards) and a net risk framework (cause-specific hazards). Sub-distribution hazards are typically used for

prediction, whereas cause-specific hazards are used to focus on etiologies/causal relationships. The core goal of this project is to predict the occurrence of any adverse event in a previously health patient. Therefore we will use the sub-distribution hazards (Fine-Gray) model in order to identify the risk of the first serious event as our primary approach. However, it should be noted that the sub-distribution hazards is designed for mutually exclusive events, which does not work well for non-mutually exclusive events (i.e. a patient can have kidney failure *and* a heart attack) that may be considered in exploratory analyses seeking to distinguish prediction of individual categories of events.

Model Selection and Predictive Accuracy: For the main analysis, we will use the described UK risk categories with minimal adjustments and examine their ability to predict the rate of new onset serious late events within a 5 year analysis risk windows, conditional on survival free of those events to specific time points (10, 15 years after diagnosis). In addition to overall mortality, we will examine the ability of low, medium, and high risk categories to predict the rate of new onset serious chronic conditions. The precision of all reported risk estimates and risk differences will be reported using associated 95% confidence intervals. Next, in the exploratory phase of the project we will expand the UK risk categorization to investigate the potential effect of age at diagnosis, age at follow-up, and decade of treatment.

3.8 Specific Objectives:

This proposal will investigate the potential of UK risk categories to stratify risk of serious late events in healthy adult female survivors of childhood cancer within the CCSS cohort via the following objectives:

Aim 1: To predict 5-year interval mortality in females within the CCSS cohort using the UK risk categorization. Using the UK calculator we will place females in low, intermediate, or high risk categories and compare interval 5 year mortality by risk category.

Objectives: We will define survival using time elapsed from initial diagnosis and examine the 5-year interval risk of a new serious late event in women with no prior serious conditions. We will identify all patients without serious late events at **1A) 10 years after diagnosis** and assess the incidence of interval mortality between 10 and 15 years from diagnosis. We will repeat this for patients **1B) 15 years after diagnosis**, examining the risk of interval mortality from 15 to 20 years following diagnosis. We will additionally examine interval adverse events in patients **1C) at age 20** and **1D) at age 30**. We will use UK low, medium and high risk categories to characterize associated mortality and serious late events during each 5 year interval. For objectives A & B, exploratory analyses will be conducted to examine the impact of patient age at diagnosis. For objectives C & D, exploratory analyses will examine the additional impact of years elapsed since diagnosis. For aims A-D we will explore the impact of decade of treatment (1970s, 80s, or 90s) on relative adverse event risk, as older decades of treatment have been previously associated with more aggressive treatment and higher rates of late toxicity. The combination of these objectives will allow us to use the UK risk categories, while exploring the extent these risks can be consistently assessed over time.

Aim 2: To predict 5-year incident serious chronic health conditions (grade 3-5) within the CCSS cohort using the UK risk categorization. Using the UK calculator we will place females in low, intermediate, or high risk categories and compare the 5-year interval incidence of new onset serious chronic health conditions including cardiovascular, pulmonary, renal conditions, and development of SMNs as previously reported within the CCSS cohort. [8] [6] We will assess these events both at **A) 10 years** after initial diagnosis, **B) 15 years after diagnosis**, **C) 20 years of age**, and **D) 30 years of age.** Women will be limited to those without any evidence of chronic health conditions at each time point, with the focus being to identify incident late events in previously healthy women. Exploratory analyses of the impact of age at diagnosis (A&B) and years elapse since diagnosis (C&D) will be conducted analogous to Aim 1.

3.9 Dissemination & Timeline:

The project is a one year supplement that will naturally extend from our current R01 funded project examining risk-based survivorship in adult female survivors of common childhood cancers. We anticipate at least two abstracts and subsequent manuscripts, one from each aim. Results from ongoing studies will be submitted to international and national conferences such as ASCO, ASCO quality of care, and other venues as appropriate pending study findings. Preliminary findings will be used to lay the foundation for grant applications to investigate expanded risk-stratification models and explore potential incorporation of personalized patient risk into survivorship care models.

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